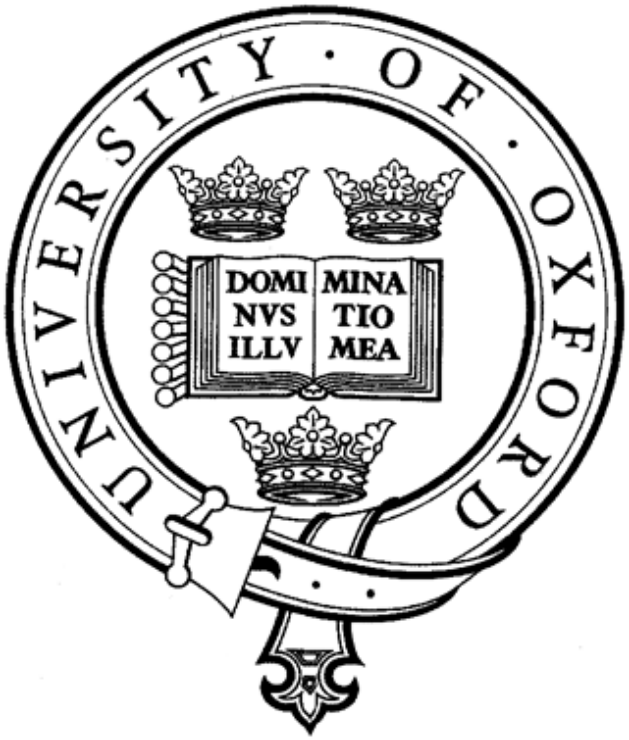
Reversible myocardial depression in critical illness



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Abstract

Introduction: Reversible myocardial depression (RMD) is a transient impairment of left ventricular systolic function. This has been described in sub-populations of patients experiencing critical illness, but it is unclear if the epidemiological features are generalisable to the broader populations of critically ill adults. Previous work has identified that RMD is not benign and has been associated with a range of adverse sequelae such as arrhythmia, left ventricular outflow tract obstruction, and intra-ventricular thrombus. Consequently, studies were designed to determine the incidence, time course, and associated risk factors for the development of myocardial depression in the general population of adults experiencing critical illness.

Methods: Myocardial depression was defined as a decrease in left ventricular ejection fraction ≥5% from AICU baseline and was assessed using serial transthoracic echocardiography. Three studies were conducted - two prospective observational cohort studies and a retrospective analysis. The incidence, absolute decrease in ejection fraction, and time course of myocardial depression was described. Routinely available demographic and clinical variables were collected. These were then rationalised and trialled as candidate explanatory variables in a logistic regression model to predict the development of myocardial depression.

Results: The incidence of myocardial depression was between 16.3 – 34%, which occurred around day four of AICU admission. The median decline in LVEF at the onset of myocardial depression was between 6.5 – 14.7%, which progressed to between 10 – 17.5% at the nadir. Myocardial depression was not entirely reversible, with between 43.7 – 71.4% of participants demonstrating some degree of recovery, with LVEF improving between 13.3 – 20.2% across the studies.

The probability of development of myocardial depression can be determined using five routinely collected variables, expressed as a factor; heart rate, systolic blood pressure, the presence of severe sepsis, cardiovascular organ dysfunction and sinus rhythm. Increasing systolic blood pressure, the presence of severe sepsis, and cardiovascular organ dysfunction were associated with increased risk. Increasing heart rate and the presence of sinus rhythm were associated with decreased risk.

Model diagnostics indicated that the model was a good fit of the data. The model had a modest discriminating ability, with the area under the receiver operating characteristic curve = 0.69.

Conclusion: The incidence of myocardial depression was between 16.3 – 34% of participants, and usually developed around day four of AICU admission. The decreases in left ventricular ejection fraction were considerable and were not always reversible. Myocardial depression can be predicted using routinely collected haemodynamic and clinical variables that are available within the first 24 hours of AICU admission.

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- Dr Graham Barker: interpretation of echocardiographic studies in all patients with known or suspected regional wall motion abnormalities.
- Dr Daniel Lunn: provision of statistical advice and coding skills in the development of the predictive models.

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Acronym	Meaning
AICU	Adult Intensive Care Unit
AMI	Acute myocardial infarction
APACHE II	Acute Physiological and Chronic Health Evaluation II
AUROC	Area under the Receiver Operating Characteristic curve
BNP	B-type natriuretic peptide
BSA	Body surface area
BSE	British Society of Echocardiography
CASP	Critical Appraisal Skills Program
CINAHL	Cumulative Index to Nursing & Allied Health Literature
CK-MB	Creatinine kinase isoenzymes M and B
CMRI	Cardiac magnetic resonance imaging
CRF	Case report form

CSA	Cross sectional area
CVS	Cardiovascular system
DICOM	Digital Imaging and Communication In Medicine
ECG	Electrocardiograph
ECMO	Extracorporeal membrane oxygenation
ELF	Evaluation of left ventricular function
EMBASE	Excerpta Medica Database
ESV	End systolic volume
ET	Ejection time
FICE	Focused Intensive Care Echocardiography
GLM	Generalised linear model
HRA-CAG	Health Research Authority Confidentiality Advisory Group
IABP	Intra-aortic balloon pump
ICNARC	Intensive Care National Audit and Research Centre
IQR	Interquartile range

ITU/ICU	Intensive Therapy/Care Unit
IVCT	Isovolumetric contraction time
IVRT	Isovolumetric relaxation time
IVSd	Interventricular septum (thickness in) diastole
LA	Left atrium
LOS	Length of stay
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVIDd	Left ventricular internal diameter diastole
LVIDs	Left ventricular internal diameter systole
LVOT	Left ventricular outflow tract
LVPWd	Left ventricular posterior wall dimension
MAPSE	Mitral annular plane systolic excursion
MeSH	Medical subject headings
MLE	Maximum likelihood estimation

MRN	Medical record number
MV	Mechanical ventilation
NHS	National Health Service
PACS	Picture Archiving and Communication System
PCA	Principal component analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RMD	Reversible myocardial depression
ROC	Receiver operating characteristics
RV	Right ventricle
RWMSI	Regional wall motion scoring index
SAH	Subarachnoid haemorrhage
SBP	Systolic blood pressure
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SQL	Structured Query Language

TDI	Tissue Doppler imaging
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
VTI	Velocity time integral
2D	Two dimensional
3D	Three dimensional

Chapter I: Introduction

1.1 Overview

This chapter reviews the current definition of reversible myocardial depression (RMD), the clinical sequelae, including its relevance to critical illness and the limitations of the existing diagnostic framework. Systematic reviews of the literature to identify the incidence, natural history and predictors of RMD are presented. The research questions are specified, using the knowledge and gaps identified in the literature review as the basis for their development. Methods of assessment of left ventricular (LV) systolic function are then discussed, with emphasis on echocardiography within the adult intensive care unit (AICU) environment. Finally, the background and role of predictive modelling and its potential use in the prediction of the development of RMD is discussed.

1.2 Reversible myocardial depression

1.2.1 Definition

RMD is an umbrella term covering a range of transient, acquired, cardiomyopathies. A consensus definition is lacking, but it is generally accepted that it is a transient impairment of LV systolic function that is triggered by an acute, severe physical or emotional stressor that resolves over time.

In a landmark paper by Parker[1] in 1984, transient impairment of ejection fraction was first described in patients with septic shock. Since then, RMD has been

observed in many settings, such as patients with subarachnoid haemorrhage[2–8] (SAH), severe emotional or physical stress[9–14], burns[15], Guillain-Barre[16], trauma[17] and after administration of catecholamines[18,19]. Despite proposals of a common pathophysiological mechanism[20–24], within the literature RMD is frequently described in the context of the concomitant disease state e.g. septic cardiomyopathy.

The majority of descriptions in the literature stem from the three most commonly observed manifestations of RMD: septic, neurogenic and Takotsubo's cardiomyopathies. These manifestations are briefly considered further.

Septic myocardial depression was first described by Parker in 1984[1], who described a transient impairment of LV systolic function in patients with septic shock, which resolved over ten days. Since then, numerous studies[25–33] have been undertaken to further characterise its sequelae and time course. Septic myocardial depression may manifest with hypotension and arrhythmias, and a variable pattern of regional wall motion abnormalities (RWMA) of the left ventricle has been observed[34]. Left ventricular systolic dysfunction typically resolves within one week[27,35,36], although a small number of patients will exhibit a delayed recovery[30]. The aetiology of this process remains unclear[37–39].

Attempts have been made to identify the presence of septic myocardial depression using cardiac biomarkers[28,40–43], but their lack of specificity[44] have hampered their utility in identifying this process. Despite being studied extensively, uncertainty remains about the incidence of septic myocardial depression[45], likely stemming

from a lack of consensus definition and heterogeneous research methodologies (discussed further in the literature review, section 1.3.2).

Transient impairment of cardiac function following neurological injury has been reported in both patients with SAH[2–5,7,8,46,47] and traumatic brain injuries[48]. The presentation of neurogenic myocardial depression is similar to that observed in sepsis, such as non-specific electrocardiograph (ECG) changes[49–51] and hypotension[49,50]. Similarly, non-specific elevation of cardiac biomarkers[2,49–52] and variable pattern of RWMA[10,49,51,53,47,54] have been demonstrated. Partial or complete recovery of LV systolic function has been observed, typically occurring around one week following neurological injury[52,47,54].

The common features observed in septic and neurogenic myocardial depression have also been observed in Takotsubo's cardiomyopathy. The term "Takotsubo's cardiomyopathy" was coined in Japan in 1991 to describe the transient apical pattern of RWMA occurring after severe emotional stress, in the absence of obstructive coronary artery disease[55]. Originally thought to be a condition predominately seen in elderly Japanese women, in the last 20 years it has been observed outside Japan[10,12,14], occurring in males[21], in younger patients[9], in response to physiological stressors[20,21], and involving the cardiac base[9]. Further research has demonstrated that the clinical presentation and non-specific biomarker release observed in Takotsubo's cardiomyopathy is similar to that observed in septic and neurogenic cardiomyopathies[2,11–13,52,56].

Diagnostic criteria for Takotsubo's cardiomyopathy have been proposed[57,58], most notably by the Mayo Clinic (Appendix 1). These, however, are strict, not always feasible to use in the clinical environment, and are not universally accepted. Impracticalities and limitations of the Mayo Clinic criteria have been identified by Redfors[59], who highlighted that the criteria do not allow for concomitant coronary artery disease, despite evidence that they can co-exist. The impracticalities of the proposed diagnostic criteria have resulted in haphazard adoption of the definition, which has resulted in inconsistencies in the reported incidence and time course of Takotsubo's cardiomyopathy.

Other manifestations of RMD are less rigorously defined, which has led to conflicting evidence on the incidence, sequelae and inadequate characterisation of its time course. This is evident by the conflicting results reported in the literature review (section 1.3.2).

Despite described as separate conditions based on concomitant disease process, the clinical manifestations of RMD are similar. Clinically, RMD is usually observed in the days[17,25,28–30,36,60] following an acute, severe physical or emotional stressor and, in the majority of cases, resolves within seven to ten days[28,31,60].

To date, RMD has been described in the literature based upon concomitant disease process, despite a proposed common pathophysiological mechanism and overlap in presentation, time course, and sequelae. Little attention has been given to the common features of RMD and the advantage of a unifying definition.

1.2.1.1 Continuum or separate entities?

Whilst the precise aetiology of RMD is unknown, review of pathophysiology, clinical features, sequelae, and natural history of the three most commonly reported types of RMD (septic, neurogenic and Takotsubo's) demonstrates striking overlap between conditions.

Catecholamine excess[14,37,61], increased levels of circulating pro-inflammatory cytokines[62,63], systemic hypoperfusion[62,63], calcium handling abnormalities[37], cardiac myocyte energy depletion[37] and microcirculatory dysfunction[64] have all been proposed as potential pathophysiological mechanisms for the development of RMD. The low elevation of cardiac biomarkers[2,11–14,36,49–52,56,65] and the transient nature and distribution of RWMA beyond the distribution of a single coronary artery territory suggests a cause other than myocardial ischaemia or occult coronary artery disease.

Investigators have postulated a catecholamine-mediated mechanism as the most likely cause of RMD, pointing to the common histopathological feature of contraction band necrosis, which is consistent with catecholamine excess[14,19,20,61,66]. This histological feature has been observed in patients with septic[67,68], neurogenic[69] and Takotsubo's[14] cardiomyopathies.

Common features have also been identified in the presentation, biomarker release, time course and RWMA pattern, these are detailed in table 1.

Table 1: Overlap in features of the three most reported reversible cardiomyopathies

	Takotsubo's	Neurogenic	Septic
Presentation	Variable ECG changes[11–14,56] Chest pain[11–14,56] Dyspnoea[11,12,14] Syncope[12]	Variable ECG changes [49–51] Hypotension [49,50]	Variable ECG changes[70,71] Hypotension[70,72,73]
Biomarkers	Mild or variable troponin- I elevation[11–14] Elevation of plasma catecholamines[14,56] Mild Creatinine kinase isoenzymes M & B (CK-MB) elevation[13,14,56]	Mild or variable troponin- I elevation[2,52] Non-specific B-type natriuretic peptide (BNP) elevation [52] Elevation of plasma catecholamines[52] Mild, non-specific CK-MB elevation[49–51]	Mild or variable troponin- I elevation[36,65] Non-specific BNP elevation[65]
RWMA pattern	Apical[13] Variable[11,12,14,56]	Apical[53] Variable[10,49,51,74]	Apical[60] Variable[75,76]
Time course	Majority resolve RWMA and systolic function during acute period <14 days[11–14,56], small proportion delayed recovery[12]	Resolution in around one week in majority of patients [52]	Majority resolve RWMA and systolic function during acute period[35] < 14 days, small proportion delayed recovery

The overlap of reversible cardiomyopathies has been recognised in the literature [20,22,23]. It has been proposed that the apex-sparing RWMA variant of Takotsubo's cardiomyopathy is unlikely to be a different clinical entity to LV dysfunction observed in sepsis and other disease states[22].

The current diagnostic criteria and definition of Takotsubo's cardiomyopathy is very precise[57], and requires coronary angiography to confirm the diagnosis. It has been suggested that neurogenic and Takotsubo's cardiomyopathy are the same clinical entity, but the narrow definition of Takotsubo's cardiomyopathy preclude unison of these conditions[23]. This theory has been supported by the European Society of Cardiology, which state that Takotsubo's cardiomyopathy is the same RMD observed in neurological conditions[24].

Given the overlap of the features, it is not unreasonable to consider reversible cardiomyopathies as a continuum, and not unique to a disease processes. This approach has been echoed by Haghi[21] who proposes that RMD classified by concomitant disease processes is likely a manifestation of the same underlying pathology of excessive sympathetic activity.

Excessive sympathetic activity, as a result of severe physical or psychological stress, results in increased production and release of catecholamines. Stimulation of the ventricular ß-adrenoreceptors occurs by local release of noradrenaline from sympathetic nerve endings or by diffusion into the myocardium from the coronary circulation[77]. The precise mechanism of injury is debated[77–79], but it is most widely

accepted that this adrenergic stimulation can lead to cardiac myocyte injury via a cyclic-AMP mediated calcium overload induced by excess adrenergic stimulation[79].

This process would explain the continuum of RMD, as it is reasonable to suggest that the physiological stress of sepsis or neurological injury is sufficient to trigger excessive sympathetic activity. Similarly, Takotsubo's cardiomyopathy has historically been described following severe emotional stress, which can trigger excessive sympathetic activity. Furthermore, adrenergic drugs such as noradrenaline and dobutamine, are often therapeutically administered in critical care units to induce vasoconstriction and increase cardiac contractility[80]. Finally, this hypothesis is supported by the identification of elevated endogenous plasma catecholamines in patients following subarachnoid haemorrhage[52], in patients with Takotsubo's cardiomyopathy[56], and in patients with sepsis[81].

1.2.2 Clinical sequelae of reversible myocardial depression

Recognised complications of RMD include arrhythmias[13,14], left ventricular outflow tract obstruction (LVOT)[11,12,82], shock[13,14,56], intra-cardiac thrombus[10–12,82,83] and pericardial effusions[10,82]. Numerous studies[11,12,84] have reported the development of LVOT obstruction, with incidence reported between 7 – 15%[9,12]. LVOT obstruction can result in increased afterload, and the resulting increase in LV wall stress can manifest as angina, heart failure and ischaemia with associated troponin or other biomarker release and ECG changes.

In a study by Lee[84], 56 patients were identified as having definite or probable stress-induced RMD. This study reported a 16% (n = 9) in-hospital mortality, with six deaths attributed to cardiac causes. Two patients had refractory heart failure, whilst the other four had fatal ventricular tachyarrhythmias. This is much higher than what has previously been reported in the literature[10,85,86], but this may be explained by a small study size and by a higher prevalence of acute physiological derangement, reflected by a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Similar outcomes were reported by Sharkey[12] in a study on stress induced cardiomyopathy (n = 136) who identified ventricular thrombus in eight patients. The most striking finding from this study, however, was that stress induced cardiomyopathy was disproportionately observed in patients exposed to therapeutic doses of catecholamines (n = 13). Furthermore, this study identified that all-cause mortality for the first 12 months following diagnosis, adjusted for age and gender, was significantly increased compared with matched population norms, suggesting that the clinical course of RMD may not be benign. Additionally, a recurrence rate of 5% (n = 7) within four years of the first episode was observed.

Intra-ventricular thrombus is also a recognised complication in patients with SAH and RMD[49,87]. Additionally, acute pulmonary oedema and severe hypotension were reported complications in studies by Mayer [49,50]. Complications arising from RMD have been less frequently reported in sepsis patients. Studies have traditionally focussed on in hospital and 28-day mortality, a standard AICU outcome measure.

Given the high mortality associated with sepsis, it may be difficult to accurately attribute deaths to either the underlying pathological process (sepsis) or RMD.

Systematic reviews have also been undertaken to try and synthesise common features, time course and outcomes. Donohue[86] and colleagues undertook a systematic review of case series of patients with Takotsubo's cardiomyopathy, and identified complications in 35 of 185 patients (19%). The most commonly identified complications were cardiogenic shock (n = 12), intra-cardiac thrombus formation (n = 7), congestive heart failure (n = 7) and death (n = 6). Similarly, an analysis by Gianni[85] identified 23 of 212 (11%) of patients with Takotsubo's cardiomyopathy required intra-aortic balloon counter-pulsation, whilst acute heart failure was reported in 38 of 215 patients (18%). Death during the study period was reported in three of 286 patients (1%).

1.2.3 Reversible myocardial depression in critical illness

1.2.3.1 Identification of reversible myocardial depression in critically ill patients

The physiological stress of critical illness is sufficient to induce RMD. This is being increasingly recognised[60,70,88,89], likely owing to greater clinical suspicion and adoption of echocardiography in critical care environments.

The delineation of reversible cardiomyopathies into highly specific sub-classifications may lead to an under recognition of the condition, particularly in AICU population. This is further compounded by lack of consensus in definitions

of illnesses commonly treated on AICUs, especially those characterised by derangements of physiology, such as sepsis.

During critical illness, patients are often unable to report symptoms, have non-specific elevation of cardiac biomarkers[44,90] or are too unstable to undergo invasive investigations[21]. Furthermore, those that report symptoms may have these attributed to another disease process[21]. These problems can result in an under reporting of the incidence of reversible cardiomyopathies in the AICU population and associated sequelae. This has been recognised by Dec[88] who suggests that reversible cardiomyopathies must be considered as a differential diagnosis in any critically ill patient with haemodynamic collapse, as the true incidence of this condition is yet to be determined.

1.2.3.2 Reversible cardiomyopathies in the AICU

RMD is increasingly recognised in critically ill patients. It has been established that RMD is associated with the development of complications such as ventricular thrombus, arrhythmia and LVOT obstruction. Greater understanding of the incidence, time course and predictors of development of RMD in the critically ill will enhance clinical suspicion which may ultimately lead to improved outcomes by earlier recognition, and the development, and implementation of therapies. Consequently, a review of the literature was undertaken to establish the incidence, time course and identify predictors of the development of RMD in critically ill patients.

1.3 Review of the literature: RMD in critical illness

1.3.1 Overview

Two literature reviews were conducted. The first investigated the incidence and time course of RMD in critically ill patients, and the second investigated the predictors of this condition. The incidence of myocardial depression is the number of patients developing LV dysfunction, expressed as a proportion of all patients included in the study.

1.3.2 Literature review 1

Question: What is the incidence and time course of reversible myocardial depression in critically ill patients?

1.3.3 Methods

1.3.3.1 Search strategy

Studies were identified using EMBASE (1992 to August 2012), Medline (1992 to August 2012), Web of Knowledge (1992 to August 2012), Web of Science (1992 to August 2012), PubMed Central (1992 to August 2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1992 to August 2012). Limits were applied to identify studies published within the last 20 years, reflecting increasing awareness of reversible cardiomyopathies and adoption of tools to identify this in routine clinical practice. In critical care units RMD is usually

identified using bedside echocardiography. Consequently, this was included as a search term.

The following general search terms were used: (critical* OR critical illness OR intensive care unit OR intensiv* OR ITU OR ICU OR critical therapy OR intensive therapy OR critical care) AND (echocardi*) AND (incidence) AND (dysfunct* OR impair* OR depress*) AND (heart OR myocard* OR cardi*). Search terms were tailored to the individual specifications of the respective databases.

Further articles were identified by hand searching reference lists of review articles and relevant articles found in the original database searches.

1.3.3.2 Study selection

Studies were initially screened by title, then abstract and ultimately by full text. Studies were selected for review provided they met the criteria outlined in table 2.

Table 2: Criteria for study inclusion in the literature review

Inclusion criteria	
Study design	Any study design
Population	Patients ≥16 years of age receiving treatment in a critical care setting
Intervention	Serial cardiac assessments using echocardiography
Outcome	Incidence of LV systolic dysfunction and reversibility

Studies of animals, children (aged <16 years), case reports/series of less than five patients, abstracts/conference proceedings and studies of chronic cardiac dysfunction, or survivors of cardiac arrest were not considered for inclusion. An absence of resources for the translation of articles prevented articles in languages other than English from being included.

Finally, only studies assessing LV systolic function were included. The majority of literature on reversible cardiomyopathies occurring during critical illness have focussed attention on the left ventricle, as right ventricle architecture renders comprehensive assessment by echocardiography extremely difficult. Furthermore, studies solely assessing diastolic function were excluded. At the time of the review there was no consensus on which variables should be used to assess diastolic function, or what constituted impairment. Consequently, this evidence was felt to be weak, heterogeneous and potentially unreliable.

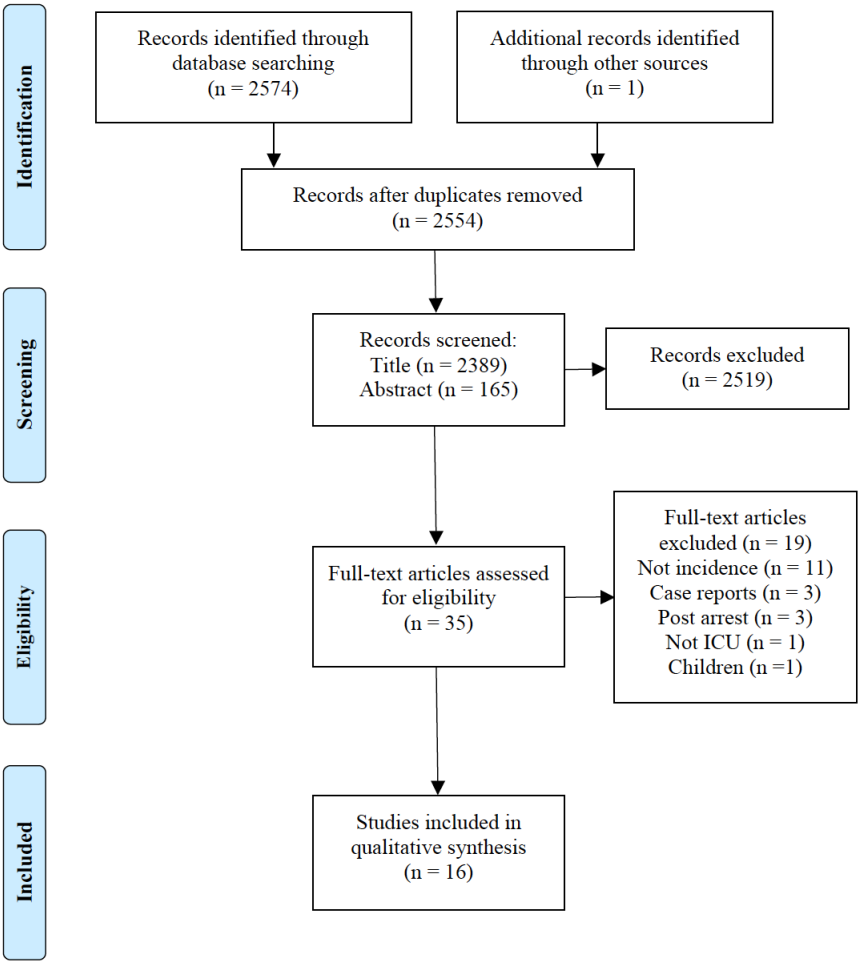
1.3.3.3 Data extraction, synthesis and analysis

Data were extracted to facilitate the description of the study population, assessments and study quality. The studies were reviewed using the Critical Appraisal Skills Programme[91] (CASP) checklist for evaluation of cohort studies. This checklist provides an assessment tool to identify the validity, relevance and reliability of published papers. The CASP checklist for all included papers is given in Appendix 2.

1.3.4 Results

The search resulted in a total of 2575 citations, from which 165 abstracts and 35 full-text articles were reviewed. Ultimately, 16[2,7,8,17,25,27–30,33,35,36,60,70,71,92] studies were included in the review. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses[93] (PRISMA) flowchart is given in figure 1 to describe study selection.

Figure 1: PRISMA flowchart for studies identified in literature review 1



Eligible studies were heterogeneous. There was substantial variation between the critically ill populations studied, inclusion/exclusion criteria, timing of assessments and definition of impairment. LV systolic function was predominately assessed by transthoracic echocardiography[2,8,25,28,29,32,33,60,70] (TTE, n = 9), a smaller number utilised transoesophageal echocardiography[17,25,36] (TOE, n = 3) or used a combination of both[7,27,30,89] (n = 4).

Left ventricular systolic function was assessed by ejection fraction in 12 studies [2,7,8,25,28–30,32,33,35,60,71], by fractional area change in three[17,27,36], and left ventricular wall motion and LV function score in one[70]. Ejection fraction is the proportion of end diastolic volume that is ejected during systole. Fractional area change is the change in LV cross sectional area between diastole and systole. Wall motion is graded from 1 – 5 with normal contraction assigned a score of one, progressing through to aneurysmal (grade five)[94].

Review of the studies identified four patient sub-groups: general AICU patients[60,70,71], patients treated for SAH[2,7,8], patients with sepsis[25,27,28,30,32,33,35,36] and other[17,29]. Fifteen[2,7,8,17,25,27–30,32,33,35,36,60,71] of the sixteen studies were prospective observational cohort studies, one study[70] was a retrospective analysis.

Given the heterogeneity of the studies, quantitative analysis was not attempted. Instead, a description of the data contained in the identified studies and the implications of the review are provided.

1.3.4.1 Myocardial depression and recovery

Three cohort studies examined LV dysfunction in general AICU patients[60,70,71]. Bailen[71] observed myocardial depression in 33 of 574 participants (6%), Park[60] in 26 of 92 participants (28%) and Sharkey[70] in 21 of 22 participants (95%). In patients who developed myocardial depression, the incidence of reversibility was given as 77%[60] and 76%[70]. Bailen[71] and colleagues did not report the incidence, nor were figures included that would allow this calculation. The author did not respond to multiple requests for these data. He did, however, report a statistically significant ($p < 0.0001$) improvement in LV systolic function over time in the study cohort.

Eight studies reported the incidence of myocardial depression in patients with sepsis[25,27,28,30,32,33,35,36]. The reported incidence of myocardial depression varied between 17.5[28] – 44%[27,30,35]. Landesberg[32] observed this in 61 of 262 participants (23%), and Furian[33] in 15 of 45 participants (33%), yet neither study observed reversibility in LV systolic function during their follow up period (day two and day seven, respectively). This is in contrast to complete or partial recovery observed in the other studies[25,27,28,30,35,36].

The inconsistency in incidence of myocardial depression and recovery were also seen in the three studies of patients treated for SAH[2,7,8]. A study by Meaudre[8] undertook bedside echocardiography at days one, two and seven following admission for SAH and did not demonstrate myocardial depression (defined as LV ejection fraction <50%) in any patient. Conversely, two other studies undertaken in

the same population (SAH) reported the incidence between 17[2] – 38%[7]. In the study by Tanabe[2], recovery of LV systolic function was observed in 12 of the 17 patients exhibiting depression (71%). Incidence of reversibility is not explicitly reported by Papanikolaou[7], although statistically significant improvements in left ventricular ejection fraction (LVEF) over time are reported, with mean LVEF initially 57.9% (SE 2.1%) improving to 62.6% (SE 1.5%).

Lastly, one study of patients treated for cancer with septic shock[29] (n = 45) reported the incidence of myocardial depression as 40% (18 of 45 patients). Reversibility was not reported, and attempts to contact the author for these data were not successful. The remaining study of patients treated for traumatic injuries[17] reported the incidence and reversibility to be 100% in their cohort (n = 7).

Details of reported incidence of myocardial depression and recovery are given in table 3. A scatter plot of LVEF definition of impairment against incidence of myocardial depression is given in figure 2. This demonstrates that the reported incidence is variable, even when using a common definition of impairment.

Table 3: Overview of the reported incidence of RMD and time to recovery in critically ill patients

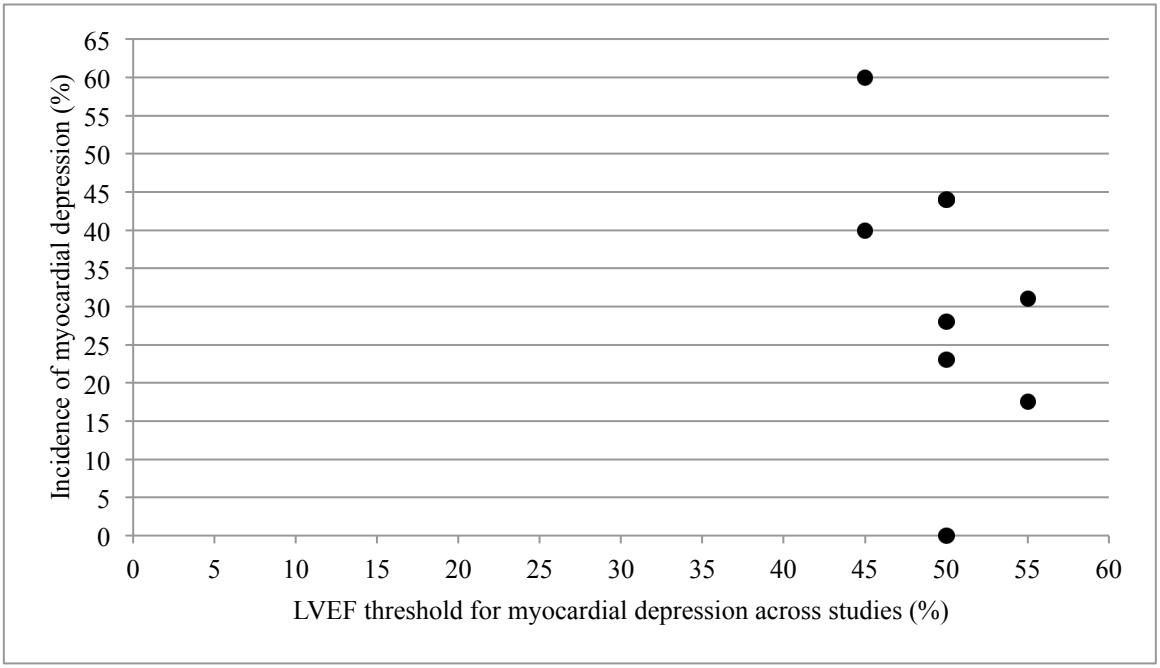
Study	Population	Definition	Incidence MD (n, %)	Incidence reversibility (n, %)	Time to recovery
Park, 2005[60]	General AICU	LVEF <50% with severe symmetrical hypokinesia or akinesia of LV wall (except base)	26/92 (28%)	20/26 (77%)	Mean 7.4 ± 5.6 days following AICU admission
Bailen, 2003[71]	General AICU	Not defined	33/574 (6%)	Not reported	Not reported
Sharkey, 1998[70]	Predominantly general AICU	LV systolic function score: 0 = hyperdynamic 1 = normal 2= mild decrease 3 = moderate decrease 4 = severe decrease	21/22 (95%)	16/21 (76%)	11 (68.8%) patients by hospital discharge 4 patients (25%) at 6.5 months after hospital discharge

Study	Population	Definition	Incidence MD (n, %)	Incidence reversibility (n, %)	Time to recovery
Bouhemad, 2008[36]	Sepsis	FAC <50%	11/54 (20%)	11/11 (100%)	By day 7 of AICU admission
Landesberg, 2012[32]	Sepsis	LVEF <50%	61/262 (23%)	0 (0%)	Not applicable
Furian, 2012[33]	Sepsis	LVEF <55%	14/45 (31%)	0 (0%)	Not applicable
Etchecopar-Chevreuil, 2007[30]	Sepsis	LVEF <50%	16/36 (44%)	16/16 (100%)	Cessation of vasopressors (75% recovered), Day 28 post AICU discharge (100% recovered)
Charpentier, 2004[27]	Sepsis	FAC <50%	15/34 (44%)	5/15 (33%)	Day 8 of AICU admission
Pulido, 2012[35]	Sepsis	LVEF <50%	47/106 (44%)	27/47 (57%)	Day 5 of AICU or discharge, whichever was earlier
Vieillard-Baron, 2008[25]	Sepsis	LVEF <45%	40/67 (60%)	40/40 (100%)	Cessation vasopressors

Study	Population	Definition	Incidence MD (n, %)	Incidence reversibility (n, %)	Time to recovery
Tanabe, 2008[2]	SAH	LVEF <55% RWMA per American Society of Echocardio graphy	17/103 (16.5%)	12/17 (70.5%)	Between days 5 – 10 following SAH
Papanikolaou 2012[7]	SAH	LVEF <50% WMSI >1	14/37 (38%)	Statistically significant improveme-nts in EF over time	Day 21 following SAH
Mokart, 2007[29]	Oncology patients with septic shock	LVEF <45%	18/45 (40%)	Not reported	Not reported
Smail, 1996[17]	Trauma	FAC <50%	7/7 (100%)	7/7 (100%)	Day 2 of AICU admission

The incidence of myocardial depression across various study definitions of impairment is given in figure 2. Each datapoint represents one study.

Figure 2: LVEF threshold vs reported incidence for studies included in literature review 1



Six papers[2,17,27,36,70,71] were excluded from figure 2 as they did not use LVEF to identify patients with myocardial depression, or were inadequately defined.

1.3.4.2 Time course

The majority of studies that demonstrated acute reversible myocardial changes undertook assessments up until a maximum day ten of AICU admission. Additionally, four studies[7,30,70,71] undertook follow up assessment after AICU discharge (range: three weeks to six months), all of these studies demonstrated recovery of myocardial function.

1.3.5 Discussion

There are inconsistencies in the reported incidence of myocardial depression and subsequent recovery amongst critically ill patients. This can likely be attributed to the variability in inclusion criteria, definition of impairment and timing of assessments between studies.

For instance, Landesberg[32] and colleagues did not observe any evidence of LV systolic function recovery. In this study, LVEF was assessed at day one and two of AICU admission. On day one, 61 patients demonstrated LV systolic impairment, defined as a LVEF <50%, repeat echocardiography on day two demonstrated no change in systolic function. These results, however, can potentially be explained by the close proximity of follow up assessment to initial imaging (undertaken the next day) and insufficient time to capture recovery. Complete recovery[25,28,30] was observed in other studies in the same population (sepsis) that had a greater duration between initial and follow up assessments.

Clustering assessments to the first few days of AICU admission may result in failure to detect delayed recovery of myocardial function, and therefore lead to under reporting. As the underlying aetiology and pathophysiological mechanisms of RMD remain yet to be fully elucidated, the choice of time frame to capture derangement and recovery is largely empirical.

The study design by Bailen[71] and colleagues may also have led to under reporting of the incidence of myocardial depression (6%) in the general AICU population.

Patients were screened within the first 24 hours of AICU admission and were excluded from follow up if there was no evidence of systolic dysfunction. As demonstrated by Vieillard-Baron[25], there may be latent LV systolic dysfunction evident during the AICU admission, which would not have been identified by Bailen[71], thus potentially underestimating the incidence.

Variability of the reported incidence of myocardial depression could be attributed to the inconsistency in the definition of systolic impairment. Amongst studies, the cut off for LV systolic impairment, assessed by ejection fraction, ranged between 45% – 55%[7,8,25,28–30,32,33,60]. Data were insufficiently reported across studies to allow the calculation of incidence using a common definition of impairment.

Quantitative assessment of study quality was not undertaken as per the recommendations of Cochrane[95]. Instead, study quality was considered from the framework provided by the Critical Appraisal Skills Program cohort study checklist. Overall, study quality was poor. Key issues include using non-standard definitions of septic shock[30], inadequately defined or highly selective inclusion/exclusion criteria[8,28,30,60,70,71], high study drop out rates[27] and a lack of inter/intra observer variability data[8,25,27]. These key issues hamper the generalisability of the finding of these studies.

1.3.6 Limitations of the review

This review only included studies of LV systolic function assessed by echocardiography. Consequently, papers utilising other methods of LV systolic

function assessment were not included, which is a limitation of the review. Papers were limited to publications in English, which may potentially have resulted in relevant papers being omitted.

Nevertheless, whilst there has been some work to establish the incidence of LV myocardial depression and recovery in the critically ill, the lack of consistency in methods has resulted in heterogeneity of the reported incidence and consequently the true incidence remains unclear.

1.3.7 Conclusion

Acute myocardial depression has been demonstrated to be associated with haemodynamic instability in critically ill patients. Whilst attempts have been made to establish the reported incidence in the both the general critically ill, and pathology-specific sub-groups, methodological limitations and inconsistencies have rendered these results to be generalised with caution.

1.3.8 Literature review 2

Question: Can the development of reversible myocardial depression be predicted in adult patients in critical care units?

1.3.8 Introduction

A review of the literature was conducted to assess the quality of the current literature and identify clinical and demographic variables used in the prediction of RMD. This served as a basis for the identification of variables that may facilitate

prediction of the development of RMD in the general adult critically ill population. Inspection of the literature also allowed for conclusions to be drawn on the generalisability and limitations of the existing body of evidence.

1.3.9 Methods

1.3.9.1 Search strategy

Papers were identified using the most useful databases identified from the first literature review. The following databases were searched: EMBASE (1994 – October 2014), PubMed (1994 – October 2014), and Medline (1994 – October 2014). Limits were applied to include only full text articles within the last 20 years, published in English and involving humans aged 16 years and over.

The following search terms were used: ("Reversible myocardial depression" OR "Takotsubo's cardiomyopathy" OR "Apical ballooning syndrome" OR "Transient left ventricular dysfunction" OR "Stress cardiomyopathy" OR "Stress induced cardiomyopathy" OR "Catecholamine cardiomyopathy" OR "Acute heart impairment" OR "Broken heart syndrome" OR "Sepsis cardiomyopathy") AND Predict*. Search terms were tailored to each database "exploded" and wildcard characters used (searching for all suffixes for a given prefix).

Additional papers were identified from hand searches of reference lists of relevant identified papers.

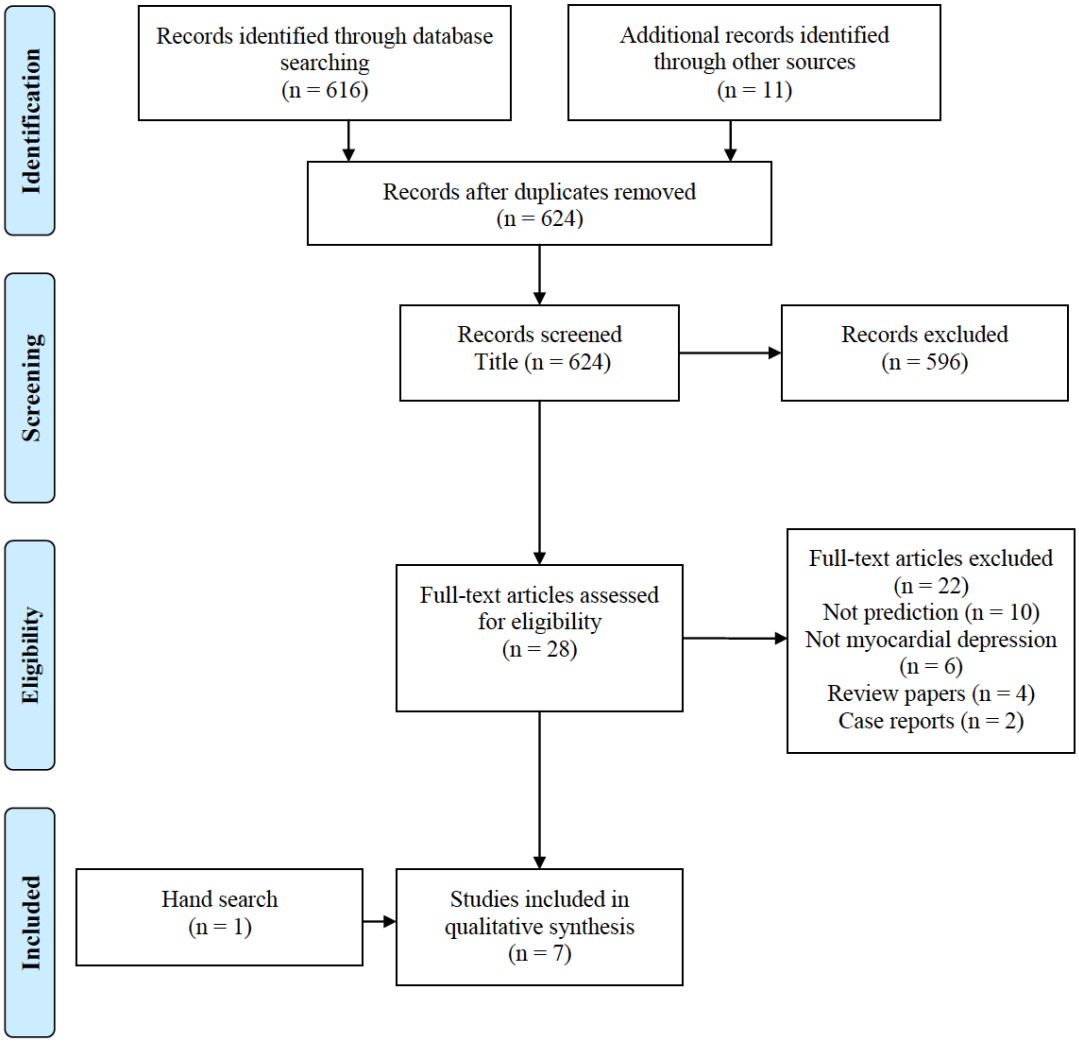
1.3.9.2 Study selection

Only primary research papers that predicted the development of RMD were included in the review. Case reports and case series without any mention of prediction were excluded. Absence of resources precluded the translation of papers not in English. Papers were screened initially by title, then by abstract and finally full text review.

Initial search identified 624 unique papers across the databases. Five hundred and ninety six were excluded by title. The remaining 28 papers underwent full text review, with seven papers [2–4,6,42,60] identified as relevant to the search question.

Close inspection of four papers[3–6] revealed these studies were conducted at the same site by the same research group, over the approximately the same period (differing by a month). Inspection of the data demonstrated the exact same proportion of females, inclusion criteria, and a mean age differing by three years, across all studies. Consequently, these papers were considered as one as they are examining, essentially, the same dataset. The PRISMA diagram is shown in figure 3.

Figure 3: PRISMA flowchart for studies identified in literature review 2



1.3.9.3 Data extraction, synthesis and analysis

Quantitative synthesis of the data was not attempted. Given the heterogeneous nature of the studies and small number of papers identified, a qualitative appraisal was undertaken. The validity, relevance and reliability of papers was assessed using the CASP[91] checklist for clinical prediction rules. The CASP checklist for all papers included in the review is given in Appendix 3.

1.3.10 Results

1.3.10.1 Population

Four unique datasets were identified, with two[2–6] studies examining cardiac sequelae after non-traumatic SAH, one predicting the development of septic cardiomyopathy in the AICU[42] and one predicting the development of apical ballooning in medical AICU patients[60]. All projects were prospective observational single centre studies. An overview of key features of the studies are given in table 4.

Table 4: Key features of the studies identified in literature review 2

				Common dataset			
	Post[42]	Park[60]	Tanabe[2]	Khush[3]	Kothavale[4]	Tung[6]	Miss[5]
Site	General AICU	Medical AICU	Neuro AICU	Neuro AICU			
Size	93	92	103	225	300	223	172
Population	Sepsis	Medical AICU	SAH	SAH			
Male (%)	55%	71%	27%	30%	32%	32%	32%
Age (years, mean, SD)	Median 65 (IQR 53 – 74)	63 (SD: 11)	55 (SD: 10)	55 (SD: 13)			
Excluded patients with pre-existing cardiovascular disease	Yes	Yes	No	Yes			
Univariate analysis	Yes	Yes	Yes	Yes	Yes	Yes	No
Multivariate analysis	No	Yes	No	Yes			
Validated	No	No	No	No	No	No	Yes

Unsurprisingly, a predominately female population was observed in the subarachnoid studies (68%[3–6] and 73%[2]), and predominately male population (55%[42] and 71%[60]) in the AICU studies. This reflects known patterns of subarachnoid haemorrhages occurring more commonly amongst women[96], and the majority of the AICU patients are men[97–99].

In studies of non-traumatic SAH, severity of injury was graded using the Hunt-Hess scale[100]. This assigns a score between 1 - 5 based upon the neurological status of the patient, with higher scores associated with worse outcomes. The mean scores in studies included in the review were 2.4 ± 1.3[3–6] and 2.6 ± 1.1[2]. Physiological derangement in the patients with sepsis[42] was assessed using the APACHE II[101] and Sequential Organ Failure Assessment (SOFA)[102] score. In the study of general medical AICU patients[60], physiological derangement was assessed by the APACHE III score[103].

Three[3–6,42,60] of the four studies excluded patients with pre-existing LV systolic dysfunction or history of acute myocardial infarction (AMI). Cardiac risk factors were recorded and used as input variables in the patients with SAH[2–6] and general medical AICU patients[60]; these were not recorded in the study of patients with sepsis[42].

1.3.10.2 Study objectives, definitions and outcome measures

The primary objective of each study is given in table 5.

Table 5: Primary objectives of predictive modelling identified in the literature review

Paper		Primary objective
Post, 2008[42]		Identify if BNP can be used as a predictor of the development of RMD in sepsis
Park, 2005[60]		Identify variables associated with the development of left ventricular apical ballooning in medical AICU patients
Tanabe, 2008[2]		Identify the level of troponin-I elevation that will predict the development of RWMA following SAH
Common dataset	Kothavale, 2006[4]	Prediction of the development of RWMA after SAH
	Miss, 2004[5]	Effect of clipping vs. coiling in SAH on development of decreased LVEF or RWMA (cardiac dysfunction) or increased troponin-I (cardiac injury)
	Tung, 2004[6]	Determine clinical predictors of cardiac necrosis, measured by troponin-I in SAH
	Khush, 2005[3]	Predict the development of apical sparing RWMA in patients with SAH

The primary endpoint in all studies was the development of cardiac dysfunction, measured either through the development of RWMA or decreased LV systolic function, measured by LVEF. Serial echocardiography was used in all studies to identify these changes.

Definitions of RMD were variable across studies. In the AICU study by Post[42], RMD was defined as the development of a LVEF <50% in patients with sepsis who had a LVEF >50% on admission to AICU, that recovered during the course of the study.

Park[60] defined RMD as severe, symmetrical hypokinesia or akinesia of the LV wall, excluding the base, with a LVEF <50%. Recovery was deemed as normalisation of regional wall motion abnormalities and improvement of LVEF >50%.

Tanabe[2] defined impairment in their study of patients treated for SAH as the presence of RWMA and a LVEF <55%, and tracked these outcomes measures over the course of the study. The remaining studies[3–6] (from the same dataset), defined cardiac dysfunction as the development of RWMA, a LVEF <50% (treated as a dichotomous variable) or both.

1.3.10.3 Input variables

Studies used a combination of demographic, haemodynamic and clinical variables in the development of predictive models. There was a lack of consensus regarding input variables, with no common variable included across all studies. Furthermore, data collection rules and rationale for variable selection were not reported and only one study[2] discussed data completeness and handling of missing values.

The most frequently investigated variables were age, gender and cardiac biomarkers. Table 6 outlines all candidate variables used in model development of each study.

Table 6: Candidate variables identified from the literature

				Common dataset (SAH)			
Variable / Paper	Post[42]	Park[60]	Tanabe[2]	Miss[5]	Tung[6]	Kothavale[4]	Khush[3]
Age	X	-	-	X	X	X	X
Gender	X	-	-	X	X	X	X
BSA	-	-	-	-	X	X	X
APACHE III score at hospital admission	-	X	-	-	-	-	-
Cardiac risk factors	-	-	-	X	X	X	X
Cocaine/ amphetamine use	-	-	-	-	-	X	-
Plasma noradrenaline and adrenaline	-	-	-	-	X	X	-
Inotropes required	-	X	-	-	-	-	-
Phenylephrine dose	-	-	-	X	X	X	X
Creatinine	X	-	-	-	-	-	-
BNP	X	-	-	-	-	-	-
Troponin-I	-	-	X	-	-	X	X
LV mass	-	-	-	-	X	-	X
Ejection fraction	-	-	-	-	-	-	X
Heart rate	-	-	-	X	X	X	X
Systolic blood pressure	-	-	-	X	X	X	X

Variable / Paper	Post[42]	Park[60]	Tanabe[2]	Miss[5]	Tung[6]	Kothavale[4]	Khush[3]
Diastolic blood pressure	-	-	-	X	-	X	X
Hypotension at hospital admission	-	X	-	-	-	-	-
Volume resuscitation	-	X	-	-	-	-	-
Mechanical ventilation	-	-	-	X	-	-	-
Pulmonary oedema	-	-	X	-	-	-	-
Sepsis	-	X	-	-	-	-	-
Hunt-Hess grade	-	-	-	X	X	X	X
Aneurysm location	-	-	-	X	-	X	X
Aneurysm repair type	-	-	-	X	-	-	-
SAH onset to troponin measurement interval	-	-	-	-	X	X	-
Hydrocephalus	-	-	-	-	-	X	-

1.3.10.4 Model construction

Predictive model development methods were haphazardly reported. Authors undertook univariate[2,42] or both univariate and multivariate analysis[3–6,60] using logistic regression.

Model construction methods were not transparent. Khush[3], Kothavale[4] and Park[60] undertook univariate analysis and variables with a p value ≤ 0.10 were then included in multivariate analysis. Tung[6] and Miss[5] also performed univariate analysis but did not specify how variables were then selected for multivariate analysis.

Only two papers reported the method of variable elimination in multivariate analysis, Khush[3] undertook step-wise forward elimination, whereas Park[60] undertook step-wise elimination but did not specify the procedure (e.g. backwards vs forwards). Finally, the study by Miss[5] undertook internal validation on a small sample of the development cohort – 39 patients with clinical data available before aneurysm therapy were compared using Fisher's exact test to examine treatment choice with troponin elevation, development of RWMA and development of LVEF <50% – this supported their findings that treatment choice did not affect cardiac outcomes. No other study attempted validation.

Tanabe[2] and Post[42] undertook a different approach, using a Receiver Operating Characteristic (ROC) curve to identify optimal cut-off values for the use of cardiac biomarkers to predict the development of RWMA and development of septic myocardial depression, respectively.

Post[42] determined the sensitivity, specificity and positive and negative predictive values of BNP concentration at different time points of AICU admission and determined the area under the ROC curve (AUROC). Logistic regression was then undertaken to determine at which time point the B-type natriuretic peptide (BNP)

concentration had the greatest ability to predict the development of septic myocardial depression.

Tanabe[2] sampled troponin-I daily until day five and used the peak value in the analysis. A ROC curve was then constructed to determine the optimal threshold of troponin-I to predict the development of RWMA in patients with SAH. The sensitivity and specificity were then determined.

1.3.11 Findings

1.3.11.1 Prediction of depressed ejection fraction

Two studies attempted to identify risk factors associated with developing a new onset depressed ejection fraction during subarachnoid haemorrhage[5] and also during sepsis[42]. This was attempted using univariate analysis with a cardiac biomarker as the explanatory variable in one study[42] and with multivariate analysis in the other[5].

Post[42] undertook univariate analysis to investigate the role of BNP has a predictor of the development of depressed ejection fraction in sepsis, defined as LVEF <50%. This study concluded that a BNP >154 pg/mL on AICU day five predicted the development of septic myocardial depression, defined as LVEF <50%. The AUROC was 0.96 (95% CI 0.890 – 0.987) and reported sensitivity 94.6% (95% CI 84.9% – 98.9%), sensitivity 100% (95% CI 90.7% – 100%).

Miss[5] undertook a study to identify if the treatment choice (clipping vs. coiling) in subarachnoid haemorrhages affected the development of cardiac dysfunction (LVEF <50%, presence of RWMA, or troponin-I >1.0 μg/L). Two multivariate models were built, one with clipping vs coiling adjusted for aneurysm position, Hunt and Hess grade, age, sex and cardiovascular risk factors, the other adjusted for heart rate, systolic blood pressure, diastolic blood pressure, mechanical ventilation, and phenylephrine dose. Despite this, treatment choice was not found to effect the development of cardiac dysfunction in patients with SAH[5].

1.3.11.2 Prediction of RWMA

Five studies[2–5,60] attempted to predict the development of RWMA using a variety of clinical, haemodynamic and demographic variables. Three of these papers were constructed from the same dataset[3–5].

Kothavale[4] investigated the predictors of RWMA following SAH. He undertook univariate analysis and retained variables for multivariate analysis if the p value was <0.10. Nineteen variables were included on univariate analysis, but only cocaine/amphetamine use, Hunt-Hess grade, heart rate, diastolic blood pressure, troponin-I and phenylephrine dose had a p value <0.10. These variables were then included in multivariate analysis, results are given in table 7.

Table 7: Results of multivariate analysis for prediction of RWMA following SAH

Author: Kothavale	Odds ratio	95% CI	p value
Hunt-Hess grades 3 – 5 (compared with grades 1 – 2)	4.22	1.03 – 17.36	0.046
Cocaine/amphetamine use	5.50	1.10 – 27.38	0.037
Heart rate per 10 bpm increase	1.34	1.04 – 172	0.024
Troponin-I >1.0 µg/L	10.47	2.77 – 39.61	0.001
Diastolic blood pressure per 10mmHg increase	1.30	1.00 – 1.68	0.050
Phenylephrine dose per 50µg/kg/minute increase	1.15	0.98 – 1.35	0.084

Khush[3] attempted to predict the pattern of RWMA following SAH. He undertook univariate analysis, and included variables in multivariate analysis if $p < 0.10$. Therefore, age, gender, ejection fraction, heart rate, Hunt-Hess grade and aneurysm position were included in multivariate analysis. Multivariate analysis determined that age, anterior aneurysm position and ejection fraction were associated with the development of the apical sparing pattern of RWMA following SAH, these results are given in table 8.

Table 8: Prediction of apical sparing RWMA pattern following SAH

Author: Khush	Odds ratio	95% CI	p value
Age per 10 year increase	0.31	0.13 – 0.75	0.009
Anterior aneurysm location vs posterior	9.71	1.52 – 62.2	0.016
Ejection fraction per 10% increase	2.06	1.05 – 4.07	0.036
Female vs male	4.2	0.47 – 37.8	0.200
Hunt-Hess grade 3 – 5 (compared with grades 1 – 2)	0.81	0.13 – 4.92	0.820

Also from the same dataset, Miss[5] determined that the choice of aneurysm treatment (clipping vs. coiling) did not effect the development of RWMA, even after adjustment for a variety of clinical, demographic and haemodynamic factors.

Tanabe[2] undertook univariate analysis to identify if troponin-I was a predictor of RWMA in patients with SAH using the process described in section 1.3.10.4. He identified that a troponin-I >1.31ng/mL had a sensitivity 76% and specificity 91% and an AUROC of 0.89. Confidence intervals for these values were not reported.

Finally, Park[60] undertook univariate and multivariate analysis to identify risk factors associated with the development of LV apical ballooning and depressed ejection fraction in medical AICU patients. Variables trialled by univariate analysis were included in multivariate analysis if $p < 0.10$. Consequently, sepsis, hypotension at hospital admission, the need for volume resuscitation, use of inotropes and APACHE II score on hospital admission were included in multivariate analysis. The results of this analysis are given in table 9.

Table 9: Multivariate analysis for prediction of LV apical ballooning

Author: Park	Odds ratio	95% CI	p value
Sepsis	9.2	2.36 – 35.79	< 0.001
Hypotension at hospital admission	1.54	0.33 – 7.16	0.585
Volume resuscitation	1.73	0.43 – 6.96	0.438
Use of inotropes	0.72	0.14 – 3.85	0.704
APACHE II score at hospital admission	1.01	0.99 – 1.02	0.507

1.3.11.3 Prediction of troponin-I release

Two studies[5,6] explored prediction of troponin-I release as a marker of myocardial damage in patients with SAH.

Tung[6] used troponin-I >1μg/mL as a binary outcome, indicating cardiac damage following SAH. Univariate and multivariate analysis was undertaken. Curiously, all variables included in univariate analysis were included in multivariate analysis, regardless of p value. The results of multivariate analysis is given in table 10. Interestingly, serum adrenaline and noradrenaline were not useful predictors, however these data were only available on a sub-group of patients (n = 50) and the handling conditions were not discussed, which may have influenced results as these samples are notoriously labile[104].

Table 10: Prediction of troponin-I release following SAH

Author: Tung	Odds ratio	95% CI	p value
Age per 10 year increase	1.54	0.90 – 2.62	0.112
Female vs male	34.96	2.47 – 495.01	0.009
Body surface area per 0.2 m^2 increase	2.20	1.11 – 4.39	0.025
Hunt-Hess grade > 2 compared with grade 1 – 2	6.62	1.25 – 34.82	0.026
Systolic blood pressure per 20mmHg increase	0.52	0.32 – 0.83	0.007
Heart rate per 10 bpm increase	1.61	1.16 – 2.25	0.005
Phenylephrine dose per 50μg/kg/minute increase	1.47	1.10 – 1.98	0.010
LV mass index per 20g/m^2 increase	1.74	1.05 – 2.89	0.032
Time from SAH to measurement of troponin-I per 1 day increase	0.70	0.54 – 0.91	0.008

Author: Tung	Odds ratio	95% CI	p value
Serum noradrenaline	1.00	NR	0.653
Serum adrenaline	0.99	NR	0.505

These results indicate that female gender, lower LVEF, increased body surface area (BSA), lower systolic blood pressure (SBP), higher heart rate and phenylephrine dose, Hunt-Hess grade, and time from SAH to be independent predictors of a troponin-I increase >1.0 μg/L following SAH.

Finally, the study by Miss[5] (using essentially the same dataset) identified that treatment choice (clipping vs. coiling) did not predict the development of a troponin-I release >1.0 μg/L.

1.3.12 Discussion

Currently, there are a small number of studies that attempt to predict the development of RMD in the acute care setting, and these are dominated by studies on patients treated for SAH. In the studies undertaken in general AICUs the sample population is selected, and the generalisability of the results remain unknown. It is evident that there is a lack of consensus regarding which clinical, haemodynamic, and demographic variables are the most useful in prediction.

Data collection rules, justification of input variables, model construction and variable elimination were inadequately reported[105]. These studies lack robust and transparent reporting of model development, which hampers reproducibility and therefore validation of these findings.

Whilst some studies[2,4] reported troponin-I as a useful predictor of cardiac outcomes, this result should be interpreted with caution as only one of these studies excluded patients with chronic renal insufficiency. In patients with chronic renal insufficiency, troponin can be chronically elevated in the absence of myocardial injury[106]. Consequently, it has been recommended that serial troponin measurements are taken in patients with chronic renal insufficiency, and a change in troponin concentration observed over 3-6 hours[106] be used to indicate myocardial injury. This approach was not followed in the study that included patients with chronic renal insufficiency, so the utility of troponin-I as a useful predictor of cardiac outcomes in patients with SAH is questionable.

There are number of conditions common to AICU that compromise the use of biomarkers, particularly troponin and BNP, as a predictive tool in the general AICU population[44,90]. Furthermore, there is a lack on consensus of the role of troponin-I, as this was used in some studies as an explanatory variable[2–4] and in others as an outcome measure[5,6].

1.3.13 Limitations

This review has its limitations. It is based on a small number of papers, and even smaller number of datasets, but this reflects the lack of evidence in the prediction of RMD. Study heterogeneity precluded quantitative analysis, but given the small number of studies, this would likely not be generalisable.

1.3.14 Conclusion

Currently there is a lack of robust, validated and generalisable data that predicts the development of RMD in critically ill patients. The studies presented here have not been externally validated and have been developed to identify cardiac dysfunction in subpopulations of critical illness. There is no evidence to suggest that these predictors are generalisable outside their intended subpopulation.

1.4 Formulation of research questions

It was evident from the literature that the incidence, natural history and predictors of RMD are not well understood in the critically ill population. Given the potential sequelae of RMD identified in other studies, questions were developed to fill the gaps in the existing literature regarding RMD and critical illness.

Four key questions were developed:

- What is the incidence of LV systolic RMD occurring in the general AICU?
- What is the natural history of LV systolic RMD occurring in the general AICU?
- Can we predict the development of LV systolic myocardial depression using routinely collected variables within the first 24 hours of AICU admission?
- Can we predict the recovery of LV systolic myocardial depression?

These questions were used as a framework to investigate the assessment of LV systolic function and design studies tailored to answer these questions. Consequently, the assessment of LV function, including imaging modalities and

measures of systolic function will be considered and an overview of the role and utility of predictive modelling will be discussed. These are considered in sections 1.5 and 1.8, respectively.

Right ventricular (RV) function was not assessed as the body of evidence of myocardial depression, from which the research questions were formulated, pertain to LV function. Furthermore, the architecture of the RV prohibits comprehensive assessment of structure and function by the imaging modality selected for these studies.

Study design focussed on assessment and changes in systolic function. Diastolic function was not assessed. At the time of study design (2012), there was no consensus on which variables are useful in the assessment of diastolic function. Additionally, diastolic function decreases with age[107], thus making interpretation of diastolic dysfunction difficult, as changes may be related to ageing or underlying pathology. Consequently, the research questions and study design are focused on LV systolic function.

1.5 Assessment of left ventricular function

Numerous modalities are available for assessment of LV systolic function. Selection of the most appropriate tool is dependent upon the patient, indication, urgency, safety, co-morbidities and portability. Tools were considered based upon the following factors: appropriate for research purposes in critically ill patients, routinely used in clinical practice and appropriate for serial studies.

Assessment of cardiac function in critically ill patients can present challenges often not present in other populations[108]. Drains, bandages, rib fractures, mechanical ventilation and injuries preventing optimal positioning can all impede or interfere with assessment[108]. Careful consideration of patient stability, co-operation and co-morbidities was essential in the selection of an assessment tool.

Computed tomography or radionuclide ventriculography were not considered appropriate given the exposure to ionising radiation and the absence of direct patient benefit to counter the risk associated with moving critically ill patients. Cardiac magnetic resonance imaging (CMRI) is considered the gold standard for quantification of LV structure and function[109,110], but given the high proportion of patients likely to be unable to consent for themselves in the acute stages of critical illness, and provide a history to facilitate CMRI safety screening, and no direct participant benefit, it was felt this was an unacceptable risk to patient safety and would introduce significant selection bias. Invasive methods of indirectly assessing LV function, such as pulmonary artery catheters and oesophageal Doppler were not considered appropriate as they are not routinely used in all patients at the recruitment site and non-invasive alternatives were available.

Cardiac biomarkers, such has troponin-I and B-type natriuretic peptide (BNP), have been trialled as indicators of RMD[28,40–43,46]. McLean[90] summarises in an excellent review paper the problems with cardiac biomarkers in the AICU setting, noting specificity and linearity between serum concentration and disease severity are often lacking. McLean[90] emphasises that whilst BNP and troponin-I can be elevated in

septic myocardial depression, their lack of specificity renders them unsuitable as a diagnostic tool in isolation. As neither of these markers are part of daily "routine" bloods at the recruitment site and their specificity is low, they were not included as part of LV function assessment.

Echocardiography can assess LV function without exposure to ionising radiation, contrast media or strong magnetic field. Traditionally, transoesophageal echocardiography (TOE) was considered superior to transthoracic (TTE) studies in critically ill patients due to unobstructed imaging windows. Improvements in echocardiography have increased image feasibility[111,112] and TTE is usually able to provide information for the assessment of LV function[112,113].

Whilst TOE can mitigate some of the challenges presented in assessing ventricular function, there are risks posed by performing TOE in critically ill patients. Although uncommon, they are not inconsequential, and include haemorrhage[114,115], visceral perforation[114], inadvertent extubation[116] and arrhythmias[117–119]. The lack of large studies characterising its safety in this population have led some to argue that TTE should be the first-line option in this population[108,112].

The advent of three-dimensional (3D) echocardiography allows measurement of cardiac volumes and mass that are independent of geometrical assumptions[94]. Improved accuracy, through measurement of true volumes rather than extrapolated values, has obvious advantages. The major limitations are that it requires the patient to be in sinus rhythm and 3D reconstruction of two dimensional (2D) images require excellent imaging windows[94]. These limitations preclude routine adoption

of 3D echocardiography in critically ill patients. Motion mode (M-mode) was considered, but ultimately discounted as the M-mode measurements rarely represent the true LV minor dimensions[120], something that is overcome by 2D echocardiography.

Given the portability, non-invasiveness, repeatability and lower risks associated with the examination, 2D TTE was considered the most appropriate method for the assessment of LV systolic function in the study population. The principles of echocardiography and selection of LV systolic function assessment methods are discussed further in the following section.

1.6 Echocardiography

1.6.1 Principles of ultrasound

Audible sound is produced when a mechanical vibration propagates through air at a suitable frequency. Ultrasound is above the audible range of human hearing with a frequency of 20,000 kHz or more, can be focussed, and obeys the laws of reflection and refraction. A focussed beam of ultrasound will reflect and refract off objects as the beam travels through the medium. The properties of the medium dictate the degree of attenuation, reflection, refraction and velocity of the sound wave.

The wavelength of the ultrasound will determine the resolution and penetration – a shorter wavelength will result in greater resolution, but will result in a reduction in depth of penetration. Whereas, a higher frequency ultrasound permits greater

resolution, at the trade off of decreased penetration. The standard ultrasound frequency used in cardiac transthoracic echocardiography is between 2– 3MHz[121].

1.6.2 Sound to image

The ultrasound transducer acts as both a transmitter and receiver of ultrasound signals. Piezoelectric crystals within the transducer change shape in response to an applied electrical voltage. An alternating voltage causes the crystals to oscillate rapidly, producing an ultrasound signal. Similarly, when ultrasound waves are reflected back to the transducer this will cause the piezoelectric crystals to oscillate and generate voltage that is registered by the transducer as a signal.

The transducer transmits ultrasound for a few microseconds, then "listens" for reflected ultrasound for a few hundred microseconds, before repeating. Some ultrasound energy will be reflected back towards the transducer as the signal crosses an interface. The time taken for the ultrasound to be "sent" and "received" is used to calculate the distance between the reflecting structure and transducer, using known propagation velocities of ultrasound in soft tissues. The intensity of the reflection of the signal is also registered. The depth and intensity of the signals recorded by the transducer are then used to compile a greyscale image. The beam is steered and the width, gain and depth of the imaging are manipulated to enhance the lateral, temporal and contrast resolution.

Acoustic impedance mismatch between structures can result in a large amount of ultrasound energy returned to the transducer, which diminishes penetration. The biggest impedance mismatch is usually between the transducer and the patient's skin. This can be mitigated by the application of gel between the transducer and the chest wall. There are instances where significant impedance mismatch is unavoidable[107], such as artificial ventilation and lung consolidation.

Doppler echocardiography can be utilised to determine the velocity and direction of blood or tissues. The Doppler shift is the difference between the originating and received ultrasound frequency[122]. Blood flow or tissue movement towards the transducer increases the frequency of the reflected ultrasound, movement away from the transducer has the opposite effect. The velocity of the blood or tissue is determined from the Doppler shift and the angle of incidence between the ultrasound beam and the area of interest. Measurement error can occur when the transducer is not parallel to the area of interest.

There are three types of Doppler echocardiography used in clinical practice: continuous wave, pulsed wave and colour Doppler. Continuous wave Doppler continuously emits and receives ultrasound, it measures velocities of all reflected waves across the length of a cursor placed in the area of interest[122]. In comparison, pulsed wave Doppler emits an ultrasound pulse and then measures the Doppler shift at fixed intervals. The signal transmission/reception rate is determined by the depth of the area of interest, and determines the maximum velocity that can be determined unambiguously[123]. The maximum frequency shift that can accurately be determined

is one half of the sampling rate (the Nyquist limit[124]). Consequently, pulsed wave Doppler is more suited to targets moving at low velocities. Finally, colour mapping (Doppler) utilises aspects of pulsed wave Doppler to determine velocities of blood flow in the area of interest; flow towards the transducer is depicted red/orange and flow away is depicted as blue. Higher velocities are shaded lighter. Colour Doppler is typically used to characterise jets of blood cause by heart valve pathology.

1.7 Echocardiographic assessment of left ventricular systolic function

Echocardiography is a valuable tool to assess LV systolic function. Echocardiographic measures of LV systolic function were reviewed to identify the most appropriate primary outcome measure of systolic function. An overview of the measures of LV systolic function is given in table 11.

Table 11: Overview of measures of LV systolic function

Measure	Overview	Considerations
Ejection fraction	Calculated either using linear or volumetric measurements. Routinely used in clinical practice. Large body of evidence linking it to outcomes.	Geometrical assumptions can hamper validity of measurements. Load dependent.
Fractional shortening	Reduction in chamber linear cross sectional measurements at end systole compared with end diastole, expressed as a percentage	Angulation of beam, and RWMA can influence validity.

Fractional area change	Change in LV cross sectional area between systole and diastole, expressed as a percentage	If RWMA present at the level of cross-sectional measurement, true LV systolic function may be underestimated.
Regional Wall Motion Scoring Index	Segments are graded as normal = 0, hypokinetic = 1, akinetic = 2, dyskinetic = 3	Semi qualitative. Requires visualisation of all LV segments.
Velocity time interval (VTI) of LVOT (cardiac output)	Calculate the cross sectional area (CSA) of LVOT and mean velocity of flow through the LVOT can be used to calculate stroke volume and subsequently cardiac output.	Requires tracing of the LVOT and consistent placement of the marker in the LVOT across serial studies.
Tissue Doppler imaging (TDI) Mitral annulus	Longitudinal function assessed by Doppler through the mitral annulus	Difficulty with myocardial tethering and translational motion.
Myocardial Performance Index	Global measure of function. Uses systolic and diastolic measurements.	Calculated from three Doppler measurements - ejection time (ET), isovolumic contraction time (IVCT) and the isovolumic relaxation time (IVRT).
Speckle tracking	Systolic shortening, rotation and stress/strain in longitudinal and circumferential directions	Lack of consensus of methods and parameters. Difficult image acquisition
dP/dt	Rate of LV pressure rise – during isovolumic contraction this is a measure of ventricular contractility.	The velocity of mitral regurgitation is essential for this calculation.

Strain/Strain rate	Myocardial deformation and velocities produced from TDI	Not reproducible enough for routine clinical practice

1.7.1 Selection of primary outcome measure

The selection of the LV systolic outcome measure was considered against the following factors: reproducibility, clinical acceptance and utilisation, and challenges presented by critically ill patients.

Strain rate[124] and speckle tracking[125] were discounted over concerns of reproducibility across serial studies. dP/dT was also excluded as it requires the presence of mitral regurgitation; continuous wave Doppler is used to determine the velocity of a mitral regurgitant jet and the time interval (dT) measured in milliseconds, between the jet velocity reaching 1m/s and 3m/s is calculated. The time between reaching 1 m/s and 3 m/s represents the time taken for a pressure change of 32 mmHg to occur in the LV, this is derived from the simplified Bernoulli equation[124]. Therefore, the dP/dT is 32 divided by the time taken for the change in pressure to occur (dT). Myocardial performance index was discounted as it has been demonstrated that is unable to consistently detect acute changes in contractility[126].

The remaining measures were reviewed for feasibility in the critically ill population. In the interest of feasibility and reproducibility, measures that relied

upon one imaging window were considered preferable. Consequently, RWMSI and VTI of the LVOT were considered unsuitable measures.

Fractional shortening, fractional area change, TDI of the mitral annulus and ejection fraction were evaluated further. Evaluation of systolic function using TDI of the mitral annulus is problematic; studies[127,128] have demonstrated age related changes amongst healthy volunteers, which are yet to be incorporated into reference values, furthermore it has been demonstrated that the mitral annular velocities are representative of longitudinal LV function and are not correlated with global LV systolic performance[127].

Fractional shortening expresses the change in LV internal dimensions in diastole and systole, given as a percentage. Similarly, fractional area change expresses the cross sectional area change of the LV in systole and diastole, expressed as a percentage. Fractional shortening and fractional area change have a similar profile of limitations as other linear measures and are not routinely utilised or reported in clinical practice.

Ultimately, ejection fraction was selected as the most accepted and reproducible measure of LV systolic function. Whilst ejection fraction can be influenced by preload and afterload, it has been argued[122] that from a clinical perspective it is more important to assess how the heart functions with the given loading conditions. Furthermore, ejection fraction has been demonstrated to be a strong predictor of clinical outcomes[129,130]. The measurement of ejection fraction is considered further in the following section.

1.7.2 Measurement of ejection fraction

1.7.2.1 Principles

An ejection fraction is a volumetric fraction of the blood pumped out of the ventricle with each cardiac cycle, expressed as a percentage. The formula for ejection fraction is: $\frac{End\ Diastolic\ Volume - End\ Systolic\ Volume}{End\ Diastolic\ Volume}$ x 100

Ejection fraction can be quantified using either linear or volumetric methods. Volumetric assessments calculate the cross sectional area of the LV in end systole and end diastole to derive volumes, which are then used to quantify an ejection fraction. Linear methods utilise LV internal dimensions on a single plane in end systole and end diastole to estimate volumes, which are, in turn, used to calculate an ejection fraction. Both methods rely upon geometrical assumptions about the LV. In general, the LV is treated as a cone which contracts equally towards the central axis. These assumptions can influence the validity of derived values. Generally, volumetric measures, such as Simpson's biplane method, are considered preferable, as there are fewer geometrical assumptions.

In certain circumstances, such as a previous myocardial infarction, the ventricle does not thicken and contract uniformly during systole, this is termed a regional wall motion abnormality (RWMA). In the presence of significant RWMA or geometrical abnormalities, linear or volumetric measurements may not be congruent with the clinical picture. Thus during all echocardiograms, care must be taken to identify implausible or incongruent measurements. A recommendation by

Lang[94] and colleagues suggested cross referencing quantitative values with an visual estimate of LV function can avoid overreliance on derived mathematical assumptions.

Some studies have found that visual estimation of ejection fraction has correlated well with formalised, quantitative methods for the assessment of ejection fraction[131,132]. This is supported by a review by McGowan[133], which suggested that subjective visual assessments are more likely to be accurate than the volumetric methods in patients with poor echocardiographic windows or in the presence of RWMA. McGowan[133] argues that subjective visual assessment by an experienced observer may be just as, if not more, reliable than measurements that rely on geometric assumptions during technically difficult examinations or in patients with known geometric abnormalities.

1.7.2.2 Selection of method

Determining the most appropriate method to calculate ejection fraction must consider the population, reproducibility, and the skills of the observer. Using 2D TTE for the calculation of ejection fraction, investigators have a choice of visual estimation, or linear or volumetric measurements. Whilst volumetric measurements, such as Simpson's biplane, are often considered superior to linear measurements[94], the difficulties in reliably obtaining good endocardial border delineation, especially in artificially ventilated patients, precluded adoption of this method. There was concern that selection bias would be introduced if only patients with adequate endocardial border delineation were included. Administration of a contrast agent to

enhance endocardial definition was considered but given the cost and number of echocardiograms to be undertaken for, this was unfeasible.

Whilst linear measurements have limitations in the presence of significant RWMA, they have excellent intra- and inter-observer reproducibility[94,134–136]. Visual estimation of LV systolic function was not considered, owing to limited the experience of observers at the commencement of the study.

Given the reproducibility and advantage of obtaining measurements from a single echocardiographic window, 2D linear measurements were used for the calculation of ejection fraction. Wall motion was reviewed in all imaging windows to assess for the presence of RWMA. All participants with a history of acute myocardial infarction (AMI), cardiac arrest or cardiac surgery were flagged as potentially demonstrating RWMA, and these echocardiograms were reviewed by an echocardiography fellow (discussed further in methods section 2.5.6). If RWMA were present, ejection fraction was visually estimated by the BSE fellow. This is discussed further in the methods chapter.

1.8 Predictive modelling

Predictive modelling is increasingly utilised to provide clinicians with the information (probability) that a condition is present (diagnostic modelling) or that it will occur in the future (prognostic modelling)[105]. In recent years, there has been a tremendous increase[137] in the number of predictive models published in the medical

literature. When done well, predictive models can assist clinical decision making and prognostication of individual patient outcomes[138].

There are a number of statistical techniques that can be used to predict a binary outcome, such as logistic regression, classification and regression trees and neural networks[137]. These approaches were considered as to which would best address the research questions. Modelling using classification and regression trees was excluded, as the process of "partitioning" of patients into subgroups would be inappropriate given the size of the dataset. Similarly, neural networks were also discounted due to substantial risk of overtraining the model given the size of the dataset.

Logistic regression is the most widely used statistical technique for the prediction of binary outcomes in medicine[137], and can potentially avoid some of the pitfalls presented by neural networks and classification and regression trees. Consequently, logistic regression was selected to answer the outstanding research questions: can we predict the development of LV systolic myocardial depression using routinely collected variables within the first 24 hours of AICU admission? And, can we predict the recovery of LV systolic myocardial depression?

To date, there is no consensus on the best method to construct a predictive model and, in clinical practice, simple models are preferable[139]. Candidate explanatory variables need to be carefully selected, with consideration of the impact of missing, or under represented, values. It has been suggested[139] that researchers look to the literature to identify candidate explanatory variables from other studies when

rationalising input variables. As demonstrated by the literature review, there is a lack of agreement of which explanatory candidate variables are useful for the prediction of reversible myocardial depression.

The "events per variable" rule proposed by statisticians[137], state that one explanatory variable can be included in the model per every ten patients with the outcome (event). Inclusion of a greater number of explanatory variables increases the risk of overfitting the model, which is where idiosyncrasies of the development dataset are modelled rather than generalisable patterns. Consequently, the incidence of myocardial depression will dictate the number of explanatory variables that can be reliably included in the model.

Once a model has been constructed its needs to be assessed. Typically, goodness-of-fit (how well the model fits the data), model calibration (agreement between observed outcomes and predictions) and discrimination (identification of outcome vs. no outcome) are measured. Finally, models need to be validated to ensure reproducibility and generalisability. Ideally, models are validated using an external (independent) dataset (external validation) but there are a number of statistical techniques available to validate a model from the development dataset (internal validation)[137].

Despite a large increase in the number of predictive models in the medical literature, few of these models have translated into clinical practice; this likely stems from inadequate reporting of model development, lack of validation, or poor generalisability. These issues were identified in the literature review (section 1.3.8)

in which no investigator adequately reported the method of model development and only one model[5] underwent any validation procedure. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis[105] (TRIPOD) statement was released in 2015 to provide guidelines in the development, validation, reporting and appraisal of predictive models. Where possible, these guidelines were adhered to in the models developed to answer the research questions outlined in section 1.4.

1.9 Summary

Reversible myocardial depression has been associated with the development of complications such as thrombus, arrhythmia and LVOT obstruction. Traditionally, RMD has been described within the context of concomitant disease process, but there is growing evidence to support the notion that this condition is a continuum, rather than separate pathological conditions. RMD has been observed in patients with critical illness, likely stemming from severe physiological stress. Little is known about the sequelae, natural history, incidence, and factors that influence its development. Consequently, studies were designed to address research questions derived from these gaps in the literature. The methods of these studies are described in the following chapter.

Chapter II: Methods

2.0 Overview

The project was comprised of three studies, with an umbrella title of the "Evaluation of Left ventricular Function" (ELF). Broadly, the objectives were to establish the incidence and time course of RMD, and to develop a predictive tool to assess the risk of subsequent myocardial depression and reversibility. The primary objective and overview of methods for each study is given in table 12 and the protocols for these studies are given in Appendix 4.

Table 12: Overview of primary objectives of the ELF studies

Study	Primary objective	Overview of methods
ELF 1	Determine the incidence and time course of reversible myocardial depression in patients with critical illness	Prospective, observational study utilising serial TTE during AICU admission and at three months following AICU discharge
ELF 2	Determine the incidence and time course of reversible myocardial depression in patients with critical illness	Analysis of an existing dataset of echocardiographs and clinical data, of patients who have had >2 echocardiographic studies whilst in AICU
ELF 3	Characterise the natural history of reversible myocardial depression using echocardiography	Prospective, observational study utilising serial (daily) echocardiography during AICU admission.

2.1 Project set up

2.1.1 The site

The John Radcliffe Hospital, part of the Oxford University Hospitals NHS Trust, is a tertiary referral centre located in Oxfordshire, which served as the recruitment site for all ELF studies. The AICU at the John Radcliffe Hospital is a 16-bed mixed intensive care and high dependency unit. This is a general AICU that admits approximately 880 medical and surgical patients annually. Additionally, there are two other critical care units located onsite, a neurosciences and a cardiac/thoracic critical care unit, these, however, were not recruitment units as they are not general AICUs.

There are two other smaller general critical care units that are part of the Oxford University Hospitals Trust, the Horton General Hospital Critical Care Unit and the Churchill Hospital Intensive Care Unit. These units were not feasible as recruitment sites due to the practical limitations of a single-operator study. It was considered preferable to concentrate recruitment efforts from the largest general AICU in the Trust, and minimise the number of missed eligible patients from this site.

2.1.2 Approvals

For all studies, ethics approval was sought from the Health Research Authority (National Research Ethics Service) and the Oxford University Hospitals NHS Trust granted Research and Development approval. The University of Oxford was the sponsor for all studies.

In the ELF 2 study, as patient records were to be accessed without consent, information governance approval was sought from the NHS Health Research Authority Confidentiality Advisory Group (HRA-CAG) under section 251 of the National Health Service Act 2006[140]. Given the retrospective nature of the study, the high mortality associated with critical illness and the large volume of records that needed to be accessed, it was unfeasible to ask surviving patients for informed consent. Furthermore, only enrolling patients that could give informed consent would introduce a significant recruitment bias. The study was reviewed and endorsed by the local Caldicott Guardian. All study protocols were peer reviewed by an independent consultant in Intensive Care Medicine from a different NHS Trust.

Correspondence from ethics committees, the Research and Development office, the University of Oxford, Confidentiality Advisory Group (ELF 2), Caldicott Guardian (ELF 2) and peer review documentation are given in Appendix 5.

2.2 Participant identification, enrolment, withdrawal and retention

ELF 1 and ELF 3 were prospective observational studies recruiting from AICU at the John Radcliffe Hospital. To minimise duplication, in the following section these studies are presented together where possible.

2.2.1 Inclusion and exclusion criteria

2.2.1.1 ELF 1 and ELF 3

Inclusion criteria were kept broad to generate a generalisable sample of critically ill patients. Inclusion criteria were all patients aged 16 years or over, admitted to AICU as an emergency with medical staff committed to continuing treatment. Exclusion criteria for the ELF 1 and ELF 3 studies are given in table 13.

Table 13: Exclusion criteria for ELF 1 and ELF 3

Exclusion	Justification for exclusion
Patients aged <16 years	Paediatric physiology is not interchangeable with adults.
Elective admissions, usually after surgery	Generally, these patients are medically optimised pre-intervention, thus represent a different patient group compared with acute, emergency admissions.
Patients/ consultee with limitations in the use of English	Absence of resources to adapt patient information to other formats.
Conditions rendering TTE contraindicated, impossible or unreliable	Patient contraindication or the inability to obtain reliable data.
Actual AICU length of stay <72 hours	Brief length of stay hampers serial studies and be inadequate duration to observe myocardial depression and reversibility.
Limitations in treatment	Limitations in obtaining serial studies.

Exclusion	Justification for exclusion
Cardiac arrest whilst in hospital, prior to AICU admission or during AICU	Myocardial stunning following cardiac arrest is a different clinical entity.
Prisoners	Difficulties in obtaining follow up data.

2.2.1.2 ELF 2

Inclusion criteria were all patients admitted to the AICU at the John Radcliffe Hospital between 1/1/2008 – 1/06/2013 inclusive who had a minimum of three echocardiograms at least six hours apart, from which ejection fraction could be determined. At least two of studies needed to occur during the AICU admission, the remaining studies could occur up to six months following AICU discharge. Patients under 16 years of age were excluded.

This study period was selected as it coincides with the implementation of CareVue (Philips Healthcare) in the AICU. This is a patient clinical information system that contains data required to characterise the ELF 2 population.

2.2.2 Identification of study population

2.2.2.1 ELF 1 and ELF 3

Potential participants were identified through review of electronic admission records on Carevue. Carevue is an integrated clinical information system that

aggregates patient demographic, physiological, laboratory and clinical data. All patients admitted to AICU have their data entered into Carevue.

Admission type (elective or emergency), age and date and time of admission to AICU were used as preliminary screening tools. Following identification of a potential participant, clinical staff were approached to discuss the remaining inclusion/exclusion criteria. Screening logs were kept for both studies, and ineligible patients were coded based on exclusion criteria or refusal by patient or consultee. Examples of the screening logs can be found in Appendix 6.

Written, informed consent was obtained prior to enrolment in all participants. Only designated research staff, who have undertaken Good Clinical Practice training and were familiar with the study protocol were authorised to consent patients and consultees. No member of the research team responsible for consenting patients was involved in the clinical care of the patient.

If a patient was unable to give informed consent, then the patient consultee was identified and opinion sought. The appropriate person to provide consultee opinion was identified by discussion with the clinical staff. Consultees were only approached when present on the AICU.

Patients and consultees were given as long as they felt necessary to consider participation in the study, and it was emphasised that they could withdraw from the study at any time without giving a reason.

In the event of a patient being incapacitated and there was not an identifiable consultee, an NHS trust approved professional consultee was appointed to consider providing opinion. In practice, this was the treating AICU consultant. If an appropriate consultee was subsequently identified, opinion was sought regarding ongoing participation in the study.

If a participant regained capacity, consent was sought for continuing involvement in the study and use of previously collected data. If a participant declined ongoing participation in the study, consent was sought to use existing data. If this was declined, the study records for the patient were destroyed.

Patient and consultee information leaflets and examples of consent and favourable opinion documentation are given in Appendix 7.

2.2.2.2 Identification of the ELF 2 population

2.2.2.2.1 Overview of process

This analysis utilised existing data to identify patients that had a minimum of two echocardiograms undertaken whilst admitted to AICU. Two databases were used for the identification of participants, the local Intensive Care National Audit and Research Centre (ICNARC) submissions database (4D MedICUs, Mela Solutions) and the echocardiography database (Xcelera, Philips Healthcare).

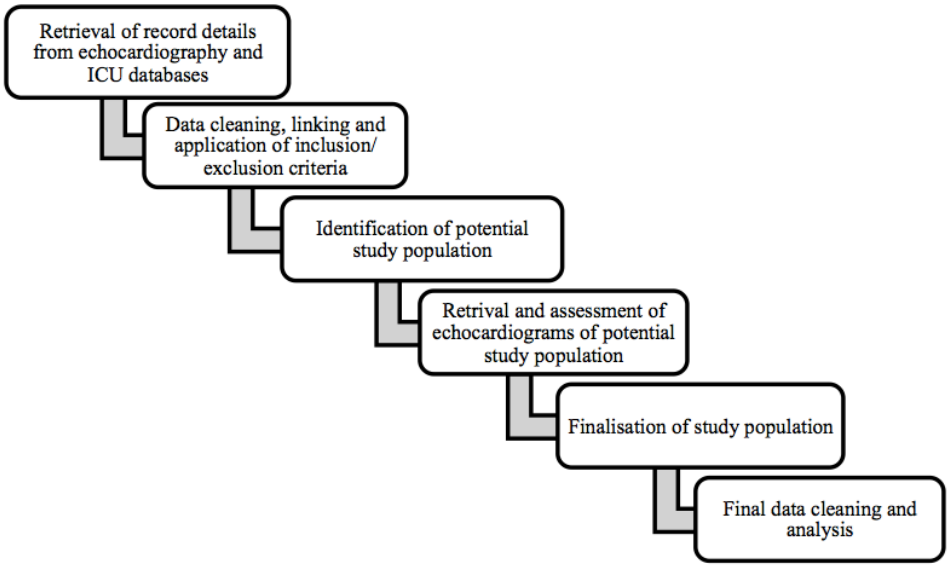
The ICNARC database contains data of all AICU admissions at the recruitment site. Data were available for the entire study period. This database was queried to identify all patients who had been admitted to AICU during the inclusion period.

This served as a reference to identify patients who had been admitted to AICU during the recruitment window.

The Xcelera database contains all the images and patient details of all echocardiograms conducted across the Trust. This includes training studies and echocardiograms conducted for research.

Queries were designed to retrieve all records within the specified time period. Filters were then applied to remove spurious or duplicate records. Echocardiography records and AICU admission data were then linked using patient identifiers (name, date of birth, hospital record number). Inclusion and exclusion criteria were applied and a provisional study population identified. Echocardiographs of the provisional study population were reviewed and unreadable studies excluded. Inclusion/exclusion criteria were rechecked, which subsequently allowed for identification of the final study population. An overview of the process is given in figure 4.

Figure 4: Overview of ELF 2 population identification



2.2.2.2.2 Xcelera

First, the Xcelera database was queried. This database is constructed in the Structured Query Language (SQL) format. The database structure was identified from the user manual[141], which facilitated construction of the appropriate query to identify all echocardiography records. Consequently, the following SQL query was generated on the Phillips Xcelera Data Analyzer (release 1.3, 2010, Philips Medical Systems, The Netherlands).

SELECT TOP 150000

Patient_Report_FileX123_Rpt.MedicalRecordNumber, Patient_Report_FileX123_Rpt.FirstName, Patient_Report_FileX123_Rpt.LastName, Patient_Report_FileX123_Rpt.StudyStartDateTime

FROM Patient_Report_FileX123_Rpt

ORDER by STUDYSTARTDATETIME DESC

Fewer than 150,000 records were identified, thus this ensured that all eligible records were captured by the query.

The data were then arranged by date of echocardiogram. Echocardiograms occurring outside of the study period were then removed.

Identifiers are required in order to facilitate data linkage. Hospital record number was the primary identifier, with patient name used a secondary identifier. Consequently, records without either a primary or secondary identifiers were removed.

Finally, hospital number, patient name, and date and time of echocardiogram were extracted as Excel spreadsheets, with each calendar year of data stored in a separate spreadsheet. At this stage, echocardiogram images were not assessed.

The data required cleaning before it could be matched against the ICNARC database. Therefore, the following steps were undertaken:

- Data were loaded into the statistical software Stata (version 10, StataCorp 2007)
- Removal of rows containing no data
- Removal of exact duplicates (identical hospital number, name, echocardiogram study date and time (to the second)).
- Removal of alphabetical characters preceding hospital number using the "substr" command, as local hospital protocol mandates "RTH" added to the beginning of

each hospital number in imaging records. The hospital record number was then saved as a numeric variable, ready for merging.

This resulted in a dataset that could be matched to the ICNARC database extract. Finally, all data were saved in the one file that encompassed the entire study period.

2.2.2.2.3 AICU data

A data extract of all admissions to the AICU over the ELF 2 study inclusion period was performed on local ICNARC submission data. Name, date of birth, hospital record number and AICU admission dates were extracted and stored as an Excel file. Data cleaning was not necessary as the data are entered under pre-defined data collection rules by a trained data collection officer.

The hospital number and surname were then used as a linkage key with the echocardiographic data to generate a list of patients who had been in AICU and had an echocardiogram within the specified 5-year period.

2.2.2.2.4 Data linkage and application of inclusion criteria

The two data files (AICU admission and echocardiography data) were then matched and merged in Stata using a merge many to many command (mer m:m). Data were matched on primary and secondary identifiers, with matched patients identified in the column "_merge". This generated a list of patients who had an echocardiogram and had, during the 5-year study period, been admitted to AICU. Conditional formatting was then applied using AICU admission date and date of echocardiography, to identify echocardiograms occurring during AICU admission.

Records were then removed if any of the criteria following were met:

- Fewer than three echocardiograms
- Patients with all echocardiograms fewer than six hours apart
- Echocardiography not undertaken during AICU stay
- Patient enrolled in the ELF 1 study
- Fewer than two echocardiograms undertaken during AICU stay
- Echocardiograms occurring outside of AICU admission must have occurred up to six months following AICU discharge

Care was taken to avoid inappropriately excluding patients with multiple AICU admissions. This process resulted in the creation of a provisional study population.

2.2.2.2.5 Finalisation of study population

Once the provisional study population was identified, all echocardiograms that met the inclusion criteria were retrieved and preliminarily reviewed to ensure that image quality and windows would permit calculation of a LV ejection fraction. Any study that was inadequate was removed from potential pool of echocardiograms for analysis, and the participant rechecked to ensure they still met the study inclusion criteria.

ELF 1 participants were removed from the ELF 2 dataset. A flow chart outlining this process is given in the results chapter (section 2.2.2.2).

2.2.2.2.6 Study variables

All recorded variables of the finalised study population were extracted from a combination of paper based and electronic medical records (Carevue and the hospital's electronic patient record (EPR)). Demographic, haemodynamic and clinical variables collected across the ELF studies were subject to pre-defined data collection rules. These rules are outlined in the data collection document (Appendix 8), and specify the appropriate source, acceptable time interval between echocardiography and variable collection, and format of recorded variables, to be used in the ELF studies.

2.2.3 Participant retention, withdrawal and follow up

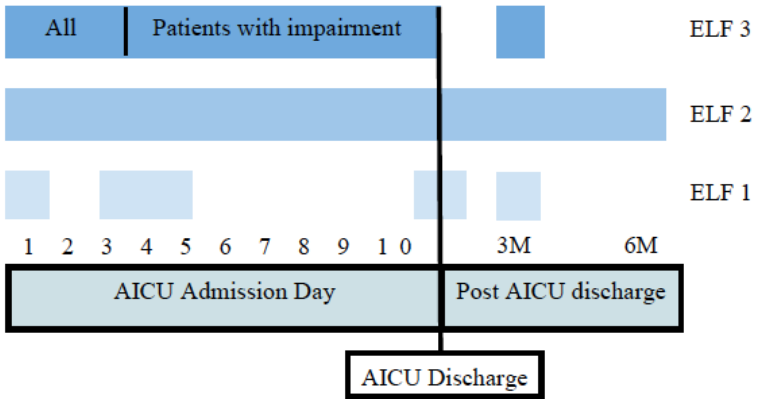
For the ELF 1 and ELF 3 studies, on-going consent was confirmed prior to all imaging. If a participant indicated that they do not wish to continue, they were withdrawn from the study. They were not replaced. Existing NHS follow up procedures were utilised, and participants were invited to attend an outpatient appointment three months following AICU discharge. Follow up transthoracic echocardiography occurred during this clinic appointment.

2.3 Patient assessment

2.3.1 Timing of assessments

Figure 5 provides an overview of the timing of echocardiography assessments of the ELF studies. The shaded areas indicate an echo assessment occurred during that time

Figure 5: Timing of study assessments



2.3.1.1 ELF 1

Echocardiography was undertaken within 24 hours of admission to AICU, repeated once during days three to five of AICU stay, within 24 hours of AICU discharge and at three months following discharge from AICU.

2.3.1.2 ELF 2

As this was a retrospective analysis, the timing of echocardiographic assessment was variable. During the inclusion period, an echocardiography machine was purchased for the AICU department and an echocardiography fellowship started, consequently the number of recorded TTE studies (including training

echocardiograms) increased. At least two echocardiographic studies occurred during AICU admission, as per the inclusion criteria.

2.3.1.3 ELF 3

Echocardiography was undertaken daily until day three of AICU admission. If an LVEF <55% was observed during this window, then daily echocardiography continued until day ten of AICU stay or discharge, whichever is earlier, and finally at three months following AICU discharge. If a participant did not demonstrate LV impairment during the first three days of AICU admission, they concluded their involvement in the study.

2.4 Population descriptors

For all studies, a number of descriptors were prospectively defined, and these were collected to characterise the study population. Study definitions, procedure for data collection, calculation and handling of missing data, are outlined in the data collection rules Appendix 8. Table 14 details the descriptor and source of collected data.

Table 14: Overview of population descriptors collected in the ELF studies

Descriptor	Source
Age at admission to AICU	Carevue
Gender	Carevue

Descriptor	Source
Primary admission diagnosis	Local ICNARC submission database
Past cardiac history	Medical records (Carevue/paper based notes)/ patient history
APACHE II score	Calculated from variables available from Carevue/electronic medical records from the first 24-hours in AICU
ICNARC physiology score	Local ICNARC submission database
Mechanical ventilation	Carevue
Weaning failure	Carevue
Hours of mechanical ventilation	Carevue
Vasopressors/inotropes required	Carevue
Vasopressor days	Carevue
Length of stay: hospital and AICU	Carevue
Mortality: AICU, hospital admission, days 30 and 90 following AICU discharge	Carevue/ hospital electronic patient record (EPR)
AICU readmission, hospital and AICU transfer data	Carevue
AICU therapies:	Carevue

2.5 Transthoracic echocardiography

2.5.1 Personnel training

2.5.1.1 Practical skills

All research staff received intensive training by British Society of Echocardiography (BSE) Fellows, in addition to attending a face-to-face course, prior to study commencement. All personnel achieved, as a minimum, Focused Intensive Care Echocardiography[142] (FICE) competency. Ongoing echocardiography skill development of junior staff was monitored by a fully accredited BSE mentor.

As the ELF 2 study uses existing data, the level of training of the echocardiographers is unknown. To deal with this, echocardiography training of research staff included identification of poor or unreliable studies. All echocardiograms from the ELF 2 study were independently reported by ELF study staff.

2.5.1.2 Interpretation

BSE fellows provided training on TTE interpretation. Training was focused on the recognition of impaired function, identification of poor study quality, identification of RWMA and accurate endocardial-blood interface detection. Training occurred during the conception, planning, and execution of all studies. Echocardiogram interpretation is outlined further in section 2.5.6.

2.5.2 Machine specifications

The Vivid-q (CE0344, 2008, General Electric Medical Systems, USA) was used for image acquisition. The probe (M4S-RS) used was a 1.5 – 3.6 MHz phased array cardiac transducer[143], which has a 90 degree field of view and is able to penetrate up to a depth of 30cm. This probe is specifically designed for cardiac ultrasound. The frame rate automatically varied with the adjustment of the focus, depth and width to optimise the imaging window.

2.5.3 Components of the focused examination

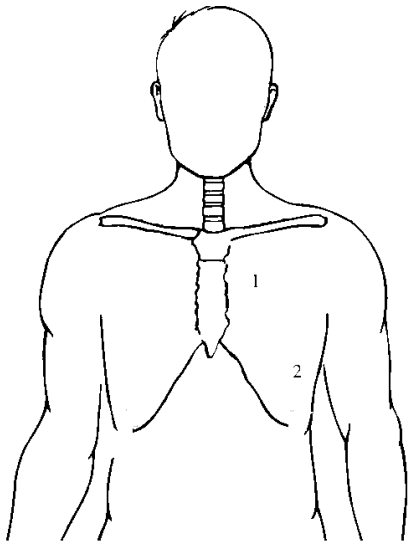
A focused echocardiographic examination was undertaken to assess LV systolic function, as measured by ejection fraction. Echocardiograms were done for research purposes (not clinically indicated) once the participant was haemodynamically stable and had undergone the informed consent/assent process. Treatment was guided by the lead AICU clinician, and treatment therapies were not changed immediately before or after echocardiography.

Parasternal long and short axis and apical two and four chamber views were attempted during each study (figure 6). Water based gel was applied to the transducer to increase ultrasound wave transmission. Table 15 details structures visualised and variables measured in each window.

The cardiac cycle was timed on a simultaneously recorded three lead electrocardiographic (ECG). All studies were recorded and archived. Studies in AICU were performed in the supine position, with left tilt where possible. During

the follow up examination participants were positioned in the left lateral position. Images were optimised by adjusting the depth, width, gain and focus position.

Figure 6: Transducer positions



Position 1:

Parasternal long axis

Parasternal short axis

Position 2:

Apical four chamber

Apical two chamber

Figure modified from Jensen[144]

Table 15: Components of the focussed echocardiogram examination in ELF 1 and ELF 3

Window	Structures visualised	Measurements
Parasternal Long Axis	LA LV size, wall thickness, radial function RV size Regional wall motion	LVIDd LVIDs IVSd LVPWd
Parasternal Short Axis	Radial LV systolic function RV size Regional wall motion	

Window	Structures visualised	Measurements
Apical Four Chamber	LV size RV size RV and LV longitudinal function Regional wall motion	
Apical Two Chamber	Regional wall motion LV longitudinal function	

2.5.4 Variables collected at the time of echocardiography

During AICU admission, data were collected to categorise whether the participants had sepsis (as defined by Padkin[145]), Systemic Inflammatory Response Syndrome (SIRS), the mode of ventilation (including, if necessary, mean airway pressure, peak inspiratory pressure and pressure support), any vasoactive drug requirements, the SOFA score and routinely collected haemodynamic variables. Echocardiograms occurring outside AICU had basic haemodynamic data recorded (heart rate, rhythm, diastolic and systolic non-invasive blood pressure). Definitions, procedure for data collection, calculation and handling of missing data are outlined in Appendix 8.

2.5.5 Image archiving and processing

All images were stored in Digital Imaging and Communication in Medicine (DICOM) format and analysed on the echocardiography software program, Xcelera

Ultrasound Viewer (release 3.3, 2013, Philips Medical Systems, The Netherlands). All measurements taken were saved for future review.

2.5.6 Measurements

Two-dimensional measurements of the left ventricle were taken in end-diastole and end-systole. End diastole and end systole were determined by visualisation of the largest and smallest left ventricular cavity, respectively. The blood-endocardial interface, just beyond the tips of the mitral valve leaflets was visualised and measurements were taken at this point in end-diastole (LVIDd) and end-systole (LVIDs). These cross-sectional linear measurements were used to calculate LV volumes using the Teichholz formula[146], with an ejection fraction calculated using the equation LVEF (%) = 100 x (EDV-ESV)/EDV. Care was taken to avoid measuring sub-endocardial bulges, off axis measurements or foreshortened views.

Multiple measurements were taken of LVIDd and LVIDs from multiple cycles. Three ejection fractions were then calculated using the paired measurements and a mean determined. Measurements were not taken from an ectopic beat or the following beat. Participants in atrial fibrillation had up to five measurements used in the calculation of the mean ejection fraction.

Linear measurements can be unreliable in the presence of significant regional wall motion abnormalities (RWMA)[94]. All studies were reviewed for RWMA in all windows. Participants with previous AMI, cardiac arrest or cardiac surgery were automatically flagged and reviewed by the BSE fellow for the presence of RWMA.

Any suspected RWMA was flagged for review by the BSE fellow, and where RWMA were present, the ejection fraction was visually estimated by the fellow and the distribution of wall motion abnormalities (single coronary artery territory or global) was recorded.

If a RWMA was identified on any imaging window, all echocardiograms for that participant were read by visual estimation by the BSE fellow. This ensured that a single operator was responsible for interpretation of all echocardiograms for a participant, and that different methods of assessing LVEF (visual vs 2D linear) were not used interchangeably. This approach avoids mixing EF assessment methods between participants, which has been identified as a source of error in LVEF measurements and has been discouraged[147]. Whilst visual estimation of LVEF is usually reported to the nearest 5% percent, the limitations of approach (less precision of reported LVEF) far outweighs the serious limitations of using a 2D linear assessment in the presence of RWMA. The approach undertaken in the ELF studies attempts to minimise error by ensuring a consistent approach to LVEF assessment for an individual participant and utilising expert opinion in the estimation of LV function in the presence of potential confounders. It is reasonable to include these data in light of this limitation as this is a rational approach to assessing participants with RWMA. To exclude these participants would introduce an unacceptable selection bias.

All values derived by the Teichholz formula were reviewed for appropriateness and plausibility. Any measurement deemed spurious was flagged for independent review by the BSE fellow.

2.5.7 Definition of myocardial depression and reversibility

Myocardial depression was defined as an absolute reduction of LVEF ≥5% from baseline occurring during AICU. Baseline was taken as the first reading of LV function occurring during AICU admission. A 5% threshold has been used extensively by other studies[148–156,157] and is greater than the mean observed echocardiographer intra-observer variability (discussed below).

Reversibility of myocardial depression was categorised as complete or incomplete. Complete reversibility was deemed to occur when LVEF returned to baseline or greater. Incomplete recovery was defined as improvement from LVEF nadir greater than 2.5% (which is beyond the upper boundary of the confidence interval of intra-observer variability), but not restoration to baseline value. The complete clinical course of participants was described. Any participant who initially demonstrated recovery but subsequently declined their ejection fraction was documented accordingly.

2.5.8 Incidental findings

Any suspected or identified abnormality was referred to the lead clinician and a formal echocardiogram recommended. This was documented in the participant's medical records.

2.5.9 Inter/intra observer agreement

Following intensive training, all echocardiographic studies were read by one investigator (VT). In the presence of suspected RWMA, these studies were referred to the BSE fellow for external review and interpretation.

Intra-observer agreement was calculated for this investigator. Twenty studies were selected at random by BSE fellows, anonymised and presented to the reader. Ejection fraction was recorded for all studies on a separate spreadsheet, with no measurements saved onto the images. These studies were then relabelled and represented to the same reader three months later. All data analysis was undertaken using SPSS Statistics (IBM, Version 21).

Intra-observer variability was calculated by a paired Student's t-test. Normality of paired differences was tested and confirmed by the Shapiro-Wilk test. There were no outliers determined by box-plot. Results demonstrated no significant difference between paired assessments with the mean of differences: -0.52%, (95% CI: -3.1 – 2.1).

Inter-observer variability was calculated between the researcher and the BSE fellow. The same 20 echocardiography studies used for intra-observer variability were independently read by the BSE fellow. A paired Student's t-test was performed. Differences between observers were normally distributed (as determined by the Shapiro-Wilk test) and no outliers were present on box-plot. Mean differences between measurements was -4.1%, (95% CI -8.3% – 0.2%), with

the BSE fellow reporting, on average, the ejection fraction lower than the researcher. The difference between observers was not statistically significant, and is far better than the mean differences and associated confidence intervals of echocardiography readings reported in the literature, that have reported confidence intervals as great as 25%[133,158].

2.6 Data handling

2.6.1 Database structure

Data from the three studies were housed in purpose built, password protected Microsoft Access databases, with a one-to-many relationship structure.

2.6.2 Data collection and entry

Predefined demographic, clinical and haemodynamic variables (described earlier) were transcribed onto study case report forms (CRF) and then entered into the database. Data were single entered. Examples of the CRFs used in the studies are given in Appendix 9. Echocardiographic measurements were calculated on Xcelera transcribed on to the study CRF.

2.6.3 Data protection and storage

Data were handled in accordance with the Data Protection Act 1998[159], with anonymisation of confidential information occurring as soon as it was practicable. In ELF 1 and ELF 3, this occurred following the last assessment of the last enrolled patient. In ELF 2, this occurred at the finalisation of the study population.

Patient identifiers were removed, and participants assigned a study number. A password protected linkage key was kept on a separate high compliance secure server, with access restricted to authorised study staff. Non-identifiable participant information was stored on a password-protected Microsoft Access databases on a different high-compliance server. Paper records were kept in a locked filing cabinet behind two swipe-access controlled doors and archived for the duration specified in the protocol.

2.6.4 Data cleaning

Validation rules were incorporated into the database design to minimise data entry errors. Database queries were generated to reveal any spurious or implausible data. Anomalies were cross-referenced against original source data and corrected as appropriate.

2.7 Statistical analysis

2.7.1 Overview of statistical analysis process

A data analysis plan was prospectively developed with advice from a statistician with a background in medical statistics. All data were analysed using R (version 3.0.3, R Foundation for Statistical Computing, Austria).

Data analysis had two objectives. Firstly, to provide a comprehensive description of the incidence and natural history of LV systolic RMD in the general AICU and

finally, to determine if the development of LV systolic RMD can be predicted using routinely collected variables available in the first 24-hours of AICU stay.

Descriptors of the incidence and natural history are reported for all three ELF studies. Myocardial depression was defined as decline of LVEF >5% from AICU baseline. Recovery from myocardial depression was classified as complete (return of LVEF to AICU baseline or greater) or incomplete (improvement in LVEF greater than 2.5% from the nadir, but not returned to AICU baseline). The time, measured to the nearest whole day since AICU admission, to myocardial depression and recovery are described.

At the time of study design, the feasibility of predictive modelling was unknown. The reported incidence of myocardial depression in the general AICU had been reported between 6[71] to 95[70]%. If the incidence was low, modelling would be unfeasible as there would be too few patients with the outcome. Fortunately, the incidence of RMD in the ELF studies was sufficient to undertake predictive modelling.

The data from all three ELF studies were combined to form the development population. This was possible as all studies collected the same variables, using the same prospectively defined data collection rules. Statistical significance testing for differences between populations was not undertaken, as the absence of statistical difference does not prove that populations are homogenous. Currently, there is no statistical test available to demonstrate homogeneity of study populations.

Construction of predictive models from individual ELF studies would not be useful, as the number of participants demonstrating the outcome in each study would not be sufficient to undertake modelling. As this is exploratory work, with a small dataset (n = 112), prediction was attempted using routinely collected variables from the first 24 hours of AICU admission; selection of this time point was a pragmatic decision, reflecting data availability.

Predictive modelling can be used to determine the probability that a condition will occur in the future. In this study, the outcomes of interest are the development of myocardial depression, and the recovery from myocardial depression. These are both binary outcomes. As discussed in section 1.8, there are a number of statistical techniques that can be used to predict a binary outcome, such as logistic regression, classification and regression trees (CART) and neural networks. Logistic regression was selected as the most appropriate technique to undertake predictive modelling, as this approach avoids the problems of partitioning and overtraining that are presented by using CART and neural networks, respectively.

Logistic regression can determine the probability of a future binary event or an existing binary outcome. Explanatory variables can either be continuous (e.g. heart rate) or categorical (e.g. sepsis present or absent). Logistic regression can also determine the change in odds (odds ratio) on the probability of the outcome, per change in unit of the explanatory variable. Predictive modelling with linear regression was not appropriate, as it requires the dependent variable to be continuous and assumes that the independent variables are linearly related to the

outcome variable. Consequently, predictive modelling using logistic regression was used in the ELF studies.

Candidate explanatory variables were then considered. All variables collected in the ELF studies were reviewed. Rationalisation of input variables is necessary to avoid overfitting of the model. Overfitting occurs when idiosyncrasies of the data are modelled, rather than generalisable patterns. This can occur when too many candidate variables are included in a model, given the number of patients with the outcome of interest. For every ten patients with the outcome, one candidate variable can be included (events per variable rule). Candidate variables should be independent to the outcome variable, and binary variables should have a sufficient number of patients with the least frequent outcome (>5% of the development population). Therefore, all variables collected in the ELF studies were reviewed for suitability as candidate explanatory variables.

Initially, a random effects logistic regression model was to be used in the prediction of myocardial depression and recovery. The random effects allow the model to account for variance within, and between, patients and variables. Preliminary work (section 5.2.3.1), however, identified significant correlation between many candidate explanatory variables.

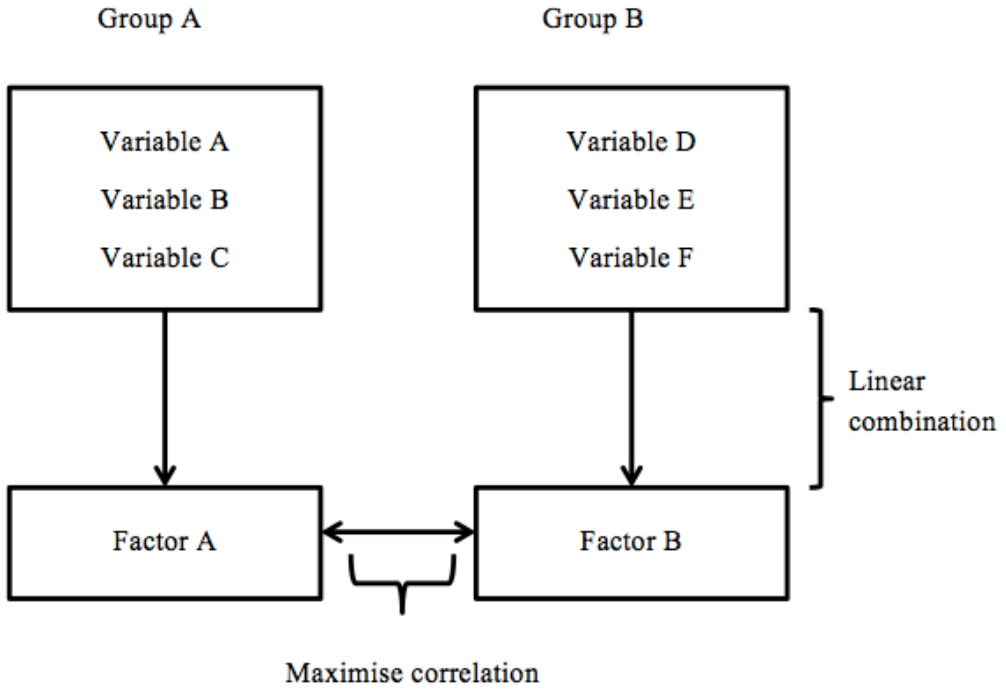
Therefore, the degree of correlation between variables that would be significant given the size of the dataset was determined. This was calculated using a formula suggested by Bickel and Dorfsum[160] that derives the degree of correlation that would be statistically significant between two sets of variables.

Correlation of candidate explanatory variables does not prohibit using logistic regression, but would result in large standard errors of explanatory variable coefficients. Consequently, a medical statistician was consulted and the statistical analysis plan revised.

The revised statistical analysis plan was to use canonical correlation to find a combination of explanatory variables to act as factor that correlates with the outcome variable.

Canonical correlation takes two groups of variables and creates a linear combination of variables within each group, expressed as a factor, which maximises correlation between the two groups of variables. In the analysis, explanatory (predictive) variables were one group, and the outcome variable the other. Canonical correlation estimates a coefficient of each explanatory variable, which, when the variables are standardised, allows for comparison of each variable's contribution to the factor. A visual representation of the process of canonical correlation is given in figure 7.

Figure 7: Process of canonical correlation



The factor produced by canonical correlation is then used as a single explanatory variable in a logistic regression model, with the development of myocardial depression, or recovery, as the outcome variable. Statistical significance was set as $p < 0.05$.

The preliminary model constructed using canonical correlation was then reviewed for inclusion of redundant variables. As canonical correlation fits a factor based on all included explanatory variables, variables that add little or no explanatory power to the model may be included (redundant variables). Inclusion of redundant variables creates a more complex model, which is penalised by measures of fit and increases the risk of overfitting.

Consequently, a vector map, produced by Principal Component Analysis (PCA), was reviewed to identify explanatory variables that are highly correlated with one another. PCA takes a set of inter-related variables and transforms these data whilst retaining as much variation of the original data as possible[161]. This produces principal components, which are new, uncorrelated variables that contain most of the variation present in all included explanatory variables[161]. These variables are ordered so majority of variation of the explanatory variables is contained in the first and second principal components[161]. A vector map plots the explanatory variables as vectors to the first and second principal components. The cosine of the angle of the vector to the horizontal axis gives the correlation with first principal component; the cosine of the angle to the vertical gives the correlation with the second principal component. The vector map is useful for the ELF studies as variables that are highly correlated with one another are easily identifiable. This is indicated by a small angle between vectors.

Explanatory variables that are highly correlated to one another were considered as pairs. Each variable from the pair was excluded from the model, and effect assessed. The variable whose removal had the least detrimental effect on the correlation of the factor to the development of the outcome was eliminated. Reduction in the number of explanatory variables resulted in a decrease in the correlation between the model factor and the outcome variable. The significance of this decrease was tested using Bartlett's approximation[162], which tested if the

canonical coefficients of the removed variables were significant. This resulted in identification of the final model.

Model sensitivity and specificity was then examined at a series of thresholds. Briefly, sensitivity is the proportion of true-positives identified from the total number of patients with the outcome, and specificity is the proportion of true-negatives from the total number of patients without the outcome. A decision threshold can then be set to classify patients with a probability greater than or equal to the threshold as positive. This threshold can be set to maximise sensitivity or specificity, or to arrive at a compromise position.

Model performance was then assessed using Receiver Operating Characteristic (ROC). Receiver Operating Characteristic curve is a graphical representation of the performance of a binary discriminator in terms of sensitivity and the true positive rate (1 – specificity). Model performance can be assessed by review of the area under the ROC curve, with an area of 0.5 indicating no discriminating ability.

Traditional methods of assessing model fit used in logistic regression cannot be performed on the explanatory factor derived from canonical correlation as the explanatory variables are treated as a factor. Consequently, model diagnostics were then performed according to Collett's recommendations for modelling binary data[163]. Therefore, a Pearson's half normal plot of residuals and an index plot was constructed.

Finally, for myocardial depression, the model was adapted into a scoring system (the Trubody score), which allows a bedside calculation of risk. This was created by rescaling the coefficients of the unstandardised explanatory variables, so that when multiplied by the raw patient value and summed, it would give the score a range between zero and ten. A graph of the probability of myocardial depression against Trubody score was then calculated for all participants in the development dataset.

The following section details the procedure for the identification of descriptors and construction and assessment of predictive models.

2.7.2 Descriptors

The following process was used in all three ELF studies:

- Identify the incidence of myocardial depression.
- Myocardial depression was defined as an absolute reduction in LVEF ≥ 5% during AICU stay, compared with AICU admission echocardiogram.
- This was identified by subtracting the admission LVEF from subsequent LVEF measurements taken in AICU.
- The outcome variable (myocardial depression) was binary.

Describe the time course of myocardial depression and recovery in participants demonstrating myocardial depression

- Day to development, degree of absolute reduction, and improvement, in LVEF was recorded.

First recorded decline in LVEF ≥5% during AICU was considered the onset of myocardial depression, taken to the nearest whole day.

- The LVEF nadir observed in AICU was used to determine the degree of absolute reduction in LVEF.
- The final LVEF captured in the study period was used to determine the absolute improvement in LVEF.

Identification of partial recovery in participants demonstrating myocardial depression

- The final LVEF captured in the study period, with reference to admission LVEF, was used to determine if recovery had occurred.
- Improvement in LVEF from nadir that is greater than 2.5% (the upper bound of intra-observer variability), but has not returned to baseline during the observation period.

Identification of full recovery

- The final LVEF captured in the study period, with reference to admission LVEF, was used to determine if recovery had occurred.
- Full recovery was defined as a return to baseline LVEF or greater during the study period.

2.7.3 Predictive modelling

2.7.3.1 Selection of input variables

Predictive modelling was undertaken post-hoc. Consequently, candidate input variables were limited to the variables collected in the ELF studies. All recorded variables were reviewed for suitability of inclusion into the models.

All recorded variables and the justification for inclusion/exclusion in the models are given in Appendix 10. Ultimately, twelve variables were identified to be trialled as candidate explanatory variables. These are given in table 16.

Table 16: Candidate explanatory variables

Variable	Unit or measure
Heart rate	Beats per minute
Sinus rhythm	Binary: yes/no
Systolic blood pressure	mmHg
Mean airway pressure	cmH_20
Vasopressors	Binary: yes/no
Respiratory organ dysfunction	Binary: yes/no
Cardiovascular organ dysfunction	Binary: yes/no
Male	Binary: yes/no
Surgical admission	Binary: yes/no
RWMA	Binary: yes/no
Age at admission to AICU	Years
Severe sepsis	Binary: yes/no

2.7.3.2 Model development

The models were developed according to the following process:

2.7.3.2.1 Logistic regression

Candidate explanatory variable data of all participants in the development population were loaded into the statistics program, R. An additional column denoted those with the outcome of interest, coded as 0/1.

The logistic regression modelling function was chosen. Candidate explanatory variables were fitted simultaneously and each variable was reviewed for significance as a main effect, or as a clinically meaningful interaction term.

Variables were removed through backwards elimination to fit the most parsimonious model. Variables with a p value <0.2 as either a main effect or interaction term were provisionally kept in the model.

Model fit was assessed by review of the explanatory variables p value, and the effect on the Akaike Information Criteria (AIC, discussed further in section 5.2.3). Reductions in p value and AIC indicate a better model fit. p values <0.05 were considered statistically significant.

Variable elimination continued until the most parsimonious fit of the data was achieved (when minimal improvements in the AIC was observed).

Logistic regression has the statistical assumption that continuous independent variables are linearly related to the log odds of the dependent variable. For logistic regression to be valid, this assumption must be met.

This assumption was tested by trialling continuous variables with polynomial terms and assessing the fit on the model. If the assumption was violated the continuous variable (with a polynomial term (e.g. squared)) would be statistically significant. This would indicate that the assumption of linearity was not met and an alternative modelling approach would need to be sought.

Model development using logistic regression was trialled, but multicollinearity between candidate input variables precluded reliable estimates of explanatory variable coefficients. Consequently, an alternative approach to predictive modelling was sought. A statistician was consulted, who advised the use of canonical correlation.

2.7.3.2.2 Canonical correlation

Again, all candidate explanatory variable data of the development population were loaded into the statistics program, R. An additional column denoted those with the outcome of interest, coded as 0/1.

The canonical correlation function was used to find the best linear combination of candidate explanatory variables, expressed as a factor, that was maximally correlated to the outcome variable. This produces coefficients for each explanatory variable included in the factor

For each participant, the raw data for each variable was then multiplied by the appropriate variable coefficient. This was then summed to produce a factor for each participant.

This factor was then used as a single explanatory variable in a logistic regression model, with the outcome of interest used as the dependent variable. Statistical significance was set at $p < 0.05$.

Potentially redundant variables were then identified by review of the vector map produced by PCA. Variables that are highly correlated to one another appear clustered on the vector map. Correlated variables were then treated as pairs. Each variable from the pair was removed from the model and the effect on correlation of the factor to the outcome was assessed. The variable whose removal had the least detrimental effect on the correlation of the factor to the outcome was eliminated.

The impact of variable reduction on the correlation of the factor to the outcome variable was assessed using Bartlett's approximation[162]. This identified that the coefficients of the variables removed from the model were effectively zero. Consequently, the final model was reached.

Model performance was then tested. This is described in the following section.

2.7.3.3 Model performance and accuracy of classification

Model sensitivity and specificity was then assessed at a series of probability thresholds. A decision threshold can be set to classify patients with a probability

greater than or equal to the threshold as positive. This threshold can be set to maximise sensitivity or specificity. In this study, minimising false negatives was preferable as the likely consequence of a false positive result is surveillance echocardiography, which poses little risk or burden to the patient.

The false negative and false positive rates across a range of probability thresholds was generated using the performance function in the statistics program, R.

Model performance was then assessed by construction of a ROC curve, and the area under the curve reviewed. Model performance of a binary outcome can be assessed by the area under the ROC curve (AUROC), which indicates the ability of the model to discriminate between those with and without the outcome of interest. A model without any discriminating ability would follow a diagonal line between zero and one, with an AUROC of 0.5.

The ROC curve was constructed by plotting the sensitivity (true positive rate, y axis) against 1-specificity (false positive rate, x axis) over a range of probability thresholds, using the plot function in R. The area under the curve was also calculated using the plotting function.

Measures of model fit typically used in logistic regression cannot be performed on the explanatory factor derived from canonical correlation. This is because all explanatory variables are expressed as a factor. Consequently, model diagnostics for binary data were performed according to the procedures recommended in the seminal work of Collett[163].

Thus, model fit was then assessed using Pearson's half normal plot of residuals and by construction of an index plot. A Pearson's half normal plot of residuals assesses model fit by plotting the absolute value of the residuals in ascending order against the inverse cumulative distribution function. A simulation envelope is also created for the plot, which allows the identification of outliers.

Pearson's half normal plot of residuals was constructed using the following process:

- The final fitted model was used to calculate the probability of myocardial depression for each participant (n = 112)
- A random number generator produced 19 probability simulations of each data point, and myocardial depression was considered present if the probability > 0.50.
- The 19 simulations were then refitted to the final model and Pearson's residuals calculated.
- The absolute values of Pearson's residuals were taken and plotted in ascending order. The simulated residual means are also plotted in ascending order.
- A simulation envelope was constructed using the maximum and minium of the absolute residuals. These were plotted against the inverse cumulative distribution function.

Any outliers will be identified with the datapoint falling outside of the simulation envelope. Poor model fit is indicated by the plot of absolute residuals not following an approximate diagonal straight line[163].

An index plot is a graphical representation of the absolute residual of each participant. The participant is described as an observation number and is plotted on

the x axis, and the standard deviation of the residual is plotted on the y axis. This identifies any residual outliers that may need to be removed from the model.

2.7.3.4 Adaption of model for prediction of myocardial depression

The model predicting the development of myocardial depression was then adapted into a scoring system to assess risk at the bedside.

All explanatory variable coefficients derived from canonical correlation were scaled. Raw participant observations were multiplied by the corresponding explanatory variable coefficient and then summed. This sum, the Trubody score, then fell within the range of zero to ten.

The Trubody score was then calculated for all participants in the development dataset. These scores were used to create a probability curve, which demonstrates risk of development of myocardial depression against Trubody score.

2.7.3.5 Model validation

Finally, there are numerous statistical methods available to validate predictive models. Broadly, these can be either classified as internal (using part of the development dataset as the validation dataset) or external (using an independent dataset, ideally containing similar patients). The intention was for the ELF 3 study to serve as an external validation population. This, however, proved impossible because of the relatively small ELF 3 cohort and the low incidence of the myocardial depression. Consequently, these data were added to the development population.

The sample size was also ultimately insufficient to undertake meaningful internal validation, as validation studies for binary data should include at least 100 patients with the outcome[137]. This represents an area of future work.

Chapter III: Epidemiology results

3.0 Chapter overview

This chapter details the incidence, reversibility and time course in participants from all three ELF studies.

The studies are presented individually. Study enrolment, timing of assessments, completeness of data, and the study population are described. Subsequently, the incidence, time course and recovery of myocardial depression are reported. Finally, a summary of the findings of the ELF studies is presented.

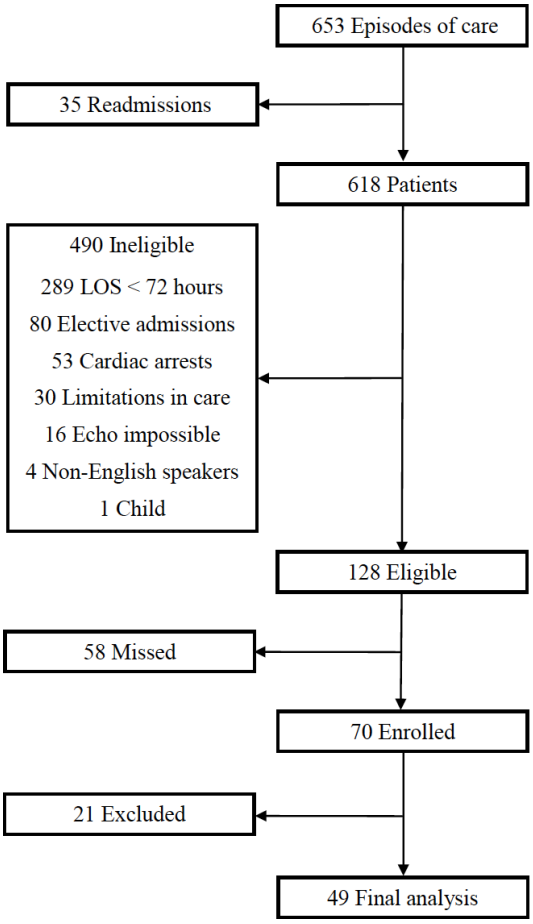
3.1 ELF 1

3.1.1 Screening and enrolment

Enrolment for the ELF 1 study was undertaken between 9th September 2012 and 2nd May 2013. The recruitment site was the 16-bed general adult AICU at the John Radcliffe Hospital. The John Radcliffe is a tertiary teaching hospital, and is the largest hospital in the Oxford University Hospitals NHS Trust. Oxford University Hospitals NHS Trust admit approximately 112,000 inpatients annually[164].

Consecutive enrolment was attempted, but proved impossible, as insufficient staff were available to provide daily cover. Consequently, enrolment was undertaken during weekdays, with weekend cover where possible. Figure 8 outlines the eligibility and recruitment during the study period.

Figure 8: Eligibility and enrolment flowchart for the ELF 1 study



Seventy participants were enrolled, with 49 included in the final analysis. Twenty-one participants were deemed ineligible following enrolment. These participants were not included in the final analysis.

The most common reason for exclusion was AICU length of stay <72 hours. Length of AICU admission is difficult to predict, and it was considered preferable to recruit all eligible patients and, if necessary, exclude them later, rather than attempt to predict length of stay and miss potential participants. The justification for exclusion is given in table 17.

Table 17: Reasons for exclusion following enrolment in the ELF 1 study

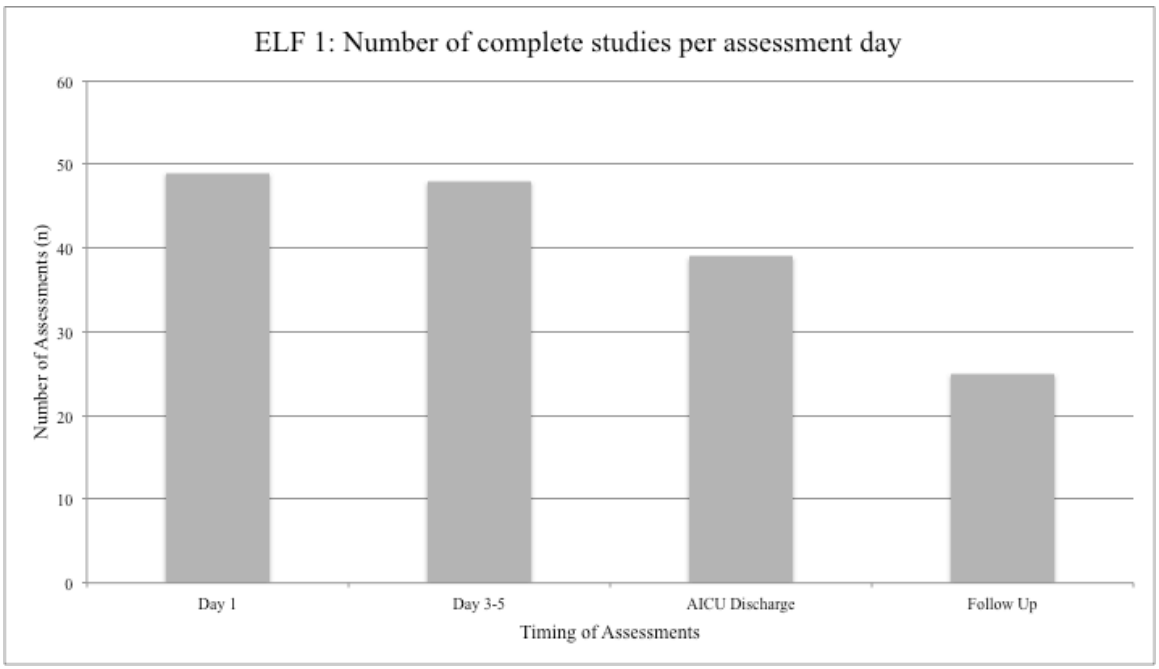
Justification	Number excluded
Length of AICU stay <72 hours	8
Inadequate image quality	7
Withdrawn from study	3
Cardiac arrest during AICU admission	2
Non-English speaking background identified following enrolment by professional consultee	1

3.1.2 Assessments and capture

Assessments were conducted within 24 hours of AICU admission, once between days three-five of AICU stay, within 24 hours of AICU discharge and finally three months following discharge from AICU. Assessments included a review of the medical notes, recording of physiological variables and a focused transthoracic echocardiogram. All participants received standard care, under the direction of the treating consultant.

Figure 9 outlines the number of complete studies undertaken per assessment day. A total of 148 echocardiographic studies and corresponding clinical variables were collected from 49 patients during the study period.

Figure 9: Number of echocardiographic studies collected per assessment day



3.1.3 Population

The final study population consisted of 49 participants, 35 (69%) were male. The age of the population was not normally distributed, as revealed by histogram, therefore the median and the interquartile range are reported. The median age of the population was 66 years (IQR 47 – 75). All participants were admitted to the AICU as an emergency, with eight participants (16%) admitted following surgery. Four participants (8%) were admitted following transfer from another hospital, but none

received intensive care at their hospitals of origin. Four participants (8%) were readmitted to the AICU following enrolment into the study.

3.1.3.1 Admission diagnosis

The primary diagnoses for admission to AICU were recorded using the ICNARC Coding Method[165] by trained, local audit staff. The ICNARC coding method is a multi-tiered auditing tool that identifies admission diagnosis based on surgical status, body system, organ, process and condition.

The primary diagnosis at admission to AICU varied amongst participants. Twenty-seven percent (n = 13) of participants were admitted with diagnoses of low incidence within the study population, these were categorised as "other". Table 18 details the admission diagnoses of the study population.

Table 18: Primary AICU admission diagnosis of ELF 1 participants

Admission diagnosis	Number (%)
Other	13 (27%)
Septic shock	12 (25%)
Trauma	6 (12%)
Pneumonia	6 (12%)
Arrhythmia/ malignant hypertension	4 (8%)

Abdominal aortic or thoracic aneurysm	4 (8%)
Renal failure	2 (4%)
Perforated viscus	2 (4%)

3.1.3.2 History of cardiac disease

Any history of hypertension, cardiomyopathy, myocardial infarction, heart failure, valvular disease, cardiac arrest, arrhythmia and coronary artery bypass grafting were recorded according to the data collection rules outlined in Appendix 8.

Participants with a history of cardiomyopathy, myocardial infarction, valvular disease, heart failure, coronary artery bypass grafting or cardiac arrest were flagged for review by a BSE fellow, as they may have pre-existing RWMA would introduce error into the estimates of LVEF.

Excluding hypertension, the prevalence of these conditions was low amongst the population. Table 19 details the prevalence of pre-existing cardiac conditions amongst participants.

Table 19: Prevalence of pre-existing cardiac conditions in ELF 1

Pre-existing cardiovascular disease	Yes (n, %)	No (n, %)
Hypertension	19 (38.8%)	30 (61.2%)
Cardiomyopathy (any)	1 (2.0%)	48 (98.0%)

Acute myocardial infarction	3 (6.1%)	46 (93.9%)
Heart failure	3 (6.1%)	46 (93.9%)
Coronary Artery Bypass Graft	2 (4.1%)	47 (95.9%)
Pre-existing cardiovascular disease	Yes (n, %)	No (n, %)
Uncorrected valvular disease	2 (4.1%)	47 (95.9%)
Valvular replacement	2 (4.1%)	47 (95.9%)
Cardiac arrest	0 (0%)	49 (100%)
Arrhythmia	4 (8.2%)	45 (91.8%)

All participants with previous coronary artery bypass grafting or valve replacement underwent surgery at least five years prior to AICU admission. All participants with a history of acute myocardial infarction presented with this during a separate hospital admission. One participant had a history of dilated alcoholic cardiomyopathy. Finally, of the two participants with uncorrected valve disease, one participant had severe mitral regurgitation (documented on formal echocardiography during the current admission), the other had aortic stenosis, the severity of which was unknown.

3.1.3.3 Length of stay: AICU and hospital

The length of stay (LOS) data was inspected by histogram and was not normally distributed. Therefore, the median and interquartile range is presented. The median length of stay in AICU for the study population was around six days (median 6.2 IQR 4 – 14). Length of stay was calculated from date and time of admission to date and time of discharge. The median hospital length of stay for the study population was 22 days (IQR 11 – 42). This was calculated from the hospital admission date, to date of cessation of acute hospital care, taken to the nearest whole day.

3.1.3.4 AICU risk adjustment tools: ICNARC and APACHE II

The ICNARC physiology score and APACHE II scores were calculated using the techniques described in the data collection rules (Appendix 8). These scores describe the severity of illness of the population[166]. Data were inspected by histogram and both scores were normally distributed. The mean ICNARC physiology score was 19 (SD: 7), similarly the APACHE II score was 20 (SD: 7).

3.1.3.5 Mortality

Five participants (10%) died in the AICU, another four (8%) participants died between AICU and hospital discharge. The 30 and 90 day mortality was calculated from the date of AICU discharge. These data were identified from medical records linked to national death registries. An additional participant died between hospital discharge and day 30, thus 30-day mortality of the cohort was 20% (n = 10). One (2%) further participant died between days 30 and 90. Two (4%) participants were

admitted to hospital just prior to their follow up appointment, both participants died in hospital before their follow up appointment.

3.1.4 Missing data

Missing values were excluded from analysis. One study was missed on days 3-5 due to staff sickness. Data were missing for ten studies at the discharge assessment, as participants were discharged/transferred after hours. Twenty-four studies were missing from the follow up assessment; 13 were due to participant dying before they returned to clinic, the remainder declined follow up assessment.

3.1.5 Incidence of myocardial depression

Myocardial depression was defined as an absolute decline in LVEF ≥5% from the first LVEF recorded during AICU admission. This threshold has been used extensively elsewhere in the literature[148,150–157,167,168]. This was determined as per the procedure outlined in section 2.7.2.

Eight participants (16.3%) demonstrated a decrease in LVEF ≥5%. Six of these depressed their ejection fraction by the second assessment (days 3 – 5 of AICU stay) whilst two participants maintained their ejection fraction during the second assessment but had developed myocardial depression by the third assessment (AICU discharge). At the first recorded drop in ejection fraction (identification of myocardial depression), the median absolute decrease in LVEF was 10.5% (IQR 6.5 – 21). The absolute decrease in LVEF to the nadir was 14% (IQR 6.9 – 24.8).

Half of the participants demonstrating myocardial depression were female. No participants demonstrating myocardial depression were readmitted to AICU. Seven of the eight participants with myocardial depression were admitted for a medical condition i.e. non-surgical. Only one participant with myocardial depression demonstrated RWMA, this participant had a previous acute myocardial infarction and demonstrated RWMA in a single coronary artery distribution.

At the time myocardial depression was first recorded only two participants were receiving vasoactive therapies (one participant receiving noradrenaline 0.021 mcg kg^{-1} min^{-1} and one participant receiving dobutamine 1 mcg kg^{-1} min^{-1}). Another two participants were identified as having severe sepsis at the time of myocardial depression, one of which was receiving mechanical ventilation. An additional two participants were mechanically ventilated at the time of myocardial depression.

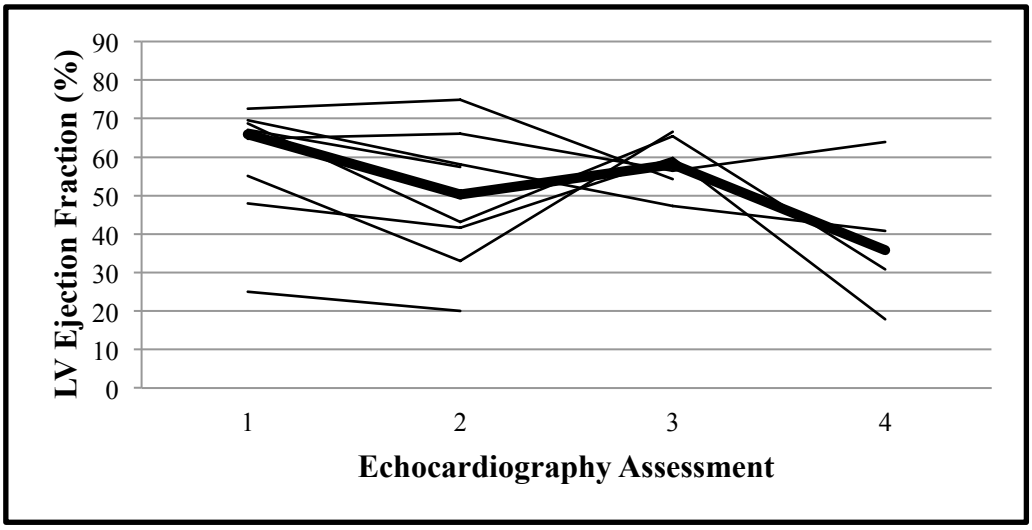
Table 20 provides a comparison of the severity of illness, length of stay, 90-day mortality, artificial ventilation and vasoactive drug requirements between those that developed myocardial depression and those that did not. Statistical significance between groups were tested for a number of outcome measures, using either the Mann-Whitney U test or Kruskal-Wallis H test , but were not significant between groups.

Finally, the changes in LVEF over time in the ELF 1 study for participants who developed myocardial depression are given in figure 10, and those who did not are given in figure 11.

Table 20: Comparison of ELF 1 participants with and without myocardial depression

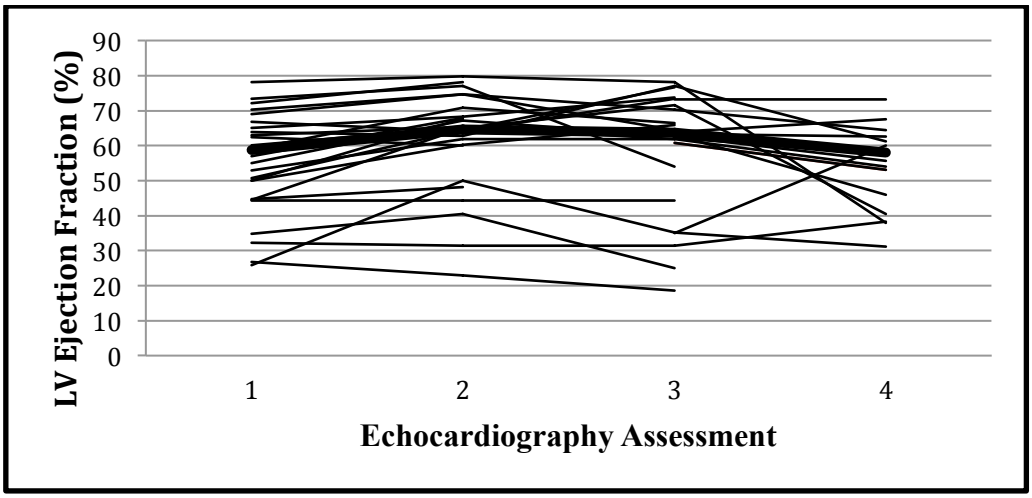
	No myocardial depression (n = 41)	Myocardial depression (n = 8)	Statistical significance
Age (years, median, IQR)	66 (47 – 79)	68 (51 – 71)	N/A
Male (n, %)	31 (75.6%)	4 (50%)	
ICNARC physiology score (mean, standard deviation)	19 (± 7)	19 (± 6)	
APACHE II score (mean, standard deviation)	21 (± 8)	19 (± 6)	
Failed extubation (n)	5 (12.2%)	1 (12.5%)	
LOS AICU (days, median, IQR)	6 (4 – 13)	11 (11 – 19)	p = 0.15
LOS Hospital (days, median, IQR)	19 (11 – 43)	28 (19 – 40)	p = 0.42
90-day mortality (n, %)	8 (19.5%)	3 (37.5%)	p = 0.43
Mechanically ventilated (n)	19 (46.3%)	6 (75%)	p = 1
Duration of mechanical ventilation (hours, median, IQR)	27 (2 – 120)	78 (19 – 189)	p = 0.53
Required only vasopressors (n) Required only inotropes (n) Required both vasopressor and inotrope (n)	20 0 2	4 0 2	p = 0.62

Figure 10: Changes in ejection fraction in ELF 1 participants demonstrating myocardial depression in AICU



The bold line is the median ejection fraction of the cohort.

Figure 11: Changes in ejection fraction in ELF 1 participants without myocardial depression observed in AICU



The bold line is the median ejection fraction of the cohort.

3.1.6 Incidence of recovery of cardiac function

Two (25%) of the eight participants with myocardial depression died in AICU without recovery. Another two participants (25%) survived until AICU discharge, but still did not demonstrate reversibility of LVEF impairment. Complete recovery was defined as return of LVEF to AICU baseline or greater during the study period. Partial recovery was defined as improvement ≥2.5% from the nadir, but not returning to baseline LVEF, this threshold is set beyond the upper bound of intra-observer variability confidence interval. Three (37.5%) participants demonstrated complete recovery, and another (12.5%) partially recovered. Curiously, one participant who demonstrated complete recovery then demonstrated decline in ejection fraction on follow up study.

The median improvement in LVEF from the nadir was 20.2% (IQR 10.3 – 30.7). The RWMA observed in the participant with a history of acute myocardial infarction did not resolve during the study period. Demographic, clinical and haemodynamic factors were not compared between those who demonstrated reversibility and those who did not, as the sample size was too small.

3.1.7 Time course

The median time to the development of myocardial depression was four days (IQR 3 – 6). The time to complete recovery of ejection fraction was variable (6, 23 and 105 days). The one participant who had incomplete recovery demonstrated this on day eight following AICU admission.

3.1.8 Summary

This study has observed myocardial depression in 16.3% of participants (n = 8), with a variable pattern of development and extent of recovery. There was a large range in the degree that LVEF deteriorated from AICU baseline (5 – 26.5%). There were an equal number of males and females affected. Physiological derangement between participants affected by myocardial depression and those unaffected were similar. Hours of mechanical ventilation, hospital and AICU length of stay was greater in those affected by myocardial depression.

3.2 ELF 2

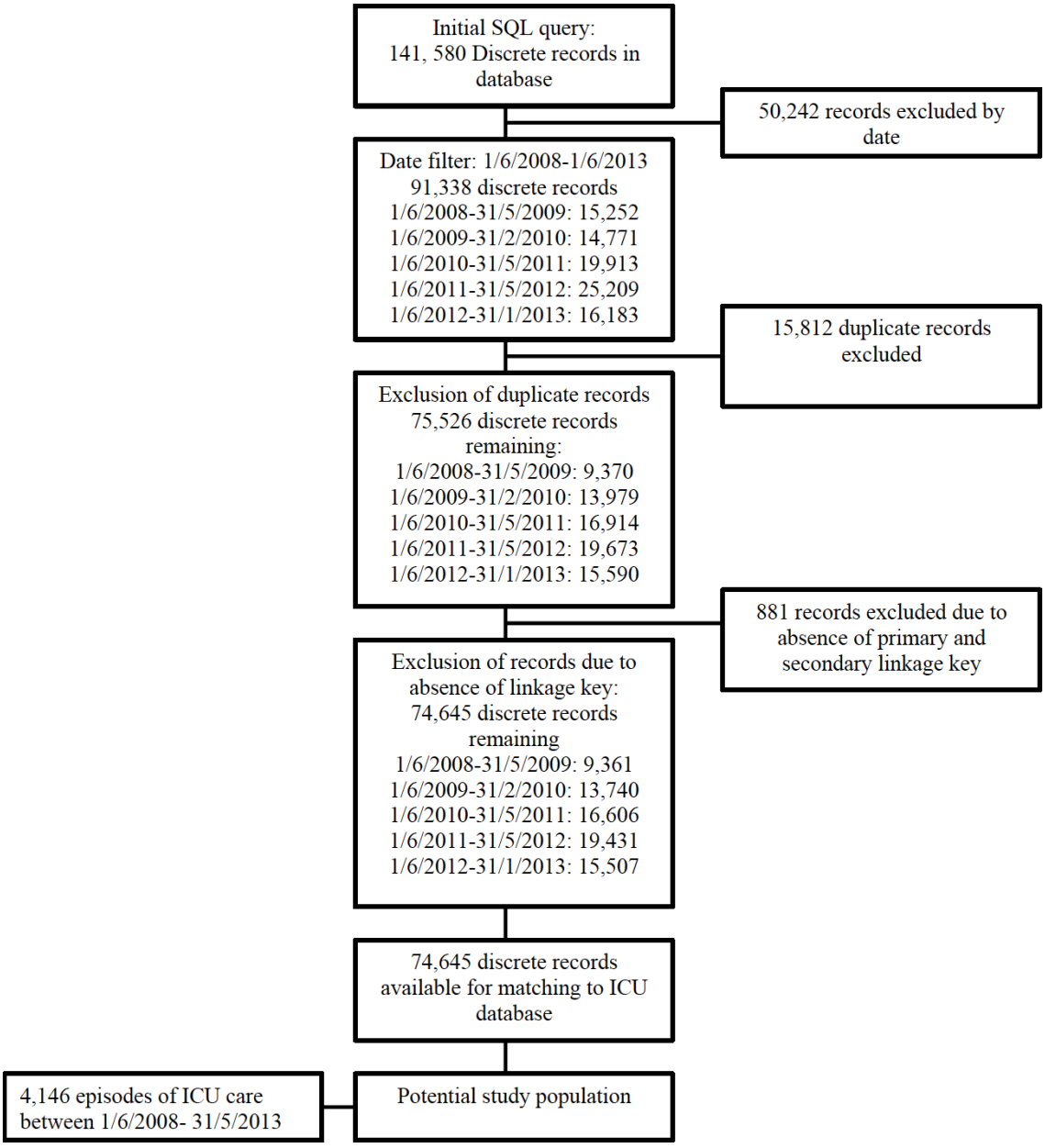
3.2.1 Identification of study population

3.2.1.1 Xcelera

The ELF 2 study utilised existing clinical records to identify patients who had at least two echocardiograms whilst admitted to AICU. All Trust echocardiographic data, including training studies, are contained on the Xcelera database. Consequently, the database was queried and all echocardiography records were retrieved. In total 141,580 discrete records were identified. Date filters were then applied to identify records that occurred during the ELF 2 study period (1st January 2008 to 1st June 2013). This study period was chosen as it corresponds to the implementation of Carevue (Philips), the AICU electronic patient clinical information system. Carevue allows identification of clinical and physiological variables that are crucial to the ELF 2 study.

Duplicates and studies that did not have a primary (hospital record number) or secondary (patient name) linkage key were removed, leaving 74,645 records for matching to the AICU local ICNARC submission database. Figure 12 details the process and number of records excluded through each step of the linkage process.

Figure 12: Xcelera data extraction and filtering



3.2.1.2 AICU records

The audit (ICNARC) database for the AICU was duplicated. From this dataset the records of all patients admitted during the study period were extracted. These records were initially matched by the primary linkage key, the hospital record number, to the equivalent fields in the Xcelera database. If the primary linkage key was missing, the secondary linkage key was then used. The process of data matching is given in section 2.2.2.2.1.

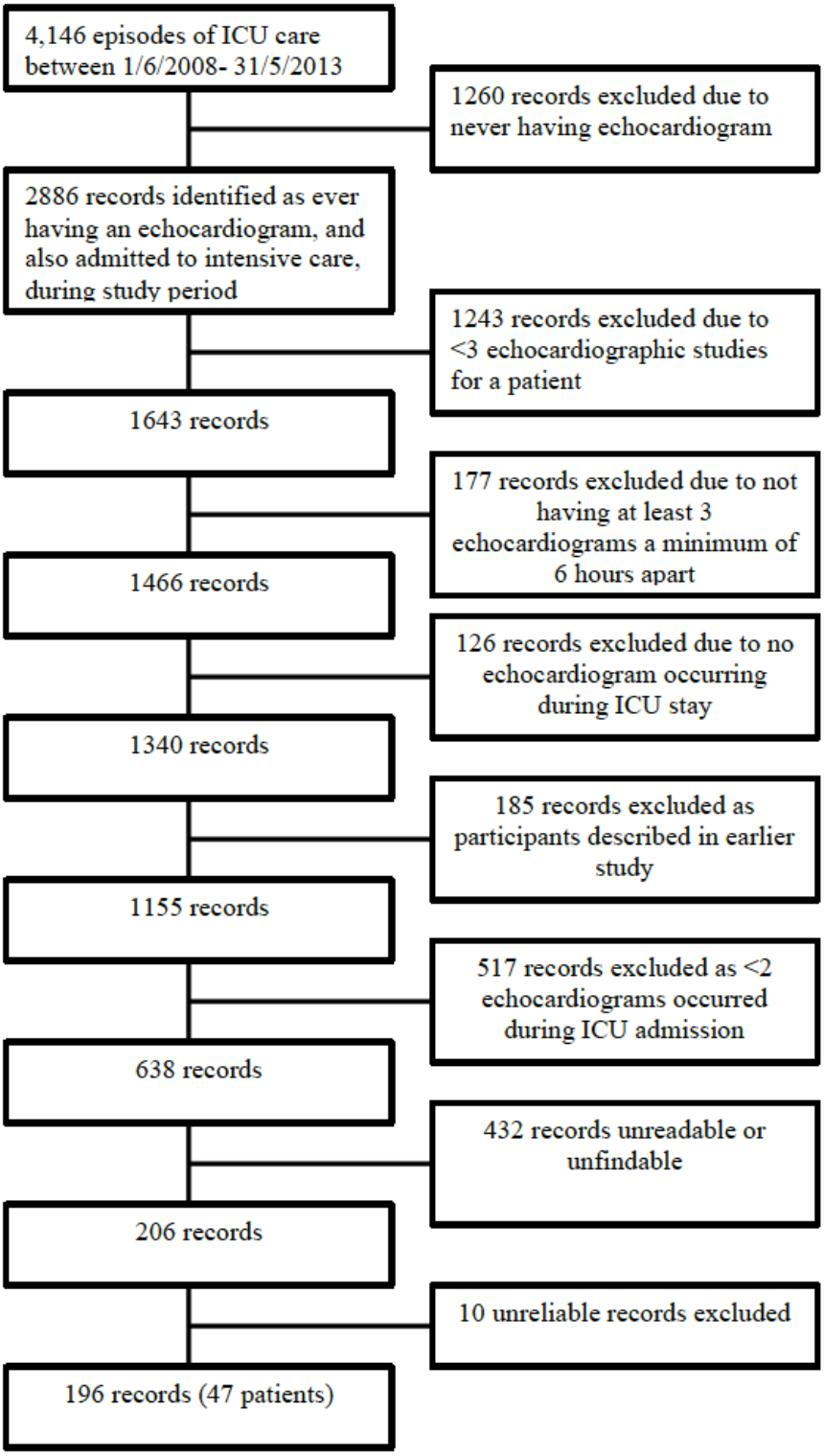
This identified patients who had an echocardiogram and had been admitted to AICU at some stage during the study period, but not necessarily concurrently. Patients were then excluded if they did not have a minimum of three echocardiograms at least six hours apart. Date criteria were then applied, excluding patients who did not have at least three echocardiograms, with at least two undertaken during AICU admission. Studies occurring outside of AICU were included if they were conducted within six months of AICU discharge. As expected, all ELF 1 participants were correctly identified in this process, which acted as a validation of the extraction process. Participants from the ELF 1 study were then removed from the dataset.

This resulted in 638 echocardiography records (image sets) included as a preliminary study population. These studies (images) were retrieved from the echocardiography database and reviewed to determine if LVEF could be determined. The Xcelera database records all images undertaken during an echocardiogram, this includes training studies conducted by novice

echocardiographers, consequently, image quality varied. Therefore, the image quality of all echocardiograms was reviewed for off-axis imaging windows, foreshortened views and inadequate or inappropriate focus, depth and gain.

Four hundred and thirty-two studies were unreadable, with inadequate image quality to read LVEF, or unfindable, no with images available for interpretation. This resulted in 206 studies eligible for inclusion into the study population. In the analysis phase, a further ten studies were excluded (one participant) due to severe valvular pathology (congenital abnormalities). Ultimately, 47 participants (196 echocardiograms) were included in the final study population. Figure 13 details the process and number of records excluded through each step of the identification process.

Figure 13: Identification of preliminary and final study population



3.2.2 Population

A total of 47 patients were eligible for inclusion in the study, 30 of which were male (64%). The median age of participants was 59 years (IQR 41 – 70). All but one participant was admitted as an emergency. Four (8.5%) participants were transferred to the site from another AICU and another nine (19.1%) were transferred from another hospital. Six (12.8%) participants were admitted following surgery. Six (12.8%) participants were also readmitted to the AICU.

3.2.2.1 Admission diagnosis

The primary diagnosis at admission to AICU for all participants was identified using the ICNARC coding method[169]. This is a hierarchical system of coding AICU admission diagnosis that is used for ICNARC auditing. These data were extracted from the local ICNARC submission database. Table 21 gives a breakdown of the four commonest diagnoses at admission, the remainder were of low frequency and classified as other.

Table 21: Primary AICU admission diagnosis of ELF 2 participants

Admission diagnosis	Frequency (n, %)
Other	20 (42.6%)
Pneumonia	10 (21.3%)
Acute myocardial infarction	7 (14.9%)
Sepsis/septic shock	5 (10.6%)
Arrhythmia	5 (10.6%)

3.2.2.2 History of cardiac disease

Obtaining past medical history from a retrospective dataset has limitations, but was attempted to identify any common pre-existing cardiac conditions amongst the study population. These were collected in accordance to the predefined study data collection rules (Appendix 8). These results are given in table 22.

Table 22: Prevalence of pre-existing cardiac conditions in ELF 2

Pre-existing cardiovascular disease	Yes (n)	No (n)
Hypertension	13 (27.7%)	34 (72.3%)
Cardiomyopathy (any)	2* (4.3%)	45 (95.7%)
Acute myocardial infarction	14 (29.8%)	33 (70.2%)

Pre-existing cardiovascular disease	Yes (n)	No (n)
Heart failure	4 (8.5%)	43 (91.5%)
Coronary Artery Bypass Graft	4 (8.5%)	43 (91.5%)
Uncorrected valvular disease	2 (4.3%)	45 (95.7%)
Valvular replacement	2 (4.3%)	45 (95.7%)
Cardiac arrest	16 (34.0%)	31 (66.0%)
Arrhythmia	10 (21.3%)	37 (78.7%)

*In both participants dilated cardiomyopathy of unknown origin was identified by cardiac magnetic resonance imaging

Importantly, the two participants with a history of severe valvular disease underwent corrective surgery at least one year prior to being admitted to AICU. Similarly, participants who had coronary artery bypass grafting also had surgery at least one year prior to AICU admission. The two participants with uncorrected valvular disease did not have the severity of the pathology reported.

Sixteen participants had a history of cardiac arrest. Of these, nine participants had return of spontaneous circulation within five minutes.

3.2.2.3 Length of stay: AICU and hospital

As determined by histogram, the length of stay data was not normally distributed. The median length of stay in AICU was around eight days (median 8.4, IQR 4 – 23). The median length of stay in hospital was 33 days (median 33.0, IQR 14 – 58). AICU length of stay was calculated from date and time of admission to date and time of discharge. Hospital length of stay was calculated from the date of hospital admission to date of cessation of acute hospital care.

3.2.2.4 AICU risk adjustment tools: ICNARC and APACHE II

The ICNARC physiology score and APACHE II scores were extracted/calculated using the techniques described in the data collection rules (Appendix 8). These scores provide a description of the severity of illness of the population. Data were inspected by histogram and both scores were normally distributed. The mean ICNARC physiology score was 24 (SD: 8) and the APACHE II score was 20 (SD: 7).

3.2.2.5 Mortality

Five (10.6%) participants died in AICU, with a further three (6.4%) dying before hospital discharge, a 17% in-hospital mortality. One (2.1%) further participant died between hospital discharge and the 30 days following AICU discharge. There were no additional deaths between days 30 and 90 following discharge from AICU.

3.2.3 Timing of echocardiographic assessments

As outlined in the inclusion criteria (section 2.2.1.2), echocardiographic studies were included if they occurred during AICU admission and up to six months following AICU discharge. The majority of studies (n = 137, 77%) occurred during AICU admission, whilst 41 (23%) were recorded following AICU discharge.

3.2.4 Completeness of retrospective data collection

A potential limitation of retrospective analyses is significant amounts of incomplete data. The source(s) of all variables, and the rules for data collection are outlined in the study data collection rules (Appendix 8).

In this study the most common missing data were haemodynamics at the time of echocardiography: blood pressure, heart rate and rhythm. The incidence of other missing variables was low. Table 23 details all missing variables for encountered from all assessments in ELF 2.

Table 23: Missing variables in ELF 2

Missing variable	Number missing (n, % of all echocardiographs)
Blood pressure	64 (36.0%)
Heart rate	57 (31%)
Heart rhythm	55 (30.9%)
SOFA score	15 (8.4%)

Missing variable	Number missing (n, % of all echocardiographs)
SIRS/infection/severe sepsis	12 (6.7%)
Peak inspiratory pressure	5 (2.8%)
Body surface area	4 (2.2%)
Hypertension	2 (1.1%)
Heart failure	1 (<1%)
Mean airway pressure	1 (<1%)
Pressure support	1 (<1%)

3.2.5 Incidence of myocardial depression

As with the ELF 1 study, myocardial depression was defined as a decrease in LVEF ≥5% from the first LVEF recorded during AICU admission. Sixteen participants (34.0%) developed myocardial depression whilst in AICU. Decrease in LVEF was not normally distributed, as assessed by visual inspection of a histogram. The median decrease in LVEF from baseline to first recorded depression was 14.7 % (IQR 7.1 – 22), the range was a 5% to 30% absolute reduction in LVEF. Twelve participants (75%) exhibiting myocardial depression were male. One participant (6%) with myocardial depression was readmitted to AICU. Three participants (18.8%) were admitted to AICU following surgery, the rest were admitted with medical diagnoses.

Six participants (37.5%) were observed to have wall motion abnormalities during all recorded echocardiograms; three demonstrating a single coronary artery territory distribution, the others demonstrated a global impairment of wall motion. All participants with wall motion abnormalities had a visual estimation of LVEF made by a British Society of Echocardiography fellow, as linear measurements can be unreliable in these circumstances.

All participants with wall motion abnormalities had a coronary angiogram during their hospital admission; two participants had mild disease, two participants had significant disease of the left anterior descending coronary artery and one participant had significant disease of the right coronary artery. One participant with global wall abnormalities had a normal coronary angiogram during hospital admission.

Seven participants who developed myocardial depression had a history of cardiac arrest, four of these had a return of spontaneous circulation within five minutes.

At the time myocardial depression was first observed seven (43.8%) participants were being treated with vasoactive therapies, eleven (68.8%) were mechanically ventilated and four (25%) were identified as having severe sepsis.

A comparison of participant descriptors between those that developed myocardial depression and those that did not is given in table 24. Statistical significance between groups were tested for a number of outcome measures, using either the Mann-Whitney U test or Kruskal-Wallis H test, but were not significant between

groups. Finally, the changes in LVEF over time in the ELF 2 study for participants who developed myocardial depression are given in figure 14, and those who did not are given in figure 15.

Table 24: Comparison of ELF 2 participants with and without myocardial depression

	No myocardial depression (n = 31)	Myocardial depression (n = 16)	Statistical significance
Age (years, median, IQR)	62 (42 – 73)	50 (33 – 66)	N/A
Male (n, %)	18 (58%)	12 (75%)	
ICNARC physiology score (mean, standard deviation)	24 (± 9)	21 (± 6)	
APACHE II (mean, standard deviation)	21 (± 7)	18 (± 6)	
Failed extubation (n, %)	6 (19.4%)	6 (37.5%)	
LOS AICU (days, median, IQR)	7 (4 – 23)	9 (3 – 30)	p = 0.87
LOS Hospital (days, median, IQR)	33 (12 – 66)	34 (16 – 51)	p = 0.87
90-day mortality (n, %)	6 (19.4 %)	3 (18.8%)	p = 0.96
Mechanically ventilated (n, %)	23 (74.2%)	13 (81.3%)	p = 1
Duration of mechanical ventilation (hours, median, IQR)	113 (21 – 195)	117 (16 – 461)	p = 0.65

	No myocardial depression (n = 31)	Myocardial depression (n = 16)	Statistical significance
Required only vasopressors (n)	13	8	p = 1
Required only inotropes (n)	1	0	
Required both vasopressor and inotrope (n)	6	2	

Note: Due to the variable timing of echocardiography assessments in ELF 2, the figures below illustrate the changes in ejection fraction over serial studies. The x axes are studies in chronological order, the time of study is not standardised, consequently, the median LVEF is not presented.

Figure 14: Changes in ejection fraction in ELF 2 participants demonstrating myocardial depression in AICU

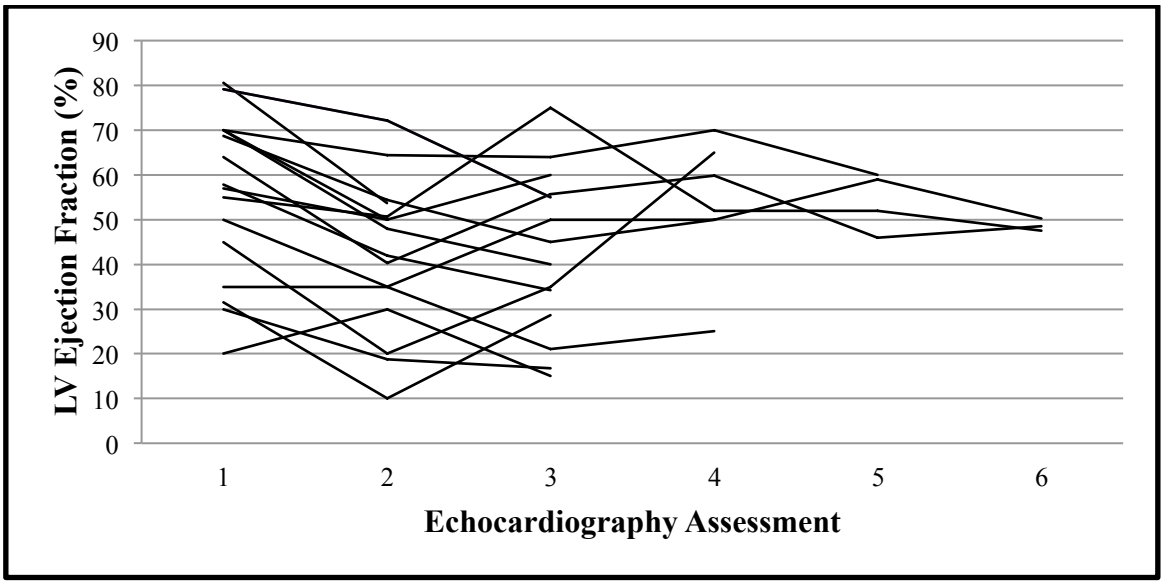
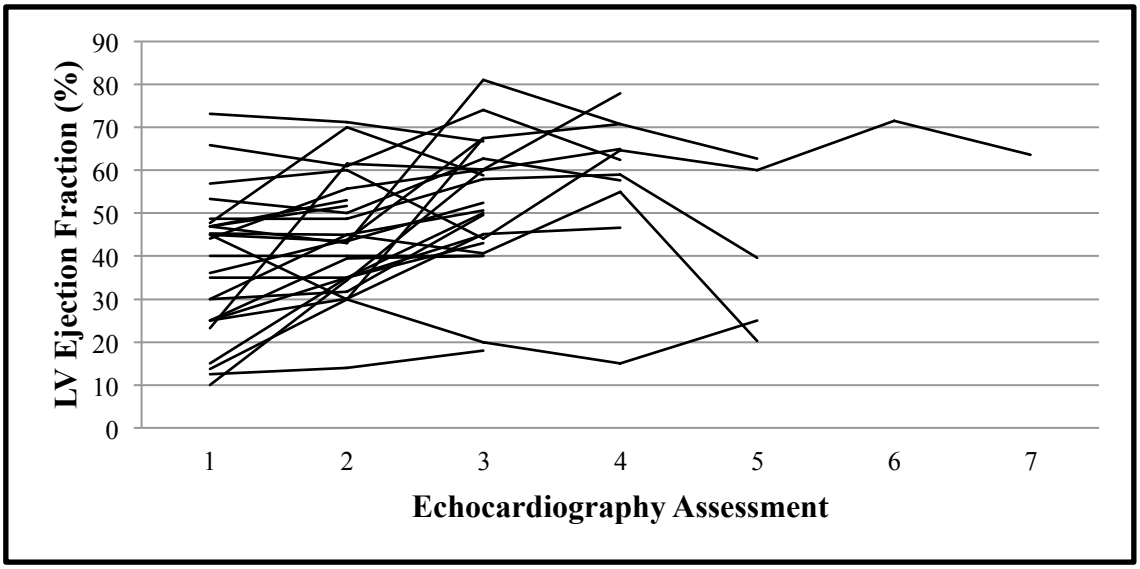


Figure 15: Changes in ejection fraction in ELF 2 participants without myocardial depression observed in AICU



3.2.6 Incidence of recovery of cardiac function

Seven participants (43.8%) displayed some degree of recovery during the follow up period. Two participants made a complete recovery with their LVEF returning to, or exceeding the LVEF first recorded in AICU. Another five participants demonstrated incomplete recovery, with LVEF improving ≥2.5% from the nadir but not returning to AICU baseline. This threshold is beyond the upper bound of the intra-observer variability confidence interval. In those demonstrating recovery, the median improvement in LVEF was 15% (IQR 8.4 – 25.5).

3.2.7 Time course

The median time to the observation of myocardial depression was four days (IQR 1 – 6) from admission to AICU. The median time to recovery, either complete or incomplete, was 11 days (IQR 7 – 33).

3.2.8 Summary

This study observed myocardial depression developing in 34% of participants (n = 16) over the course of the study period. Myocardial depression occurred at a median time of four days following AICU admission. The degree of observed depression was variable, ranging from 5 – 30%. Of these participants, seven demonstrated some degree of recovery during the follow up period.

Six participants with myocardial depression demonstrated wall motion abnormalities. All of these participants had angiograms, which in those with severe coronary artery disease (n = 3), corroborated with the distribution of regional abnormalities. Global wall motion abnormalities was observed in three participants, one of which had a normal angiogram, whilst the other two had minor disease of their left anterior descending artery.

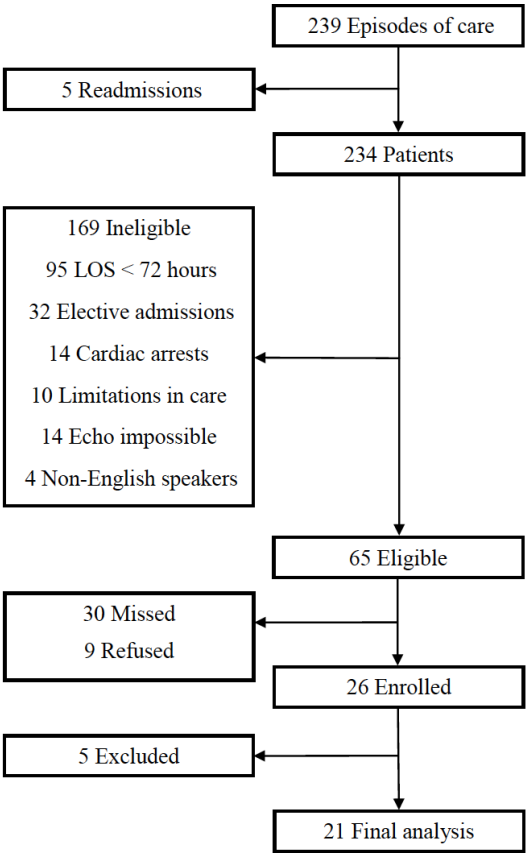
Physiological derangements, as assessed by ICNARC physiology and APACHE II scores, hours of mechanical ventilation, and hospital and AICU length of stay were similar between those with myocardial depression and those without.

3.3 ELF 3

3.3.1 Screening and enrolment

Screening was undertaken between 20th September – 11th November 2014 and 13th January – 25th February 2015. Consecutive enrolment had been previously demonstrated to be unfeasible, owing to staffing constraints, in the ELF 1 study. Therefore, enrolment was therefore undertaken in blocks. During these blocks the researcher visited the AICU daily to screen and enrol participants and undertake echocardiography, as per the study protocol. Conducting the research solely during weekdays would have resulted in missing data, as the protocol stipulates that in participants demonstrating impaired LVEF, echocardiography must be undertaken daily to day ten of AICU stay, or AICU discharge, whichever is earlier. Figure 16 outlines the eligibility and enrolment of the ELF 3 study.

Figure 16: Eligibility and enrolment for the ELF 3 study



Thirty patients were missed enrolments. This was commonly due to difficulties in contacting the appropriate consultee within the necessary time frame. It was not considered appropriate to "cold call" the patient's friends and relatives regarding the research study. The researchers are not involved with the delivery of care, and are therefore not privy to clinical discussions, nor are they in an appropriate position to answer questions posed by friends or relatives. Therefore, the first point of contact the research team had with consultees occurred on the AICU. Five participants voluntarily withdrew from the study.

3.3.2 Assessments and capture

Transthoracic echocardiography was undertaken on 21 participants, with a total of 97 studies recorded. All participants underwent daily TTE for the first three days of AICU admission. If LVEF <55% was demonstrated during this time, then daily echocardiography continued until day ten of AICU stay or discharge, whichever was earlier.

Recorded variables were identical to those collected in ELF 1 and ELF 2 and were subject to the same data collection rules (Appendix 8).

All participants had a minimum of three TTE studies during their AICU admission.

3.3.3 Population

Twenty-one participants were included in the final analysis. Of these, 15 (71%) were male. The median age was 70 years (IQR 58 – 79). All participants were admitted to AICU as an emergency. Six participants (28.6%) were admitted following surgery. Three participants (14%) were transferred to AICU from a hospital outside the Trust, but did not receive prior intensive therapy at their hospitals of origin. Two participants (10%) were readmitted to AICU following participation in the study.

One participant (5%) required transfer to another site for extracorporeal membrane oxygenation (ECMO), 15 (71%) participants required treatment with a vasoactive drug and 16 participants (76%) required mechanical ventilation. Finally, two

participants (10%) underwent coronary angiography, neither demonstrated obstructive lesions.

3.3.3.1 Admission diagnosis

The primary diagnosis at admission to AICU were coded using the ICNARC coding method[165] by trained audit staff. The majority of participants were medical admissions (n = 15, 71%). The primary admission diagnoses for the ELF 3 study are given in table 25.

Table 25: ELF 3 primary AICU admission diagnosis

Admission diagnosis	Frequency (n, %)
Pneumonia	9 (42.9%)
Other	5 (23.8%)
Ruptured abdominal aortic aneurysm	3 (14.3%)
Trauma	2 (9.5%)
Lactic acidosis	2 (9.5%)

3.3.3.2 History of cardiac disease

Table 26 outlines pre-existing cardiovascular disease amongst the ELF 3 population. Data were collected according to the data collection rules outlined in Appendix 8.

Table 26: Prevalence of pre-existing cardiac conditions in ELF 3

Pre-existing cardiovascular disease	Yes (n, %)	No (n, %)
Hypertension	13 (61.9%)	8 (38.1%)
Cardiomyopathy (any)	0 (0%)	21 (100%)
Acute myocardial infarction	1 (4.8%)	20 (95.2%)
Heart failure	1 (4.8%)	20 (95.2%)
Coronary Artery Bypass Graft	0 (0%)	21 (100%)
Uncorrected valvular disease	1 (4.8%)	20 (95.2%)
Valvular replacement	2 (9.5%)	19 (90.5%)
Cardiac arrest	0 (0%)	21 (100%)
Arrhythmia	3 (14.3%)	18 (85.7%)

One participant had a history of a prior AMI, whilst another had a history of heart failure (NYHA classification unknown). Two participants had a prior history of severe valvular disease but had undergone replacement in a previous hospital admission. The severity of the valvular pathology in the participant with uncorrected disease is unknown. No participant had a history of cardiomyopathy, coronary artery bypass grafting or cardiac arrest.

3.3.3.3 Length of stay

The length of stay data was not normally distributed. The median length of stay in AICU was 7 days (median 7.0, IQR 4 – 10). Length of stay was calculated from date and time of admission to date and time of discharge. The median hospital length of stay was 18 days (median 18.0, IQR 12 – 29), this was calculated from the date of hospital admission to the date of cessation of acute hospital care.

3.3.3.4 AICU risk adjustment tools: ICNARC and APACHE II

The ICNARC physiology score and the APACHE II score were extracted/calculated as outlined in the study data collection rules (Appendix 8). These scores provide a description of the severity of illness of the population. Data were inspected by histogram and both scores were normally distributed. The mean ICNARC score was 19 (SD: 7) and the mean APACHE II score was 24 (SD: 7).

3.3.3.5 Mortality

Three participants (14.3%) did not survive their admission to hospital. Two died whilst in AICU and one died unexpectedly following AICU discharge. No further participants died during the follow up period (90 days following discharge from AICU).

3.3.4 Missing data

Missing values were excluded from the analysis. One participant missed a TTE study during AICU stay, due to staff sickness. Two participants with persisting impairment at AICU discharge declined follow-up studies.

3.3.5 Incidence of myocardial depression

Myocardial depression was defined as a decrease in LVEF ≥5% from the first LVEF recorded in AICU, the same definition used in ELF 1 and ELF 2.

Seven (33.3%) participants (five of which are male) demonstrated myocardial depression during the study period. Two participants were admitted to AICU following surgery. The absolute decrease in LVEF to the nadir ranged between 5% and 30% amongst participants. The median decrease in LVEF at the onset of myocardial depression was of 6.5% (IQR 5 – 10).

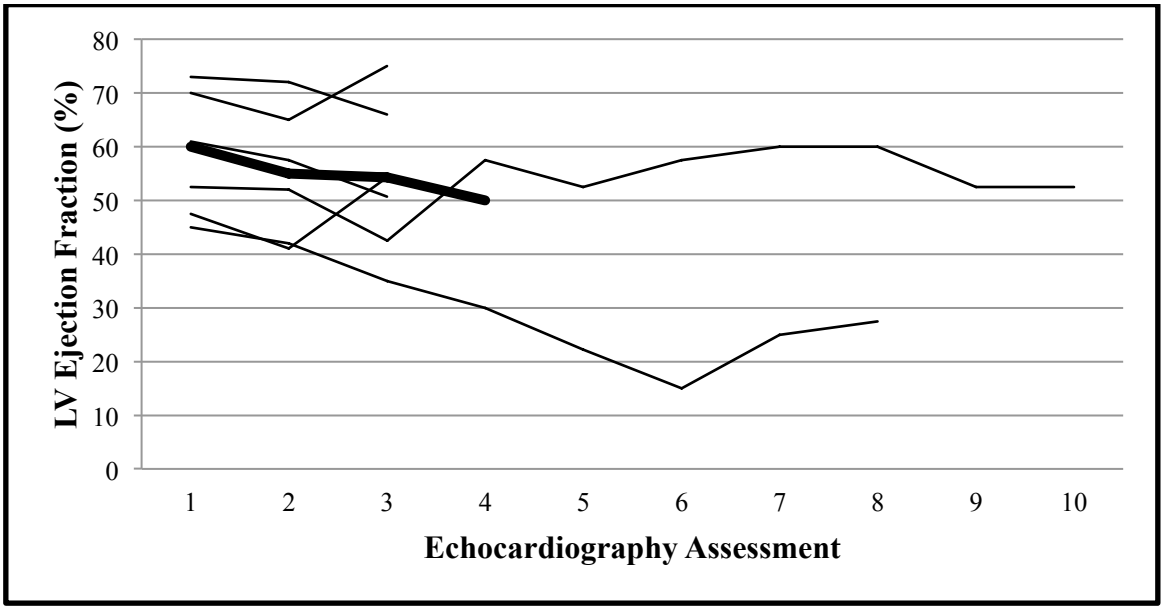
Two participants with myocardial depression demonstrated wall motion abnormalities. One participant had wall motion abnormalities corresponding to a single coronary artery territory throughout AICU admission, the other developed a global hypokinesia at day six of AICU admission, which persisted at AICU discharge (day eight). In this participant, the onset of the global hypokinesia corresponded with LVEF nadir. Neither participant had a history of cardiac arrest, acute myocardial infarction or underwent angiography.

At the time myocardial depression was observed three participants required mechanical ventilation, two were identified as having severe sepsis and one participant required vasopressor therapy.

Table 27 compares population descriptors of severity of illness, length of stay, mortality, artificial ventilation and vasoactive drug requirements between those that demonstrate myocardial depression and those that do not. Statistical significance between groups were tested for a number of outcome measures, using either the Mann-Whitney U test or Kruskal-Wallis H test, but were not significant between groups.

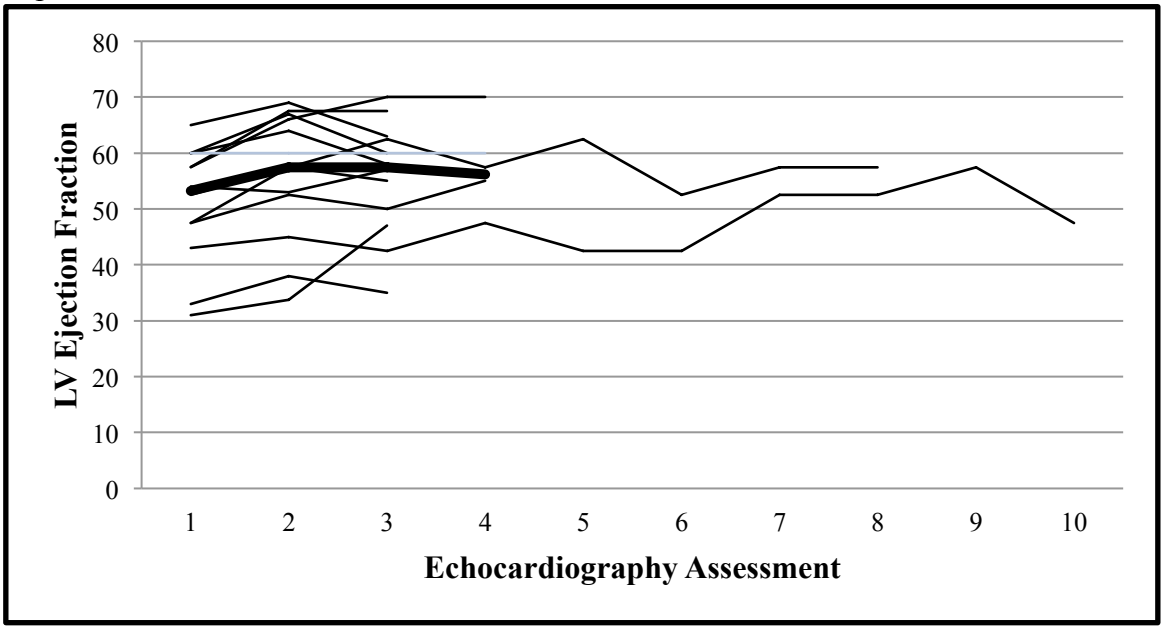
Figure 17 demonstrates the changes in ejection fraction in participants demonstrating myocardial depression and figure 18 plots the changes in ejection fraction in those without myocardial depression.

Figure 17: Changes in ejection fraction in ELF 3 participants demonstrating myocardial depression in AICU



The bold line is the median ejection fraction of the cohort.

Figure 18: Changes in ejection fraction in ELF 3 participants without myocardial depression observed in AICU



The bold line is the median ejection fraction of the cohort.

Table 27: Comparison of ELF 3 participants with and without myocardial depression

	No myocardial depression (n = 14)	Myocardial depression (n = 7)	Statistical significance
Age (median, IQR)	72 (58 – 81)	66 (40 – 78)	N/A
Male (n, %)	10 (71.4%)	5 (71.4%)	
ICNARC physiology score (mean, standard deviation)	17 (± 7)	20 (± 8)	
APACHE II score (mean, standard deviation)	23 (± 6)	25 (± 10)	
Failed extubation (n, %)	3 (21.4%)	2 (28.6%)	
LOS AICU (days, median, IQR)	7 (5 – 9)	4 (3 – 15)	p = 0.65
LOS Hospital (days, median, IQR)	17 (11 – 26)	19 (15 – 36)	p = 0.39
90-day mortality	2 (14.3%)	1 (14.3%)	N/A
Mechanically ventilated (n, %)	11 (78.6%)	4 (57.1%)	p = 1
Duration of mechanical ventilation (hours, median, IQR)	55 (11 – 92)	43 (0 – 363)	p = 0.82
Required only vasopressors (n) Required only inotropes (n) Required both vasopressor and inotrope (n)	9 0 1	2 0 1	p = 1

3.3.6 Incidence of recovery of cardiac function

Myocardial recovery was defined as complete or incomplete. Complete recovery was a defined as the LVEF returning to AICU baseline or greater. Incomplete recovery was improvement in LVEF ≥2.5% from the nadir, but not returning to AICU baseline. This threshold is greater than the upper bound of intra-observer variability confidence interval.

Five participants (71.4%) demonstrated complete recovery during the study period. The median increase in LVEF was 13.3% (IQR 10 – 32.5%). Four demonstrated recovery during AICU admission and one had made a full recovery of both LVEF and global wall motion abnormalities by the follow up assessment (73 days following AICU discharge). One additional participant demonstrated partial recovery, with their LVEF increasing by 10% from the nadir, but not reaching their AICU baseline.

Two participants with myocardial depression persisting at AICU discharge declined follow up assessment.

3.3.7 Time course

Median time to development of myocardial depression was three days (IQR 2 – 4). Median time to recovery from myocardial depression occurring in AICU was day four (IQR 3 – 7). One participant demonstrated a delayed recovery, with return to baseline function observed at the follow up appointment, 73 days following AICU discharge.

3.3.8 Summary

The incidence of myocardial depression in the ELF 3 study was 33.3% (n = 7). Five (71.4%) of the affected participants are male. No participant that developed myocardial depression was admitted to AICU with sepsis, although two participants met the criteria[145] at the time nadir in LVEF was observed. Two participants demonstrated wall motion abnormalities, one throughout the entire duration of AICU stay which corresponded to a single coronary artery territory, the other developed global hypokinesis at day six of AICU stay which persisted at discharge (day eight), but had resolved by the follow up study (73 days later). Only three participants with myocardial depression required vasoactive therapy.

Whilst the sample size is too small to undertake meaningful statistical analysis between those with myocardial depression and those without, similar severity of illness scores, hospital length of stay and numbers of participants failing extubation was observed.

3.4 Summary of epidemiology results

The ELF 1, ELF 2 and ELF 3 studies presented report the incidence, time course and recovery of myocardial depression in critically ill adults. A comparison of the population and key findings of the three studies is given in table 28.

Table 28: Comparison of the ELF studies

Variable	ELF 1	ELF 2	ELF 3
Sample size (n)	49	47	21
Male (n, %)	35 (69%)	30 (64%)	15 (71%)
Age (years, median, IQR)	66 (47 – 75)	59 (41 – 70)	70 (58 – 79)
Admitted to AICU following surgery (n, %)	8 (16%)	6 (12.8%)	6 (28.6%)
APACHE II (mean, SD)	20 ± 7	20 ± 7	24 ± 7
ICNARC physiology score (mean, SD)	19 ± 7	24 ± 8	19 ± 7
AICU LOS (days, median, IQR)	6 (4 – 14)	8 (4 – 23)	7 (4 – 10)
Hospital LOS (days, median, IQR)	22 (11 – 42)	33 (14 – 58)	18 (12 – 29)
Incidence of myocardial depression (n, %)	8 (16.3%)	16 (34.0%)	7 (33.3%)
Decrease in LVEF at the time myocardial depression first observed (median, IQR)	10.5 (6.5 – 21)	14.7 (7.1 – 22)	6.5 (5 – 10)

Variable	ELF 1	ELF 2	ELF 3
Decrease in LVEF from AICU admission to nadir (median, IQR)	14.0 (6.9 – 24.8)	17.7 (10.8 – 24.0)	10.0 (6.5 – 10.3)
Myocardial depression observed on AICU day (median, IQR)	4 (3 – 6)	4 (1 – 6)	3 (2 – 4)
Incidence of myocardial recovery (n, %)	4 (50%)	7 (43.7%)	5 (71.4%)
Median improvement in LVEF (median, IQR)	20.2 (10.3 – 30.7)	15.0 (8.4 – 25.5)	13.3 (10 – 32.5)
Wall motion abnormalities (n, %)	1 (12.5%)	6 (37.5%)	2 (28.6%)

The populations of the ELF studies were similar. The gender composition, AICU length of stay and severity of illness, as assessed by APACHE II and ICNARC physiology score, were alike (shown in table 28). The median age at admission to AICU, however, was slightly younger for the ELF 2 study, in comparison with the ELF 1 and ELF 3 studies.

Myocardial depression was defined as an absolute reduction in LVEF ≥5%. The reported incidence of myocardial depression across the ELF studies was 16.3%, 34% and 33.3% in ELF 1, ELF 2 and ELF 3, respectively.

The incidence in the ELF 2 and ELF 3 studies is nearly identical, however, the incidence in the ELF 1 study was much lower and may be potentially attributed to the timing of assessments. The ELF 1 study undertook assessments at day one, between days three to five of AICU admission, at AICU discharge and at three months following AICU discharge. The median day to the development of myocardial depression was day four of AICU admission. Therefore, participants may have had an echocardiogram at day three, but subsequently developed myocardial depression, resulting in an under-reporting of the incidence.

The day to development of myocardial depression was similar across the studies, with it typically occurring around days three to four of AICU admission. This is interesting, as the timing of the ELF 2 echocardiograms were largely dictated by clinical need, whereas the timing of the echocardiograms in the ELF 1 and ELF 3 studies were set by protocol.

Across the studies, the median decrease in LVEF from AICU admission at the time myocardial depression was first observed ranged between 6.5 – 14.7%, whilst the median decrease to the nadir ranged between 10.0 – 17.7%. The ELF 3 study reported lower absolute decline in LVEF for both the first observation of myocardial depression and the nadir (table 28).

The incidence of recovery from myocardial depression varied between 43.7 – 71.4% across studies. This reversibility demonstrated in the ELF 3 study (71.4%) is similar to other studies of general AICU patients, which reported reversibility in

76%[70] and 77%[60] of participants. The incidence of reversibility in the ELF 1 and ELF 2 studies, however, was much lower, 50% and 43.7%, respectively.

The degree of recovery of LVEF from the nadir was similar across studies, with a median improvement of 20.2%, 15.0% and 13.3% in ELF 1, ELF 2 and ELF 3, respectively. All studies reported a large range in the degree of recovery observed amongst participants.

Finally, wall motion abnormalities were common. Across the 31 participants demonstrating myocardial depression, nine (29%) demonstrated contraction abnormalities. Although, in at least a third of these participants this is likely attributable to pre-existing cardiovascular disease, as the pattern of contraction dysfunction follows the distribution of severe obstructive disease demonstrated by angiography, or prior history of acute myocardial infarction.

To date, there is no way to predict which patients will develop myocardial depression, nor who will recover. Consequently, this area will be considered further in the following chapters.

3.5 Alternative approaches to describing epidemiological features

The aim of these projects was to identify the incidence and natural history of myocardial depression occurring in the general population of patients experiencing critical illness. Myocardial depression was defined as a decline in LVEF ≥5% from

AICU baseline. The incidence was described with reference to myocardial depression occurring during admission to AICU.

Using an absolute change in ejection fraction, rather than a threshold, mitigates some major problems caused by using a classification method. Nevertheless, as the onset of critical illness cannot be definitively identified, it is possible that some patients were at the nadir of their LV systolic function when the baseline AICU study was performed.

Consequently, in the interests of completeness, the incidence of patients with a LVEF <55%, who then subsequently demonstrated an improvement ≥2.5% during the study period, was determined. Using this approach, myocardial depression (and recovery) was observed in 28.6% (n = 14), 53.2% (n = 25), 33.3% (n = 7) in ELF 1, 2 and 3, respectively. As discussed earlier, the time course of myocardial depression cannot be described, as it is unknown if the depression (LVEF <55%) on day one is the nadir.

Furthermore, the ELF studies described the incidence of myocardial depression observed whilst the patient was critically ill in AICU. This approach attempted to relate the depression in systolic function to critical illness and not to potential confounders.

Whilst this approach results in a description of changes observed during AICU admission, it will not identify latent myocardial depression that may occur during following AICU discharge. Therefore, in the interests of completeness of reporting

the actual incidence related to critical illness, the incidence of myocardial depression occurring beyond AICU discharge was determined.

These data were available for ELF 1 as AICU discharge and follow up studies were conducted. This demonstrated that nine participants (18.4%) demonstrated a decline in LVEF ≥5% occurring following AICU discharge, occurring at a median time of 21 days (IQR 8 – 309) following AICU discharge. Therefore the total incidence of myocardial depression in the ELF 1 study is 35%. Similarly, these data were available to for ELF 2 as any echocardiography conducted up to six months following AICU discharge were included in the study. Eight participants (17%) demonstrated a decline ≥5% following discharge from AICU, occurring at a median of 20 days following AICU discharge (IQR 2 – 24). Therefore the total incidence of myocardial depression in ELF 2 is 51%. These data were unavailable for ELF 3 as only patients who demonstrated myocardial depression were followed beyond AICU discharge.

Chapter IV: Epidemiology discussion

4.0 Overview

This chapter contextualises the findings and the novelty of the results from the ELF studies. The similarities and differences between the findings and the existing literature are discussed. The strengths of the study design and novelty of the descriptors provided by the study are considered. Finally, the limitations of results and areas for future work are discussed.

4.1 Incidence of myocardial depression

The reported incidence of myocardial depression in critically ill patients on general AICUs ranged between 6[71] – 95[70]%. As discussed in section 1.3.5, the heterogeneity in the reported incidence likely stems from lack of agreement of the definition of myocardial depression, and differences in the timing of LV function studies, and selective sampling.

The majority of studies[2,7,19,22–25,27,28,75] have undertaken echocardiography within 24 hours of AICU admission, classified patients as demonstrating myocardial depression based on a fixed ejection fraction threshold rather than a change, and then tracked the changes in LV systolic function of these patients. This method is problematic in establishing the true incidence of myocardial depression in critical illness; as observed by Pulido[35] and Vieillard-Baron[25], approximately 20% of patients with myocardial depression develop it beyond the first 24 hours of AICU

admission. Furthermore, this approach may include patients with a chronically reduced LVEF, rather than capturing acute depression in LVEF occurring during critical illness.

The ELF studies determined the incidence of myocardial depression occurring during AICU admission. The term "critical illness" is ill defined and there is no definitive way to determine its onset or resolution. Consequently, the method taken in the ELF studies, to determine the incidence of myocardial depression occurring in AICU, represents a pragmatic approach to the nebulous definition of critical illness and the desire to characterise the changes in LV systolic function that occur during critical illness, rather than due to other processes.

This approach has limitations, however, and may miss patients who develop delayed myocardial depression whilst still experiencing critical illness but are sufficiently well to be discharged from AICU. As described in section 3.5, myocardial depression was also observed following AICU discharge in nine participants at a median duration of 21 days, and in nine participants at a median of 20 days, in ELF 1 and ELF 2, respectively. These data are unavailable for ELF 3 due to the study design.

Whilst it is possible that the delayed myocardial depression observed in ELF 1 and 2 could be related to critical illness, with increasing time between discharge from AICU and the onset of depression, that relationship becomes less clear. Whilst the approach taken in the ELF studies has obvious limitations, the changes in LV

systolic function observed during AICU are arguably more likely to be attributable to critical illness than those observed weeks after discharge.

Some authors defined myocardial depression using an LVEF threshold of <45%[25,29] or <50%[8,30,32] and others as <55%[28,33], but using a threshold presents problems. Firstly, using a threshold can inappropriately classify patients with a stable, but impaired, baseline LVEF as demonstrating myocardial depression that does not recover. To mitigate this risk, some studies[7,8,17,27,29,30,32,33,35,36,60,71] have excluded patients with pre-existing cardiac disease. These patients, however, do not necessarily have impaired LV systolic function. Additionally, this approach will not capture patients with an impaired LV systolic function who then subsequently develop further myocardial depression. Furthermore, the definitions and methods of establishing pre-existing cardiac disease are infrequently described in the literature. Finally, this approach does not exclude occult cardiac disease, which in the medical AICU has been reported to be present in up to 36%[170] of patients.

Whilst consensus guidelines[94] do exist that classify ejection fraction measurements into "normal", "mild", "moderate" or "severe", these values were derived from outpatients and their relevance and applicability to critically ill patients remains unknown[171].

Consequently, these problems were considered when defining myocardial depression for the ELF studies. Intra and inter-observer variability were determined, and a decision reached to define myocardial depression as >5% decline in LVEF

from baseline, which is greater than the confidence interval of intra-observer variability.

Intra-observer variability is of paramount importance in these studies as the definitions of myocardial depression and recovery hinge on changes in LVEF over time. Low intra-observer variability was essential as a single researcher (VT) was responsible for interpretation of the vast majority of serial echocardiography data, which was used to determine the presence of myocardial depression and recovery. Intra-observer variability was determined from 20 anonymised echocardiograms selected by the BSE fellow. These studies were read by the researcher, then stripped of their measurements and re-anonymised by the BSE fellow and represented to the researcher three months later for interpretation. The three-month interval was selected to minimise recall bias. The intra-observer variability on repeated measures taken three months apart was not significant, with a mean difference in ejection fraction -0.52% (95% CI -3.1 – 2.1).

In cases where RWMA were known or suspected, a BSE fellow reported a visual estimate of ejection fraction, as linear measurements can be unreliable in this setting. Consequently, assessment of inter-observer variability between VT and the BSE fellow was necessary, which demonstrated that the mean difference in measurements of ejection fraction was -4.1% (95% CI -8.3 – 0.2), with the BSE fellow more likely to report a lower ejection fraction than the researcher. Reliability of changes in serial measurements is essential to appraise the validity of study findings.

Currently, there is no agreed clinically significant decline in ejection fraction, but a 5% threshold has been used extensively by other researchers[148,150–157,167,168]. Serial echocardiography was conducted on all participants enrolled in the ELF studies, to document changes in ejection fraction over time. Pre-existing cardiac disease was documented, but did not preclude enrolment in the ELF studies.

The incidence of myocardial depression in the three ELF studies (defined as a decline in LVEF ≥5% from first recorded echocardiogram in AICU) was between 16 – 34%. Regional wall motion abnormalities were observed in nine participants with myocardial depression. In at least one third of cases, these contraction abnormalities can likely be explained by pre-existing cardiovascular disease, demonstrated by an obstructive lesion or a history of AMI in the corresponding coronary artery distribution.

These results are similar to those seen by Park[60] (incidence 28%), who undertook a prospective observational study in a medical AICU to identify patients with LV mid/apical RWMA, with an LVEF <50%. There are two key differences in study design between Park[60] and the ELF studies; Park[60] excluded surgical patients and patients with pre-existing cardiac disease (not defined) and considered patients to demonstrate RMD if RWMA affected the mid/apex of the LV. As discussed in section 1.2.1, the RWMA pattern observed in RMD is variable, and inclusion only of mid/apical RWMA pattern in the study protocol overlooks the basal variant of RMD[172] and therefore the approach taken by Park may under report the true incidence of myocardial depression.

The results of the ELF studies are, however, inconsistent with two other studies undertaken in the general adult critically ill population. Sharkey[70] reported the incidence of RMD to be 95% in their cohort, although the discrepancy between this reported incidence and that observed in the ELF studies could likely be attributed to a potential selection bias. Inclusion criteria in the retrospective analysis by Sharkey[70] mandated that patients demonstrate ECG changes (deep T wave inversion on precordial leads) and RWMA. As described in section 1.2.1.1, ECG changes and RWMA are recognised features, albeit non-specific, of myocardial depression. Furthermore, patients were identified for inclusion to the study when referred to the cardiology department. A selection bias of only including patients exhibiting features associated with myocardial depression and referred for cardiology opinion may explain the very high incidence reported by the authors.

Ruiz-Bailen[89] reported the incidence of myocardial depression to be 6% (33 of 574) in their study of critically ill patients. These results are inconsistent with those reported in the ELF studies, but can likely be explained by differences in the timing of study assessments and inclusion/exclusion criteria. Ruiz-Bailen[89] undertook echocardiography on patients admitted to the critical care unit that did not have a history of cardiovascular disease (not defined) and excluded patients with conditions associated with RMD e.g. sepsis. Serial echocardiography was undertaken, but the intervals between assessments were large (minimum of a week), which may have resulted in missed observation of RMD. This is further supported by data from the ELF studies, which demonstrate myocardial depression occurring

in the early stages (within a week) of critical illness (discussed further in section 4.2.1).

Seven participants who developed myocardial depression had a history of cardiac arrest. The myocardial depression observed in these participants is unlikely to represent post cardiac arrest myocardial stunning as this was observed at mean of six days following AICU admission. This is well beyond the anticipated onset of post-arrest myocardial stunning, which has been observed in the minutes following coronary artery occlusion[173–175].

It has been argued that the decreased systemic vascular resistance observed in severe sepsis sufficiently decreases the afterload of the LV so, ostensibly, the systolic function appears normal[176]. Consequently, when vasopressors are administered the increase of the LV afterload unmasks impaired systolic function[45]. Only eight of the 31 participants with myocardial depression demonstrated sepsis during their AICU stay, and the pattern of myocardial depression, vasopressor administration and sepsis was only observed in four.

This argument has also been used to explain the wide range of incidence reported in septic myocardial depression. Vieillard-Baron[45] argued that measures of LV systolic function undertaken before full resuscitation may show an ostensibly well functioning LV, but this is due to the significant reduction in afterload induced by sepsis. This is unlikely to have influenced the results reported in the ELF studies. Firstly, sepsis was uncommon, affecting only eight of 31 participants, secondly, the echocardiograms undertaken for ELF 1 and ELF 3 were for research purposes and

conducted when the participant was haemodynamically stable. Finally, whilst the ELF 2 studies were predominantly conducted for a clinical indication and it is unknown if the participant was haemodynamically stable, the incidence of myocardial depression in this study was effectively the same as the ELF 3 study (34% vs. 33%).

To date, the incidence of myocardial depression occurring in critical illness has been unclear. Few studies have been undertaken in the general critically ill population, with the majority of literature describing sub-populations within critical care. Previous studies have excluded patients with cardiac disease[7,8,17,27,29,30,32,33,35,36,60,89] and conditions associated with the development of myocardial depression[89] (e.g. sepsis). Additionally, limitations in the methods of these studies may have resulted in under reporting the incidence.

Consequently, The ELF studies address this gap in the literature by reporting the incidence that is generalisable beyond sub-populations of critical illness, and including those with pre-existing cardiac disease. The definition used in the ELF studies aims to mitigate some of the pitfalls associated with using a threshold to identify myocardial depression.

4.2 Natural history of myocardial depression

4.2.1 Time to development of myocardial depression

The time to development of myocardial depression was similar across the three ELF studies. Myocardial depression was observed on day four (median) of AICU stay in

both ELF 1 (IQR 3 – 6) and ELF 2 (IQR 1 – 6) studies, and day three in ELF 3 (IQR 2 – 4). Furthermore, a delayed pattern of depression was observed in eight participants in ELF 1 (median 21 days, IQR 8 – 309) and in nine participants (median 20 days IQR 2 – 24) in ELF 2.

In the ELF 1 and ELF 3 studies, the timing of assessments was set by protocol, but in ELF 2 they could take place at any time. Thus in effect the ELF 2 results show that the time to onset of myocardial depression in the ELF 1 and ELF 3 studies was not simply a function of assessment schedules.

The literature describing the time to development of myocardial depression is sparse, with only two studies[25,60] presenting these data. Park[60] and Vieillard-Baron[25] both reported that myocardial depression occurs within 24 hours of AICU admission in the majority of cases, but a delayed onset pattern was observed between days two and three in 19.2%[60] and 20.9%[25] of patients. Whilst both of these studies used a threshold of LVEF to define myocardial depression, the limitations of which are previously described, they continued to undertake surveillance echocardiography in all eligible patients.

This "delayed" depression was observed much earlier than the delayed depression seen in the ELF 1 and 2 studies, but given the interval between onset of myocardial depression and discharge from the critical care unit, the relationship between critical illness and the delayed onset of myocardial depression observed in the ELF 1 and 2 studies remains speculative.

Finally, the study by Vieillard-Baron was undertaken in patients with sepsis whereas the study by Park, whilst undertaken in the general AICU population, excluded surgical patients and those with pre-existing cardiac disease. Consequently, the generalisability to the broader critically ill population remains uncertain.

The ELF studies addressed this gap in the literature by undertaking serial assessment of LV systolic function using echocardiography across a critically ill cohort and documenting changes over time. By including participants with pre-existing cardiovascular disease and describing the general critically ill cohort, not just a sub-population, the ELF studies provide a description of the time to the development of myocardial depression observed in critical illness.

4.2.2 Degree of myocardial depression

The ELF studies defined myocardial depression as an absolute decrease in LVEF ≥5% from baseline. This threshold is double the intra-observer variability confidence interval of the researcher responsible for interpreting the majority of studies (section 2.5.9). Consequently, the changes in LVEF reported in the ELF studies are highly likely to represent true changes in LV systolic function, rather than measurement variation. The threshold of a 5% change in LVEF has also been used extensively in other studies[148,150–156,167,168] assessing changes in LV systolic function over time. The median absolute reduction in LVEF when myocardial depression was first observed in the ELF 1, 2 and 3 studies was 10.5% (IQR: 6.4 – 21.0), 14.7% (IQR: 7.1 – 22) and 10.0% (IQR: 6.5 – 10.0), respectively.

There are two potential confounders when interpreting changes in LVEF over time: measurement error (intra/inter observer variability) and loading conditions. Whilst some studies have described the changes in LVEF observed in their cohorts, intra/inter observer variability data is scarcely reported, and therefore the reliability of the reported reductions in LVEF cannot be interpreted. No paper identified from the literature review (section 1.3) reported both the intra/inter observer variability and the degree of myocardial depression observed.

A recognised limitation of LVEF is that it is a load dependent measure, and therefore influenced by changes in preload and afterload e.g. a hypovolemic patient may, ostensibly, have a normal ejection fraction, that, when adequately resuscitated, does not reflect the true LV function. Ideally, changes in LVEF (as a indicator of contractility) are contextualised by considering the loading conditions of the patient. Whilst some researchers[25,30] have attempted to mitigate the variability of loading conditions on ejection fraction, these approaches are inconsistent. Many studies[2,7,8,27–29,32,33,36,60,70,89] simply do not attempt to control for loading conditions, and recognise this as a limitation of their results. The precise effect of loading conditions and interventions (e.g. mechanical ventilation) on absolute values of LVEF is unquantified[177].

These results from the ELF studies are, to the best of our knowledge, the first to reliably describe the degree of LVEF depression in RMD. The degree of myocardial depression observed across all three studies is beyond intra-observer variability. Whilst LVEF is load dependent, there is no consistent approach for

controlling loading conditions. Finally, to date, the effect of therapies used in critical care on echocardiographic parameters remains unquantified[178].

4.2.3 Recovery from myocardial depression

Recovery from myocardial depression was classified as either complete (return to baseline LVEF or greater) or partial (an improvement from the nadir >2.5% but not returned to baseline).

Across the ELF studies, complete recovery was observed in less than 29% of participants with myocardial depression, whilst partial recovery was observed in less than 22% of participants with myocardial depression. In those that recovered, the median increases in LVEF from the nadir were 20.2% (IQR 10.3 – 30.7), 15% (IQR 8.4 – 25.5), 13% (IQR 10.3 – 32.5) in ELF 1, ELF 2, and ELF 3, respectively. In the ELF 1 study, the median time to recovery was eight days (IQR: 6 – 23), excluding the outlier in which recovery was observed at 105 days. This is slightly earlier than the median of 11 days (IQR 7- 33) reported in the ELF 2 study, but this could potentially be explained by the variable timing of studies included in the ELF 2 retrospective analysis. Similarly, an earlier recovery (median day four, IQR: 3 – 7) was seen in the ELF 3 study, again excluding the outlier in which recovery was observed at 73 days following AICU admission.

The natural history of myocardial depression is difficult to establish from the existing literature. Many studies[7,27,33,35,36,89] report an improvement of LV systolic function over time, but do not report on the clinical course of individual patients. In

the studies that have reported these data, the natural history remains unclear. Some authors[17,25,28,30] have reported 100% recovery, others[2,60,70] (including the ELF studies) have reported mixed findings on the resolution of myocardial depression, and one[33] paper reported no recovery. There is not a clear explanation for the differences in observed recovery amongst studies, whilst this is possibly explained by the variable follow up periods amongst studies, it is an area for future research.

In those that demonstrated recovery, the median increase in LVEF from the nadir observed in the ELF studies was 20.2% (IQR 10.3 – 30.7), 15.0% (IQR 8.4 – 22.5), and 13.0% (IQR 10.0 – 32.5) in ELF 1, ELF 2, and ELF 3, respectively. In the literature, the absolute improvement of LVEF is scarcely reported, with only two[35,71] studies reporting the median improvements in LVEF observed in recovery. The median absolute improvement in LVEF was reported as 19% by Pulido[35] and 26% by Ruiz-Bailen[71], which are not dissimilar to that reported in the ELF studies.

To conclude, the time course, and pattern of recovery observed in the ELF studies are congruent with existing reports[30,70]: the majority of participants that recovered from myocardial depression did so by AICU discharge, whilst a smaller number demonstrated a delayed recovery. The degree of myocardial depression (with intra-observer variability data) was, to the best of our knowledge, reliably reported for the first time. The median improvement in LVEF observed in the ELF studies is similar to the values reported by other authors[35,71].

4.3 Limitations

As with all research, these studies have limitations. They were undertaken at a single tertiary referral site in the general adult Intensive Care Unit. The recruitment site is large and has specialised neurological and cardio-thoracic intensive care units, but due to staffing constraints, neither served as recruitment units. Consequently, cardio-thoracic and neurological disorders may be under-represented in the study case-mix. Patients from a non-English speaking background were excluded, which may result in an under-representation of minority groups in the included case-mix.

The John Radcliffe AICU admits approximately 800 patients annually. Ostensibly, this throughput, coupled with the incidence of myocardial depression, presents ample patients to provide a comprehensive and generalisable description of the epidemiological features. This, however, is not so straightforward. As described earlier (section 4.2.1), the onset of myocardial depression occurs around days three to four of AICU admission, yet nationally the median length of AICU stay is around two days[97–99]. Consequently, the number of patients available to facilitate a comprehensive description of myocardial depression is far less than the number patients of admitted to AICU. Subsequently, patients who have longer AICU admissions are likely to represent a more acutely unwell cohort. Therefore, the participants recruited to the ELF studies are a selected population.

The sample sizes of the ELF studies are small, but reflect the constraints of a single-operator study. Despite this, the sample sizes are on par or greater than a substantial number of studies[7,8,17,25,27–30,33,36,70] reported in the literature.

Nevertheless, the results of the ELF studies are at high risk of selection bias. The single centre, single operator, non-sequential cohort of patients that were admitted for a minimum of 72 hours represent a select group, and this must be considered when interpreting these results. Furthermore, whilst the size of the ELF studies are on par, or greater, than many in the field, the total capture only represents around 10% of eligible patients.

Furthermore, as a minimum length of stay of 72 hours in AICU was necessary to facilitate serial echocardiography data, included patients may reflect a more unwell cohort. Whilst this reflected a pragmatic decision in order to support serial studies to capture changes in LV function over time, the results from ELF 1 and 3 are consistent with the retrospective dataset, which did not have the minimum 72 hours length of stay inclusion criteria. This provides some reassurance that the findings of the ELF 1 and ELF 3 studies are not purely a function of a protocol driven by pragmatic decisions.

Whilst bias is unavoidable in research, observational cohort studies (such as ELF) are particularly prone to selection bias, and the limitations the ELF studies are not unique. Undoubtedly some sources of bias may have been ameliorated by alterations to the study design, but these compromises reflect the single operator nature of a DPhil project. Furthermore, whilst in hindsight some decisions may be

different, these choices reflect the scant epidemiological data that was available at study design, which ultimately motivated the work.

Ejection fraction is influenced by preload and afterload. Furthermore, the effect of therapies used in AICU, such as mechanical ventilation and inotropes/vasopressors, on echocardiographic measurements remains unquantified[178]. These are recognised limitations of this measure, but currently there is no consensus on how to control or account for these influences.

A linear method of calculating LVEF was used, which can be unreliable measure in the presence of RWMA. Consequently, participants with a history of significant cardiac disease had their echocardiograms reviewed by a BSE fellow, and a visual estimation of LVEF was made if the linear measurements were not congruent with the clinical picture. Additionally, this process was followed in participants without a cardiac history but who were suspected of demonstrating RWMA on echocardiography. Although these steps were taken, it is possible that some participants demonstrating RWMA were missed.

As it stands, there is no agreement on what constitutes a clinically significant decrease in LVEF. Although the threshold of a 5% decrease has been used in other studies[148,150–156], given the potential for loading conditions to influence LVEF, it may be argued that a higher threshold of impairment may have been warranted. Across all three studies only three participants (one from each study) demonstrated a depression of 5%. The median decrease in LVEF to the nadir reported in the ELF

studies was between 10 – 17.7%, which suggests that a higher threshold of impairment would not greatly affect the reported incidence.

Additionally, reporting of echocardiogram measures was not blinded, which may have introduced bias. Finally, whilst the intra-observer variability of the research responsible for the vast majority of echocardiogram interpretation (VT) was quantified, the intra-observer variability of the BSE fellow was not assessed.

4.4 Future work

The incidence of RMD in critical illness reported in the ELF studies is between 16 – 34%. Consequently, it would be reasonable to suggest that a relatively large sample of patients demonstrating myocardial depression could be identified from a large single-centre AICU. This, however, would extremely labour-intensive as this would require serial echocardiography to identify and characterise changes in LV systolic function. Until echocardiography becomes a routine part of daily assessment in the AICU, it is logical that future work on the epidemiological features of RMD should involve collaboration from multiple centres.

Whilst the ELF studies have provided a comprehensive description of the incidence, time to depression and recovery, and degree of recovery of LV systolic myocardial depression, attention should shift to characterising diastolic function during critical illness. Diastolic function was not included in the ELF studies, as at the time of study development there was a lack of consensus on accepted measures. Diastolic function is gaining increasing attention in the literature[171], and has been linked to

acute pulmonary oedema and failure to wean from mechanical ventilation[179]. Consequently, this represents a promising area of future work once consensus on measures of diastolic function, and validity of these parameters in patients experiencing critical illness, has yet to be established.

Cardiac magnetic resonance imaging (CMRI) is able to exclusively provide non-invasive characterisation and quantification of the myocardium that can be used to differentiate between reversible and non-reversible causes of cardiac dysfunction[180]. CMRI sequences can be tailored to characterise LV and RV function as well as characterise any areas of oedema, necrosis, inflammation or fibrosis[180]. This is particularly useful in characterising right ventricular function, as this is poorly characterised by echocardiography.

Some authors[10,83,181] have identified the presence of myocardial oedema on CMRI in patients with Takotsubo's cardiomyopathy, but this is an emerging area. Undertaking CMRI studies in critically ill patients with myocardial depression is a novel, but in practice, challenging, idea. Undertaking CMRI studies were considered as a potential sub-study of ELF 3, but was ultimately unfeasible. This area will be the subject of post-doctoral work.

4.5 Conclusion

The ELF studies describe the incidence and natural history of myocardial depression in the general adult critically ill population. The methodological limitations and omissions of previous work have been identified and subsequently addressed to establish the true incidence and provide a comprehensive description of the natural history.

The studies have demonstrated that myocardial depression is not uncommon, typically occurs 3 – 4 days after the onset of critical illness, and is not always reversible. Historically, myocardial depression induced by severe physical or emotional stress was thought to predominantly affect females. As demonstrated by the ELF studies, myocardial depression is well represented in males, reflecting the dominance of male admissions to critical care units.

Regional wall motion abnormalities were infrequent (n = 9) and were, in most cases, likely attributable to pre-existing cardiac disease. Three participants demonstrated a global hypokinesis, which resolved within 90 days of AICU admission.

The ELF studies add to the existing knowledge by providing a comprehensive and generalisable description of the incidence, time course and recovery of myocardial depression occurring in critical illness. Furthermore, the degree of myocardial depression (absolute reduction in LVEF) is described for the first time, the clinical

significance of this may become apparent with future work establishing normative echocardiographic parameters for critical illness.

Whilst these sample sizes are relatively small, they are on par or larger than many studies reported in the literature. It seems logical that given the labour intensive nature of identifying myocardial depression, future work to characterise this during critical illness would be a multi-centre initiative.

Chapter V: Predictive modelling

5.0 Overview

The aim was to determine if the development of myocardial depression and recovery occurring during critical illness could be predicted using haemodynamic, demographic and clinical variables routinely collected in the first 24 hours of AICU admission. All data were analysed using R (version 3.0.3 R Foundation for Statistical Computing, Austria).

Originally, the ELF 1 and ELF 2 studies were intended to serve as a development dataset for the predictive models and the ELF 3 study was to serve as an external validation population. Unfortunately the number of participants demonstrating myocardial depression in ELF 3 was too small (n = 7) i.e. there were insufficient events for formal statistical analysis. Consequently the study data for ELF studies 1, 2 and 3 were reviewed and combined into a single dataset for the development of predictive models. Additionally, review of the development population revealed that too few participants (n = 16) demonstrated recovery from myocardial depression to facilitate construction of a predictive model. Thus, the remainder of the overview pertains to prediction of the development of myocardial depression.

All variables collected in the ELF studies that are available within the first 24 hours of AICU were reviewed for suitability as input variables. These were then rationalised to a shorter list of candidate input variables (Appendix 10). Data availability, frequency of binary outcomes, and demonstrated utility as a predictor variable in similar studies, were considered in the selection process.

Logistic regression modelling was selected to determine the probability of the development of myocardial depression. The choice of logistic regression over alternative methods of predictive modelling is discussed in section 1.8. A key theoretical assumption of logistic regression is that continuous independent variables are linearly related to the log(odds) of the dependent variable. This assumption was tested as part of model development.

A random effects logistic regression model was constructed to identify useful explanatory variables. The model was constructed according to the procedure discussed in section 2.7.3.1.

Preliminary work identified that, given the size of the dataset, some of the candidate explanatory variables were significantly correlated (multicollinearity). Multicollinearity was identified using a correlation matrix and a vector map produced by principal component analysis, discussed earlier in section 2.7.1.

Construction of a logistic regression model with correlated explanatory variables would result in unreliable estimates of explanatory variable coefficients[137], which would hinder model generalisability. Consequently, canonical correlation was used

to create a new factor, that is a linear combination of candidate explanatory variables. This factor is an expression of all candidate explanatory variables and is maximally correlated to the development of myocardial depression.

This factor was then used as the explanatory variable in a logistic regression model, with myocardial depression as the dependent variable. This factor was then used to get a simple threshold for assessing patient risk of myocardial depression.

A preliminary factor of all candidate explanatory variables was produced. Correlated candidate explanatory variables were then reviewed for potential redundancy. Highly correlated candidate explanatory variables were identified from the vector map, and highly correlated variables were treated as pairs.

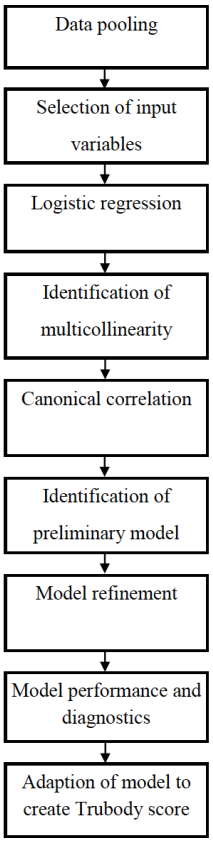
Variables from the pair were removed one at time and the model refitted, to assess the impact the elimination had on the correlation of the factor to the development of myocardial depression. The variable whose removal had the least detrimental effect on the correlation of the factor to the development of myocardial depression was eliminated. This resulted in a reduced, final model of five explanatory variables.

The sensitivity and specificity of the model was then considered, and the optimal probability threshold was determined to minimise the number of false negatives. Model performance was then assessed by construction of ROC curve and determining the area under the curve (AUROC). Model diagnostics for binary data were then undertaken as per the procedures suggested by Collett[163] (discussed

earlier in section 2.7.3.3). Consequently, a half normal plot of residuals and an index plot were constructed to assess model fit and identify outliers.

Finally, the model coefficients were scaled to create a score between zero and ten. This score (the Trubody score) estimates the risk of developing myocardial depression, with greater score associated with increased risk. An overview of the statistical analysis process is given in figure 19.

Figure 19: Overview of statistical analysis process



5.1 Development population

In order to create an adequately sized development population for predictive modelling, the datasets from the three ELF studies were combined. Combination of smaller datasets to facilitate predictive modelling is common practice in medicine, particularly in conditions where the incidence is low, or where huge datasets are required e.g. genetic modelling. The pitfalls of combining datasets include amalgamating data from different study designs (e.g. randomised control trial and observational studies), non-standardised variable definitions, missing data and capturing data across a period that encompasses a significant change in clinical practice[182].

Many of these pitfalls were avoided in combining the data from the ELF studies. All data were collected using the same variable definitions, missing data were uncommon and there was not a significant change in clinical practice over the study period (1st June 2008 – 22nd March 2015). All participants were admitted to AICU at the same tertiary centre.

Key demographic, severity of illness and clinical outcomes of study population were similar (table 29). Statistical comparison between datasets was not attempted, as the absence of statistically significant differences would not demonstrate that they are statistically similar. Table 29 compares the datasets across a number of key demographic, clinical, severity of illness and mortality descriptors. Comparison of the three studies across the candidate explanatory variables, discussed in the next section, is given in Appendix 12.

The combined dataset from the three studies had a total of 117 participants, however the final development population contained 112 participants, as five ELF 2 participants did not have data available from the first 24 hours. As the ELF 2 study was a retrospective analysis of participants who had serial echocardiography in AICU, the timing of the echocardiography studies was variable. Four of the five excluded participants developed myocardial depression.

Table 29: Comparison of the variables across the model development population

	ELF 1	ELF 2	ELF 3
Sample size (n)	49	42	21
Developed myocardial depression (n, %)	8 (16.3%)	12 (28.6%)	7 (33.3%)
Male (n, %)	34 (69.4%)	26 (61.9%)	15 (71.4%)
Age at AICU admission (years, median, IQR)	66 (47 – 75)	57 (38 – 70)	70 (58 – 79)
ICNARC score (mean, SD)	19 (± 7)	24 (± 9)	18 (± 7)
APACHE II score (mean, SD)	20 (± 7)	20 (± 7)	24 (± 7)
AICU LOS (days, median, IQR)	6 (4 – 14)	7 (4 – 23)	7 (4 – 10)
Hospital LOS (days, median, IQR)	21 (12 – 42)	33 (14 – 58)	18 (12 – 29)
AICU mortality (n, %)	5 (10.2%)	3 (7.1%)	2 (9.5%)

5.2 Prediction of myocardial depression

5.2.1 Objective

The objective was to develop a model that would predict the development of myocardial depression (defined as reduction in ejection fraction ≥ 5% from baseline recorded in AICU) using clinical, haemodynamic and demographic variables collected in the first 24 hours of AICU admission.

5.2.2 Candidate input variables

The mean time to collection of variables in participants with myocardial depression was 13 hours after admission to AICU. This is the mean time to first conducted echocardiogram. The first 24 hours of AICU admission was selected as this time point has the most data available for construction of the predictive models. Nationally, the median length of AICU admission is two days[98,99], thus, selection of a time point beyond this would impede generalisability of the results.

Inclusion of too many variables in a predictive model, given the number of patients with the outcome of interest, increases the risk of overfitting. Overfitting is where idiosyncrasies of the data are modelled, rather than generalisable patterns. Steyerberg[137] suggests that to avoid this a minimum of ten patients with the outcome are required per explanatory variable. Therefore, with approximately 30 patients demonstrating myocardial depression, inclusion of greater than three explanatory variables would run the risk of overfitting the model.

Consequently, variables should be rationalised so that candidate input variables are likely to be useful predictors. Steyerberg[137] suggests a literature review to identify variables that were useful in similar studies.

The literature review (section 1.3.8) indicated that prediction of myocardial depression in the general AICU had not been attempted. One[60] study had attempted to predict a specific pattern of RWMA and decreased LVEF in medical AICU patients without pre-existing cardiac disease, but the generalisability of these findings are uncertain. Few studies[2-6,42] had been undertaken on the prediction of myocardial depression in sub-populations of patients treated for critical illness, but these were inconsistent in the selection method and reported usefulness of explanatory variables. No candidate variable was included across all studies, although, as expected, routinely collected demographic and physiological data were commonly trialled as input variables.

All variables from the ELF studies that were available within the first 24 hours of AICU studies were reviewed for inclusion as a candidate input variable. These variables were collected at the time of echocardiography. As the predictive modelling was undertaken post-hoc, the list of available candidate input variables was not exhaustive. The feasibility of predictive modelling was unknown at the time of study development, as it is intrinsically linked to the incidence of myocardial depression. Consequently, variables that were recorded for the ELF studies reflect routinely collected haemodynamic, clinical and demographic data.

Variables were reviewed for data availability and demonstrated utility as a predictor variable in similar studies. Binary variables were also reviewed by frequency tables for rare events. This was defined as variables that had <5% of participants with the least frequent outcome. Binary variables with an infrequent outcome (rare events) are unlikely to be useful predictors. This was not identified in any binary candidate variable.

A list of all collected variables and the justification of inclusion or exclusion is given in Appendix 10.

Ultimately, twelve candidate input variables were trialled in model development (table 30). Variables were collected using standardised data collection rules to ensure consistency (Appendix 8). Additionally, few observations were missing from the development population (third column, table 30). A comparison of the candidate explanatory variables from the three ELF studies is given in Appendix 12.

Table 30: Candidate explanatory variables

Variable	Notes	Number of missing observations
Heart rate	Continuous variable. Recorded in beats per minute. In the ELF studies this was recorded at a mean time of 13 hours following AICU admission.	Two
Sinus rhythm	Binary variable, defined as a heart rate between 60 – 100 beats per minute, in a regular rhythm. In the ELF studies this was recorded at a mean time of 13 hours following AICU admission.	One
Systolic blood pressure (SBP)	Continuous variable. Recorded in millimetres of mercury. In the ELF studies this was recorded at a mean time of 13 hours following AICU admission.	One
Mean airway pressure	Continuous variable. Recorded in centimetres of water. In the ELF studies this was recorded at a mean time of 13 hours following AICU admission. Participants not receiving invasive mechanical ventilation were recorded as a mean airway pressure of zero.	One
Vasopressors	Binary variable. Any administration of adrenaline, noradrenaline, dopamine, terlipressin or vasopressin within the first 24 hours of AICU admission.	Nil

Respiratory organ dysfunction	Binary variable. PaO_2/FiO_2 ratio <33.3 kPa OR if the lung is the sole organ meeting an organ dysfunction criterion[145] and primary or secondary reason for AICU admission is due to a lung infection, PaO_2/FiO_2 must be <26.7 kPa. Recorded at any stage within the first 24 hours of AICU admission.	One
Cardiovascular organ dysfunction	Binary variable. Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or the use of vasopressor and/or inotrope for >1 hour recorded at any stage in the first 24 hours of AICU admission.	One
Severe sepsis	Binary variable. Defined as per the criteria outlined by Padkin[145] (systemic inflammatory response syndrome (SIRS), known or suspected infection and at least one organ dysfunction).	Nil
Regional wall motion abnormalities (RWMA)	Binary variable. Presence of global or segmental hypokinesis on echocardiography recorded within the first 24 hours of AICU admission.	Nil
Male	Binary variable. Chromosomal sex of the participant.	Nil
Age	Continuous variable. Recorded in whole years (rounded down to the nearest whole year) at the time of AICU admission.	Nil
Surgical admission	Binary variable. Coded as per the first tier of the hierarchical ICNARC coding method[169].	Nil

5.2.3 Logistic regression

A logistic regression model was built. Whilst consensus on the ideal method of model construction (backwards vs. forwards) has not been reached, backwards elimination is preferred[137] as it allows the effect of the removal of an explanatory variable to be assessed across the whole model.

Logistic regression assumes that the continuous independent variables need to be linearly related to the log(odds) of the dependent variable (assumption of linearity). This was tested by trialling continuous variables with polynomial terms (square, cubic and quadratic), and assessing fit on the model. No continuous variable with a polynomial term was significant at the 0.05 level, and thus the linearity assumption was met. Furthermore, if the linearity assumption was violated, this would be detected in the half-normal plot of absolute residuals (Collett's diagnostics) as a poor model fit.

All candidate variables were simultaneously fitted and were reduced by backwards elimination. An iterative process was followed until the most parsimonious fit of the data was achieved. Initially, candidate explanatory variables were reviewed as a main effect in the model - variables with a p value <0.2 were provisionally kept in the model[137]. Candidate variables that were not significant as a main effect were then trialled as an interaction term. To avoid overfitting, only clinically meaningful interaction terms were trialled.

Variables were eliminated and the model refitted until minimal changes in Akaike Information Criteria (AIC) were seen. The AIC compares models based upon their fit of the data and penalises models with many explanatory variables[183]. Specifically, the AIC = 2K – 2log(L), where K is the number of predictor variables and L is the maximised likelihood estimation (MLE)[184]. The MLE gives a probability of observing a set of data, given model parameters. Smaller values of AIC indicate a better model fit[184].

Expected reductions in AIC were not observed through elimination of explanatory variables. The AIC of the model with all candidate variables included (n = 12) was 117.6, which reduced to 108.4 with only two variables (systolic blood pressure and severe sepsis) kept in the model.

A chi-squared test on the differences of the residual deviance of the models was used to determine if the models were statistically different. The residual deviance is another method to describe the model fit of the data, with smaller values indicating better fit. A reduction in explanatory variables would result in a worse fit, as there are fewer variables to explain the data.

This differences in the residual deviance between models was compared and demonstrated that there was no significant differences in the fit, χ^2 =10.85 (11 df), p = 0.456, i.e. a model with two explanatory variables is statistically equivalent to a model with all explanatory variables.

The lack of improvement in model fit with the reduction in the number of explanatory variables raised concerns of multicollinearity. A heuristic approach to the effect of multicollinearity on model development would be to consider any statistical significance as shared between correlated variables. Consequently, it may be difficult to elucidate the true effect of a candidate explanatory variable on the development of the outcome.

5.2.3.1 Identification of multicollinearity

The effect of multicollinearity on modelling procedure is related to the number of variables affected, and the degree of correlation between the explanatory variables. Highly linearly correlated variables ($r > 0.90$) may be expressed as a single, combined variable.

Multicollinearity can result in unreliable estimates of explanatory variable coefficients in regression models. Owing to concerns about multicollinearity, the degree of correlation between explanatory variables that would be significant ($p < 0.05$) given the size of the dataset was determined using the formula proposed by Bickel and Dorfsum[160]. This was determined to be $r > 0.19$ ($p < 0.05$).

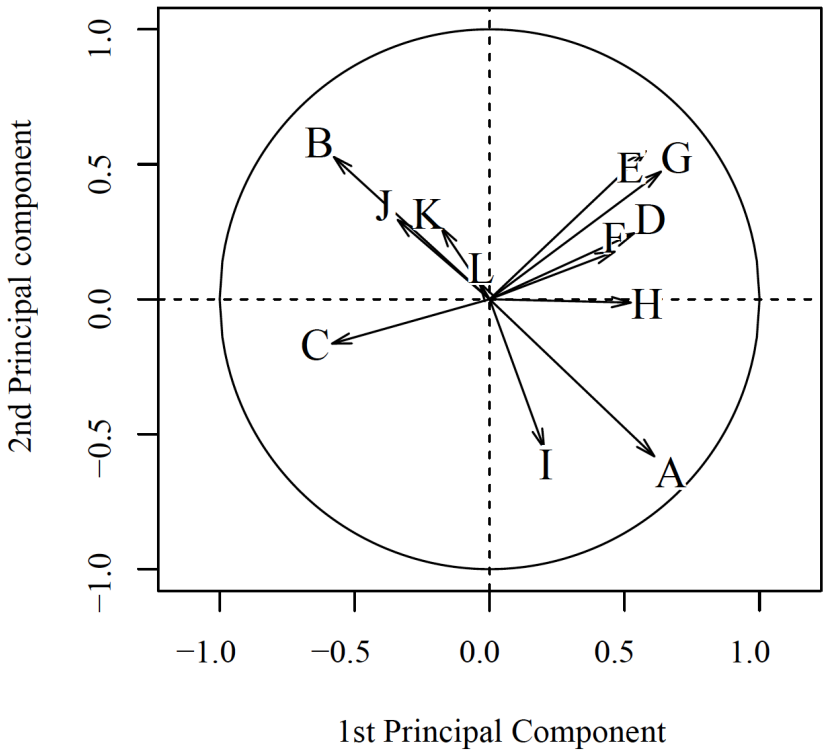
Multicollinearity was assessed through a correlation matrix and by a vector map produced by principal component analysis (PCA). The correlation matrix presents the Pearson's correlation between variables. This is a value between +1 and -1 and expresses the linear dependence between two variables. The correlation matrix for the candidate explanatory variables is given in table 31.

Table 31: Correlation matrix of explanatory variables

	Rate	Sinus rhythm	Systolic BP	Mean airway pressure	Vasopressors	Resp. dysfunction	CVS dysfunction	Severe sepsis	RWMA	Male	Age	Surgical admission
Rate	1.00	-0.58	-0.13	0.17	0.18	0.21	0.16	0.25	0.21	-0.43	-0.24	0.00
Sinus rhythm	-0.58	1.00	0.25	-0.13	-0.26	-0.24	-0.17	-0.20	-0.28	0.17	0.80	0.02
Systolic BP	-0.13	0.25	1.00	-0.29	-0.32	-0.06	-0.45	-0.14	-0.15	0.11	0.14	0.00
Mean airway pressure	0.17	-0.13	-0.29	1.00	0.34	0.31	0.26	0.29	0.19	0.08	-0.17	-0.09
Vasopressors	0.18	-0.26	-0.32	0.34	1.00	0.22	0.51	0.20	-0.11	0.03	0.06	0.01
Resp. dysfunction	0.21	-0.24	-0.06	0.31	0.22	1.00	0.27	0.26	0.03	-0.25	-0.01	-0.11
CVS dysfunction	0.16	-0.17	-0.45	0.26	0.52	0.27	1.00	0.35	0.05	-0.15	-0.02	-0.11
Severe sepsis	0.25	-0.20	-0.14	0.29	0.20	0.27	0.35	1.00	0.04	-0.18	-0.04	-0.15
RWMA	0.21	-0.28	-0.15	0.12	-0.11	0.03	0.05	0.04	1.00	-0.05	-0.08	-0.04
Male	-0.43	0.17	0.011	0.08	0.03	-0.25	-0.15	-0.18	-0.05	1.00	-0.01	-0.13
Age	-0.24	0.08	0.08	-0.17	0.0.6	-0.01	-0.02	-0.04	-0.08	0.00	1.00	0.01
Surgical admission	0.00	-0.02	-0.02	-0.09	0.00	-0.11	-0.11	-0.15	-0.04	0.13	0.00	1.00

A vector map was constructed by PCA by plotting candidate explanatory variables as vectors to their first and second principal components (discussed earlier section 2.7.1). The cosine of the angle between vectors represents the degree of correlation between the variables, with a smaller angle indicating greater correlation. The vector map was used twice in model construction, firstly to visualise the correlation between candidate explanatory variables, and later to identify potentially redundant variables. The vector map is given in figure 20.

Figure 20: Vector map



Legend

A Heart rate
B Sinus rhythm
C SBP
D Mean airway pressure
E Vasopressors
F Respiratory organ dysfunction
G Cardiovascular organ dysfunction
H Severe sepsis
I RWMA
J Male
K Age
L Surgical admission

The correlation matrix (table 31) identified that, given the size of the dataset, many candidate explanatory variables were significantly correlated. The degree of correlation between variables was insufficient to combine them ($r < 0.90$). This correlation is visually represented on the vector map (figure 20). The vector map demonstrates that some variables are clustered together, indicating that they are highly correlated with one another. For example, sinus rhythm (B), male gender (J), age (K) and admission to AICU following surgery (L) were all highly correlated, as were mean airway pressure (D), vasopressor use (E), respiratory organ dysfunction (F) and cardiovascular organ dysfunction (G).

Given the multicollinearity between candidate explanatory variables, estimated regression coefficients of correlated variables would be unreliable and the standard errors of the coefficients would be large[137]. Consequently, statistical advice was sought and canonical correlation was recommended.

5.2.4 Canonical correlation

A canonical correlation takes all explanatory variables and expresses them as a single factor, which is maximally correlated to the outcome variable.

This process mitigates the problem presented by correlated explanatory variables, as the variables (and their underlying relationships) are expressed as a factor.

The factor was then used as the explanatory variable in a logistic regression model, with myocardial depression as the dependent variable.

As these are expressed as a factor, the statistical significance of individual explanatory variables cannot be described.

5.2.4.1 Canonical correlation process

First, all 12 candidate explanatory variables (table 30) were standardised. The mean of all individual variables (including binary data) was obtained and divided by the variable standard deviation.

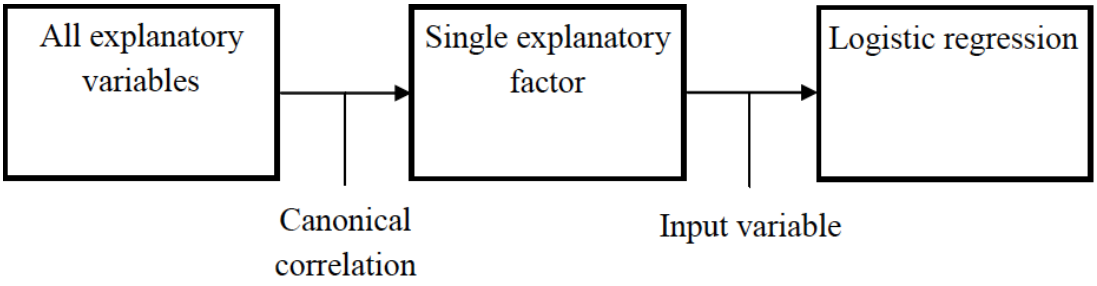
Variables were then used to create a single factor using the canonical correlation package in the statistics program used for the analysis, R. This creates a linear combination of the 12 explanatory variables, expressed as a factor, which maximises the correlation with the development of myocardial depression.

Coefficients for each explanatory variable are also produced by canonical correlation. These coefficients act as weightings for each variable. In the calculation of the factor, for each variable, the raw patient data is multiplied by the coefficient. These values are summed and a factor for each patient is produced.

This factor was then used as a single explanatory variable in a logistic regression model, with myocardial depression as the outcome variable. This process produced a single factor that was useful for determining individual patient risk of the development of myocardial depression.

Finally, the coefficients of the standardised variables can indicate each variable's influence on the factor, with a greater size indicating a greater contribution.

Figure 21: Process of canonical correlation



5.2.4.2 Preliminary model results

A preliminary factor produced by canonical correlation was then fitted as the explanatory variable in a logistic regression model. This preliminary factor contained all 12 original candidate explanatory variables. The fit of this factor, as an explanatory variable in a logistic regression model, is given in table 32.

Table 32: Preliminary model fit

	Estimate	Standard error	p value	AIC
Intercept	-1.13	0.24		
Preliminary model factor	9.36	2.78	0.0007	123.0

The model with all explanatory variables, treated as a factor, was statistically significant (p value <0.05). The correlation of the factor to the outcome variable (development of myocardial depression) is r = 0.33.

5.2.4.3 Model refinement

All twelve candidate explanatory variables were included in the canonical correlation. Canonical correlation will create a factor from the input variables, but does not identify variables that add little or no explanatory power to the correlation with the outcome variable (redundant variables). Therefore, redundant variables may have been included in the model.

Consequently, the vector map (section 5.2.3.1, figure 20) was re-reviewed. The angle between vectors and the length of the vector were visually inspected. A smaller angle between vectors suggests more closely correlated explanatory variables and a smaller vector length indicates less contribution to the factor. The vector map identified clustering of explanatory variables.

Thus, closely correlated variables were paired and each variable from the pair was eliminated in turn. The variable whose removal had the least detrimental effect on the correlation of the factor to the development of myocardial depression was eliminated. Four pairs of highly correlated variables were identified on the vector map. Table 33 describes the pairs and reports eliminated variables.

Table 33: Variable elimination

Pair	Eliminated
Mean airway pressure vs. cardiovascular organ dysfunction	Mean airway pressure
Respiratory organ dysfunction vs. severe sepsis	Respiratory organ dysfunction
Age vs. male	Male
Heart rate vs. regional wall motion abnormalities	RWMA
Vasopressors vs. cardiovascular organ dysfunction	Vasopressors

Additionally, another two variables (age and surgical admission) were eliminated to see the effect on the model; this had minimal effect on the correlation, and thus these variables were eliminated. Details of the effects of variable elimination are given in Appendix 13.

Ultimately, five explanatory variables were included in the final factor. The reduction from 12 to five explanatory variables resulted in the correlation between the factor and the outcome variable to drop from $r = 0.33$ to $r = 0.28$. Bartlett's approximation[162] (described earlier in section 2.7.1) was used to determine if this reduction in correlation was statistically significant; χ^2 5.16 (7 df), $p = 0.64$. This indicates that there was no statistical difference in the loss of correlation caused by reducing the number of explanatory variables from 12 to 5.

5.2.4.4 Final model

The final factor correlation to the development of myocardial depression was r = 0.28. The model specifications are given in table 34, and demonstrate that the model is statistically significant ($p < 0.05$). Explanatory variables are treated as a factor in the model, rather than independent variables, therefore odds ratios or statistical significance of individual variables cannot be reported.

Table 34: Final model fit

	Estimate	Standard error	p value	AIC
Intercept	-1.06	0.23		
Final model factor	7.15	2.50	0.0042	127.5

Once the final factor had been reached the explanatory variables were standardised by taking a mean of the individual variable and dividing this by the standard deviation. By standardising the variables, the effect size of each of the explanatory variables on the factor can be compared by assessing the size and direction of the coefficient.

Standard deviations of the standardised explanatory variable coefficients were also estimated. The standard deviations of the coefficients derived through canonical correlation must be calculated through simulation.

Therefore, a program was written in the statistics package (R) to generate the probability of development of myocardial depression of all participants in the dataset (n = 112). Then, these probabilities were used to simulate 50,000 binary outcomes (myocardial depression: yes or no) for each participant in the dataset. The raw variable data for each of the 112 participants was then used to simulate 50,000 sets of explanatory variable coefficients. The standard deviation of the simulated coefficients was then determined. These are given in table 35.

Table 35: Standardised variable coefficients and standard errors

Standardised explanatory variable	Coefficient	Standard deviation of coefficients
Heart rate	-0.0536	0.0401
Sinus rhythm	-0.0608	0.0429
Systolic blood pressure	0.0854	0.0499
Cardiovascular organ dysfunction	0.0598	0.0399
Severe sepsis	0.0312	0.0315

The coefficients of the standardised variables allow comparison of effect size of explanatory variables to the model factor. Table 35 indicates that systolic blood pressure has the greatest effect size, and the severe sepsis had the least effect, of any explanatory variable included in the factor. Furthermore, heart rate and the sinus rhythm negatively impact the factor i.e. decrease risk.

This is discussed in further detail in section 6.2, chapter six. The standard deviations of the standardised variable coefficients are large, owing to the relatively small size of the dataset.

The coefficients of the unstandardised explanatory variables are given in table 36. Whilst these coefficients cannot be interpreted in the same manner as unstandardised variable coefficients in logistic regression, they were essential for the creation of the Trubody score. The Trubody score (section 5.2.6) facilitates a bedside calculation of risk of myocardial depression.

Table 36: Unstandardised variable coefficients

Unstandardised explanatory variable	Coefficient
Heart rate	-0.0024
Sinus rhythm	-0.1213
Systolic blood pressure	0.0042
Cardiovascular organ dysfunction	0.1191
Severe sepsis	0.0710

5.2.5 Model performance and diagnostics

5.2.5.1 Sensitivity and specificity

Model sensitivity and specificity was examined at a series of thresholds. Briefly, sensitivity is the proportion of true-positives identified from the total number of patients with the outcome and specificity is the proportion of true-negatives from the total number of patients without the outcome.

A decision threshold can be set to classify patients with a probability greater than or equal to the threshold as positive. The optimal threshold can be set to maximise sensitivity or specificity. This is a more sensible approach than the traditional method of setting the threshold at 50%, where false positives and false negatives are weighted equally.

Minimising the number of false negatives was considered preferable. In patients identified as high risk for the development of myocardial depression, surveillance echocardiography may be initiated. Echocardiography is non-invasive, places little burden on patients, and is increasingly adopted in critical care units. Surveillance echocardiography in a patient that does not develop myocardial depression (a false positive) was deemed preferable than a threshold set to maximise specificity that missed patients with myocardial depression. Therefore, the optimal probability cut-off was then identified to minimise the number of false negatives.

The predicted probabilities derived from the final model were taken and different thresholds trialled to determine the optimal cut-off to minimise the number of false

negatives (Appendix 14). The probability threshold of ≥ 0.25 was determined to be the cut off that minimised the number of false negatives, this is reported in table 37.

Table 37: False positives and negatives for the probability threshold in the final model

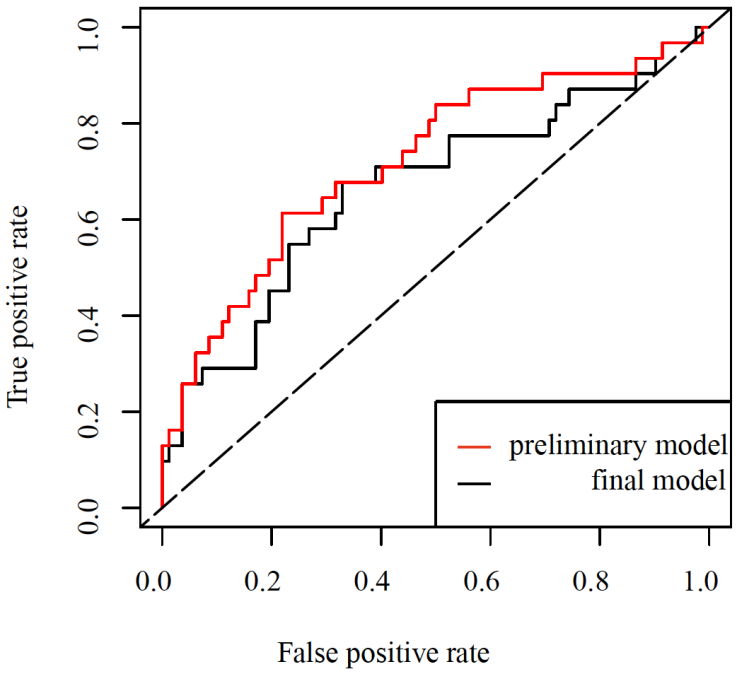
Threshold	False positives	False negatives
Pr ≥ 0.25	31/52 (59.6%)	9/60 (15.0%)

5.2.5.2 Receiver Operating Characteristics

Model performance was assessed by review of the Receiver Operating Characteristics (ROC) curve. The ROC curve was constructed by plotting the sensitivity (true positive rate, y axis) against 1-specificity (false positive rate, x axis) over a range of probability thresholds.

Model performance on a binary outcome can be assessed by the area under the ROC curve, which indicates the ability of the model to discriminate between those with myocardial depression and those without. Ideally, an ROC curve would be fitted towards the top left hand corner, which would indicate greater sensitivity and specificity[185], and have a maximum possible area under the curve (AUROC). A model without any discriminative ability would follow a diagonal line between 0 and 1, with an AUROC of 0.5.

Figure 22: ROC curves of preliminary and final model



The area under the ROC curves is 0.72 for the full model and 0.67 for the reduced model, which indicate a modest discriminating ability. Whilst inclusion of all variables (red curve) results in a ROC curve that is closer to the top left, inclusion of all variables (n = 12) would drastically increase the likelihood of overfitting the model, as this would violate the events-per-variable rule[137].

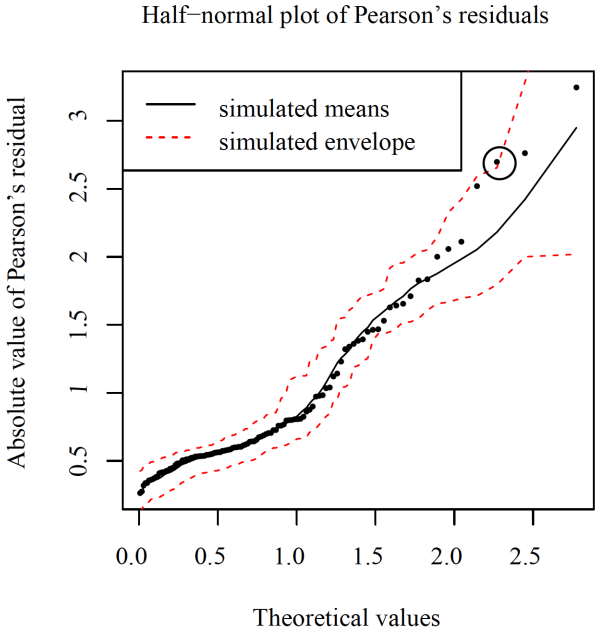
5.2.5.3 Model diagnostics

Model assessment of explained variance and an appropriate goodness-of-fit statistics cannot be calculated from the model. This is due to explanatory variables being expressed as a factor, rather than individual variables. Alternative methods of model checking were then sought.

Consequently, model diagnostics were performed according to the recommendations of Collett[163] for modelling binary data. Therefore, a half normal plot of Pearson's residuals and index plots were produced.

Half normal plots are useful to assess model fit and to identify outliers. This was constructed using the process outlined by Collett (section 2.7.3.3). Half normal plots of Pearson's residuals plot the abolute value of the residuals in ascending order against their theoretical value. These data are then plotted with a simulated envelope, which, unsurprisingly, is constructed by simulation. The simulated envelope allows assessment that the model is correctly fitted, this is illustrated with red dashed lined as boundaries in figure 23. In a correct model, all data points will fall within the boundaries of the simulation envelope. This plot is given in figure 23.

Figure 23: Half normal plot of Pearson's residuals



The black dots are the ELF data set.

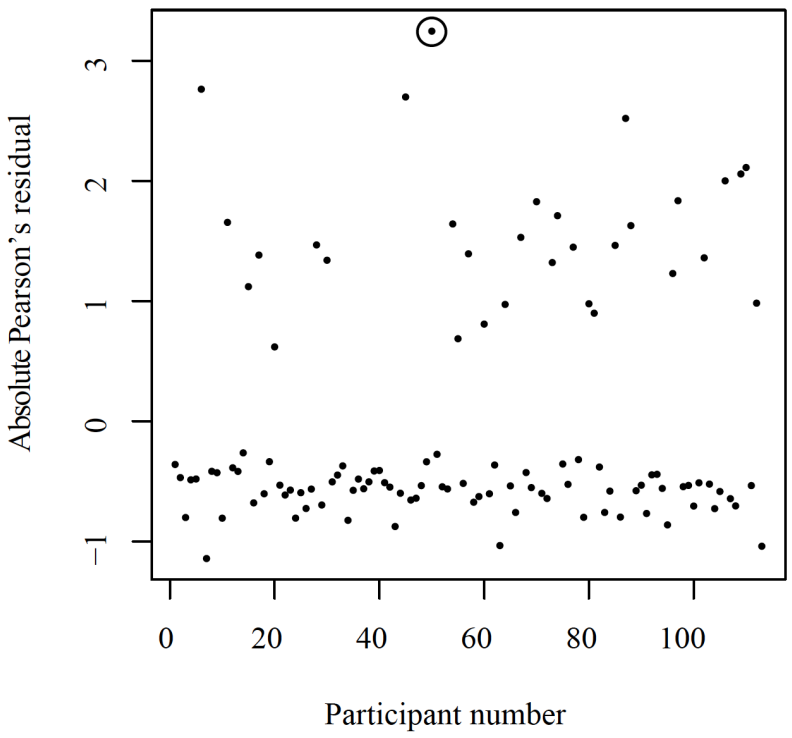
The solid line are the means of the simulated dataset

The red dashed line represents the simulated envelope (the minimum and maximum standardised deviance residuals)

The half normal plot of Pearson's residuals demonstrate that the model is a good fit of the data, and although there is some divergence between observed and simulated means on the top right, values still fall within the simulation envelope.

One potential outlier (datapoint 50, circled) was identified straddling the upper boundary of the simulation envelope. Consequently, an index plot was constructed as it is useful for identifying outliers. An index plot maps the absolute value of Pearson's residuals of each datapoint (i.e. each participant). The participant study number is plotted on the x axis, and the absolute value of the residual on the y axis. The Index plot is given in figure 24.

Figure 24: Index plot



Datapoint 50 was suspected as an outlier from the half normal plot of residuals, which was confirmed by index plot (circled datapoint). Therefore, datapoint 50 was removed from the dataset and the model refitted to assess the impact of removal of outlier from the model. Comparison of model fits are given in table 38.

Table 38: Comparison of model fits with and without the outlier

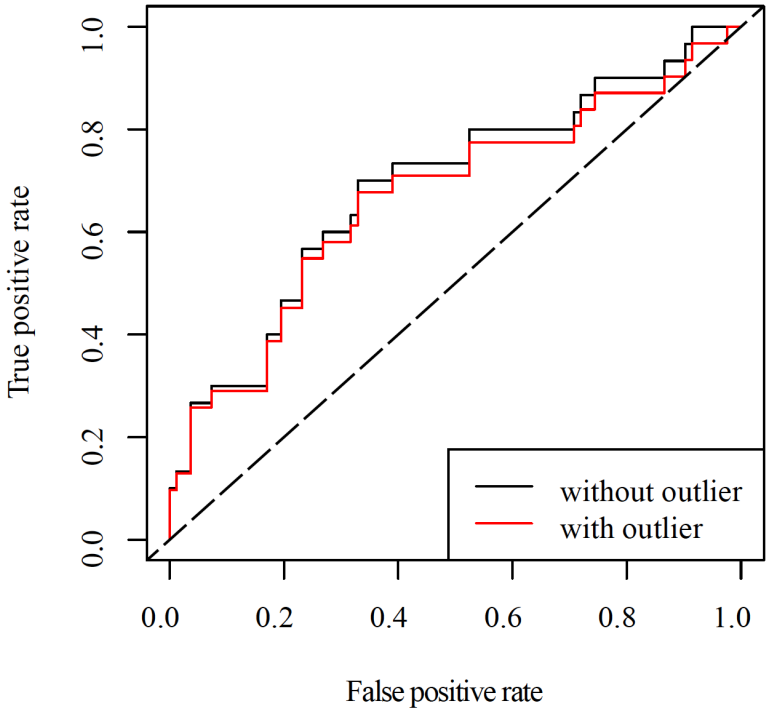
	Final model	Final model less outlier
Intercept	-1.06 (SE 0.23)	-1.14 (SE 0.24)
Model	7.15 (SE 2.50)	8.41 (SE 2.65)
p value	0.0042	0.0015
AIC	127.5	122.4
Residual deviance	123.5 (111 df)	118.4 (110 df)

The models were then compared by assessing the significance of the decrease in residual deviance in the model without the outlier. Residual deviance indicates how well a model explains the data, with smaller values indicating better fit. This demonstrated a statistically significantly improvement in model fit without the outlier, χ^2 5.16 (1 df), p value = 0.0231. The variable coefficients of the refitted model (with the outlier removed) were identical to the final model.

Finally, the ROC curve was refitted with the outlier removed. This is given in figure 25, and demonstrates a slight improvement in model performance, as assessed by

ROC. The AUROC improved to 0.69 with the removal of the outlier (compared with 0.67 with the outlier included)

Figure 25: ROC curves with and without inclusion of outlier



5.2.6 Prediction of myocardial depression and clinical utility

To translate the model into a practical form, the model was adapted to create a scoring system (the Trubody score) that can be used to determine the probability of the development of myocardial depression.

The Trubody score was created by dividing the coefficients of the five unstandardised explanatory variables used in the factor, by the absolute value of the rate coefficient (0.0024). This keeps all coefficients in the same ratio, but they are

rescaled to give the score a range between zero and ten. The coefficients are given in table 39.

Table 39: Coefficients used in the calculation of the Trubody score

Variable	Coefficient value in the Trubody score
Rate	-0.04
Sinus rhythm	-2.04
Systolic blood pressure	0.07
Cardiovascular organ dysfunction	2.00
Severe sepsis	1.19

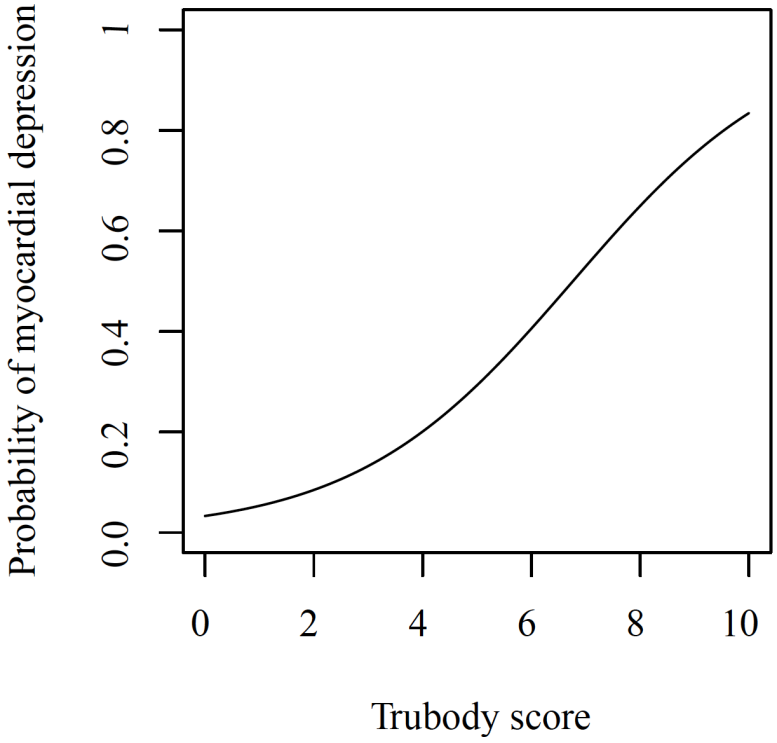
Thus;

Trubody score = sum ((explanatory variable coefficient (EVC) [i] x explanatory variable patient value (EVPV) [i]) + (EVC [ii] x EVPV [ii]) … (EVC [v] x EVPV [v]))

This produces a score between zero and ten, with a higher score associated with greater risk of myocardial depression. The scaling is drawn from the development dataset, thus extreme values not present in these data may result in scores outside the range. This problem can be easily mitigated in future work by recalibration with an appropriate dataset.

To generate a graph of probability of myocardial depression against Trubody score, the score was calculated for all participants in the development dataset and plotted against the predicted probability of myocardial depression (figure 26). The range of Trubody scores observed in the dataset are given in table 40.

Figure 26: Probability of development myocardial depression vs. Trubody score



The figure demonstrates that Trubody scores greater than four are associated with a probability of ≥ 0.20 of developing myocardial depression. From the figure, a score of ten results in a probability ≥ 0.80. The predicted probability from the figure does not exceed ≥0.80 because the curve was fitted from the raw data of the development cohort, and few participants had high Trubody scores from which to generate the curve, this is confirmed by the interquartile range of the raw Trubody scores (table 40).

Table 40: Trubody scores of the development dataset

Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
0.69	3.59	4.40	4.48	5.46	9.24

5.3 Prediction of recovery

A model was to be developed to predict the recovery of myocardial depression. Recovery was defined as complete (return of ejection fraction to baseline or higher) or incomplete (improvement from nadir greater than intra-observer variability, but not to baseline). Of the 31 participants who developed myocardial depression, only 16 demonstrated complete or incomplete recovery. This was an inadequate number of participants with the outcome of interest from which to build a predictive model.

5.4 Summary

This work represents, to the best of my knowledge, the first attempt at the prediction of myocardial depression in the general population of adult experiencing critical illness. Predictive modelling was attempted using logistic regression, but collinearity of explanatory variables precluded reliable estimates of variable coefficients.

Consequently, canonical correlation was used to express explanatory variables as a factor, that was maximally correlated with the development of myocardial depression. The factor was used as a single explanatory variable in a logistic

regression model. Redundant variables were identified by review of the vector map and were removed, resulting in the final model.

Five explanatory variables were included in the final factor: systolic blood pressure, heart rate, and the presence or absence of sinus rhythm, severe sepsis and cardiovascular dysfunction. The correlation of the final factor to the development of myocardial depression was $r = 0.28$, and the final model was statistically significant (p value < 0.0015).

Model sensitivity and specificity was then considered. Owing to the non-invasive nature and minimal patient burden of surveillance echocardiography, minimising the number of false negatives was considered preferable. Therefore, the predicted probabilities derived from the final model were then taken and different thresholds trialled to identify the cut-off that minimised the number of false negatives; this was identified as $Pr \geq 0.25$.

Model performance was assessed by ROC curve, with a calculated area under the curve of 0.67, indicating modest discrimatory ability. Model diagnostics for binary data were conducted as per the recommendations of Collett[163]. These diagnostics indicated a correct fit of the model and identified an outlier.

The outlier was removed from the dataset and the model refitted, which demonstrated a statistically significant improvement in model fit, as assessed by AIC ($p = 0.02$) and improvement in AUROC to 0.69.

Finally, explanatory variable coefficients were scaled to create the Trubody score. This gives a score between zero and ten, with greater score associated with greater risk of developing myocardial depression.

Disappointingly, the prediction of recovery from myocardial depression could not be modelled due to the small number of participants demonstrating recovery (n = 16). Nevertheless, this represents an area of future work and will be discussed further in the subsequent chapters.

In the following chapter the results and implications of the prediction of myocardial depression are discussed further.

Chapter VI: Modelling discussion

6.0 Overview

This chapter discusses the results of the model to predict the development of myocardial depression. Firstly, the challenges presented by predictive modelling are discussed, and what challenges were encountered by the ELF dataset and how these were overcome. The merits of candidate input variables, the novelty of the research and potential applications are discussed, followed by a review of the strengths and limitations of the model. Finally, areas for future work and a summary of findings are presented.

6.1 Challenges of predictive modelling

Previously, the incidence of myocardial depression in critically ill patients had been unclear. The reported incidence of myocardial depression in the general AICU population ranged between 6[71] – 95[70]%. In AICU sub-groups the reported incidence ranged between 17.5[28] – 60[25]% in sepsis and between 0[8]– 38[7]% in patients with subarachnoid haemorrhages. The ELF studies sought to establish the true incidence of myocardial depression occurring during critical illness. As reported in detail in section 4.1, the incidence of myocardial depression across the ELF studies was 16.3%, 34.0% and 33.3% in ELF 1, ELF 2 and ELF 3, respectively.

In constructing the predictive models, the development of myocardial depression is the outcome of interest. Consequently, the incidence will determine the effective sample size and therefore the feasibility of modelling, the complexity of the

research question and the number of explanatory variables that can be included without overfitting the model. The wide range of reported incidence resulted in the inability to effectively estimate the sample size required, or to determine feasibility of predictive modelling ahead of the study.

The sample size from any single-centre prospective study in critically ill patients will be limited by the availability of patients. Furthermore, the single-operator set up of the ELF 1 and ELF 3 studies coupled with the specialised skills required for echocardiography, presented a practical limitation to the number of enrolled participants. Therefore, the sample size was increased through the collection of retrospective data (ELF 2).

Overall, a total of 117 participants were enrolled across the three studies, myocardial depression was observed in 31. Only 112 of 117 participants had data available within the first 24 hours of AICU admission, this was due to the variable timing of echocardiographic studies in ELF 2. Twenty-seven participants of the development population (total n = 112) developed myocardial depression.

The challenges faced in predicting the development of myocardial depression from the ELF dataset stem from the event rate (n = 27). Had the incidence (and subsequently effective sample size) been greater, a more precise model may have been constructed. Consequently, the model built from the available data appropriately reflects a simple question and represents proof-of-concept work.

To date, prediction of myocardial depression in the general adult critically ill population has not been attempted. Therefore, the rationalisation of candidate variables by review of the literature was not possible. Review of papers (section 1.3.8) on myocardial depression in sub-populations of critical illness demonstrated a lack of agreement regarding candidate input variables, although a preference for routinely collected demographic and haemodynamic data was observed. This is unsurprising, as data that are collected as part of routine care should be explored as explanatory variables before collecting data that results in additional health expenditure and increases the burden of data collection on the patient. Obviously, this approach is not comprehensive, but it does provide a reasonable starting point for the selection of candidate variables in the absence of prior studies.

Initial work on model development (section 5.2.3.1) demonstrated that, given the size of the dataset, many explanatory variables were significantly correlated. This, however, was not entirely unexpected as collinearity is rife amongst variables in all areas of medicine. Even ostensibly unrelated variables, such systolic blood pressure and age are not truly independent as the prevalence of hypertension increases with age. Although collinearity amongst explanatory variables can result in unreliable estimates of explanatory variable coefficients, the presence of collinearity does not preclude reliable predictions[137].

Provided that collinearity is recognised, steps can be taken to mitigate the influence on model validity. One approach is to combine highly correlated ($r > 0.9$) variables into a single variable[137]. This, however, was not undertaken in the prediction of

myocardial depression, as whilst a number of explanatory variables were significantly correlated given the size of the dataset, none demonstrated the degree of correlation that would justify combination into a single variable. Even alternative prediction techniques, such as classification and regression trees or neural networks, do not mitigate the problems presented by collinearity between explanatory variables.

Canonical correlation mitigated the challenge presented by collinearity amongst explanatory variables by expressing all variables as a single factor. This factor is then treated as an explanatory variable in a logistic regression model, with myocardial depression as the dependent variable. Furthermore, expressing variables as a factor, that was maximised to the development of myocardial depression, facilitated the production of the Trubody score, which can provide a simple threshold to assess patient risk.

6.2 Explanatory variables

The explanatory variables included in the final factor were heart rate, systolic blood pressure, sinus rhythm, severe sepsis and cardiovascular organ dysfunction. These variables were collected at the time of echocardiography, which occurred at a mean time of 13 hours following AICU admission.

As explanatory variables were expressed as a factor that is correlated to the development of myocardial depression, odds ratios cannot be calculated for individual explanatory variables. Nevertheless, each variable's contribution to the

factor can be identified by review of the standardised variable coefficients. The effect of a one-unit increase, or change of reference category, of an explanatory variable on the model factor could be determined by review of the unstandardised variable coefficients; but this not particularly useful as this effect is on the model factor, not directly to the development of myocardial depression.

Consequently, the effect size of each standardised explanatory variable to the model factor was reviewed. This identified that systolic blood pressure had the greatest effect on the factor, followed by sinus rhythm, cardiovascular organ dysfunction, heart rate, and finally, severe sepsis had the least effect on the factor.

Review of the coefficients of the standardised variables reveal that increased or decreased (as evidenced by vasopressor use) systolic blood pressure, the presence of severe sepsis and cardiovascular organ dysfunction are all associated with increased risk of myocardial depression. In contrast, increased heart rate and the presence sinus rhythm were associated with decreased risk. This is unsurprising, as cardiac output = heart rate x stroke volume. The increase in heart rate is likely a physiological compensation mechanism to maintain cardiac output when stroke volume decreases, due to impaired contractility during myocardial depression. Similarly, the presence of sinus rhythm decreases the risk of myocardial depression. This is not unexpected given that arrhythmia has been well documented in patients with myocardial depression[12,13,84].

As expected, the presence of the severe sepsis is associated with increased risk of myocardial depression. Interestingly, this variable had the least effect on the factor.

Increasing systolic blood pressure and the presence of cardiovascular organ dysfunction are associated with increased risk of myocardial depression. Ostensibly, this presents a paradox, as cardiovascular organ dysfunction is present with low systolic (or mean arterial) blood pressure or the use of vasopressors for >1 hour. This, however, likely demonstrates a non-linear relationship of the variables, to the development of myocardial depression, at extreme values.

The majority of these variables are either directly related to cardiovascular function, the exception is severe sepsis, however, this has been associated with the development of myocardial depression and also has well-described pattern of cardiovascular responses[186].

Whilst individually none of these variables are particularly surprising as explanatory variables, it is the underlying relationship to the development of myocardial depression that is intriguing. The removal of any of these five variables is significantly detrimental to the model performance, thus each variable is contributing to the correlation to the outcome. Individually, none of the five explanatory variables was able to act as a predictor to the development of myocardial depression, but as a factor, a meaningful relationship to the outcome variable has been elucidated.

As the prediction of myocardial depression in the general population of adults experiencing critical illness has not been previously attempted, it is impossible to compare the utility of the variables identified in this modelling with the work of others. It is also important to consider the candidate variables that were not useful

in the prediction of myocardial depression and potential explanations for their lack of predictive ability.

A number of explanatory variables were identified as redundant from the vector map produced by principal component analysis and model refitting. Interestingly, some variables that intuitively may be relevant, did not demonstrate additional explanatory power in this analysis. For instance, Takotsubo's cardiomyopathy, a variant of myocardial depression, has previously been described to occur more commonly in older women[55], however neither age nor gender were identified as giving additional explanatory power in the prediction of myocardial depression in this analysis.

Traditionally, men are responsible for 55 – 60%[98,99,187,188] of admissions to AICU, and, in this study comprised 68% (n = 79) of total participants. Of the 27 participants exhibiting myocardial depression, women represented one third (n = 9), and were therefore not under represented in the development population. Nevertheless, in this analysis, gender did not add any additional explanatory power to the prediction of myocardial depression nor were females predominantly affected by this condition.

Within the UK the mean age of admission to AICU has hovered around 60 (SD ± 18)[97–99,187,188] years, this is marginally older than the mean age of participants with myocardial depression observed in this study (mean 56, SD ± 18). This suggests that the range of ages observed in the sample of participants with myocardial depression, are representative of the broader AICU population. Interestingly, age

was not identified as a good explanatory variable for the development of myocardial depression. This is likely attributed to myocardial depression, including Takotsubo's cardiomyopathy, increasingly reported to occur across a range of ages[189], which is supported in the present study (range: 18 – 82).

Respiratory function was assessed through two variables; respiratory organ dysfunction, a binary variable based on PaO_2/FiO_2 measurement, and mean airway pressure, a continuous variable. Neither variable gave additional explanatory power to the model, which suggests that respiratory dysfunction, as assessed by PaO_2/FiO_2 and mean airway pressure, do not play a major role in prediction of myocardial depression.

Interestingly, the presence of wall motion abnormalities on baseline AICU echocardiography was not a useful predictor for the development of myocardial depression. Whilst other studies have described wall motion abnormalities to be a common feature or indeed necessary for the diagnosis of myocardial depression, as described in section 3.4, this was not a common feature in the ELF studies. This could potentially explain why the presence of wall motion abnormalities was not a useful discriminator for the development of myocardial depression in this analysis.

AICU admission category (medical vs. surgical) was also not a useful predictor of the development of myocardial depression. Seventeen percent (n = 20) of ELF study participants were admitted following emergency surgery, which is nearly identical to the national AICU case mix (18%)[97–99,188,190]. Yet only four of these participants developed myocardial depression.

Future work should re-examine the influence of emergency surgery on the development of myocardial depression - it has been reasonably suggested that the physiological stress of surgery is sufficient to induce myocardial depression in susceptible patients[60]. The precise effect of surgery on the development of myocardial depression could be more reliably elucidated with a greater sample size.

Vasopressor therapy was defined as treatment with noradrenaline, adrenaline, terlipressin or vasopressin at the time of echocardiography, treated as a binary variable. In isolation, this was not a useful predictor of myocardial depression. Potentially, the effect of vasopressor administration could have been indirectly captured by the binary cardiovascular organ dysfunction variable, as this is coded positive in the event of systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or the use of vasopressors for >1 hour. In model refinement, cardiovascular organ dysfunction was identified as a more useful explanatory variable than vasopressor use. The precise effect of vasopressor administration on the development of myocardial depression could potentially be elucidated from a larger sample size.

6.3 Novelty

Prediction of the development of myocardial depression in the general population of adults experiencing critical illness has not been previously attempted. As described in section 1.3.8, a limited number of studies have been undertaken to predict the development[4,5] and pattern[3] of cardiac dysfunction observed following SAH, medical AICU patients without pre-existing cardiovascular disease, and also

in sepsis[42]. It is unknown if the results observed in these sub-populations are generalisable beyond their development cohort.

This model presents a means to predict the development of myocardial depression in patients experiencing critical illness using routinely collected clinical and haemodynamic variables. The correlation of the model to the development of myocardial depression is r = 0.28. Whilst the correlation is weak[191], it does demonstrate a dependency of the outcome variable on the explanatory variables.

As this is new work, it has not benefitted from the experience of others. Firstly, there was uncertainty of the incidence of myocardial depression, and therefore the feasibility of predictive modelling. Consequently, selection of candidate variables was restricted to routinely collected data available within the first 24 hours of AICU admission. Unfortunately collinearity amongst explanatory variables precluded reliable estimates of odds ratios and regression coefficients of individual variables by logistic regression. This work does, however, provide a starting point from which future research can build on to elucidate the relationship of individual variables to the development of myocardial depression.

Even in the current form, this model has the potential application of providing decision support for clinicians by identifying patients at risk of myocardial depression. The final model demonstrated modest discriminating ability (ROC AUC 0.69), and a threshold of Pr $\geq$0.25 was determined as the cut off that minimised the number of false negatives. Minimising false positives is generally considered preferable when identification of the outcome would result in

burdensome or costly investigations or treatment. As myocardial depression can be identified using transthoracic echocardiography, which is non-invasive, has minimal patient burden and minimal on-going expenditure beyond the initial cost of infrastructure, minimising the false negatives was considered preferable.

Finally, the model was transformed into a simplistic form by the development of the Trubody score. The scaling provided by the calculation of the score facilitates simplistic interpretation and may trigger early review or surveillance echocardiography in at-risk patients. This algorithm could easily be integrated into a patient clinical information system to produce the score, and estimate of risk.

Intuitively, the Trubody score is most useful in patients with higher risk of myocardial depression. A higher Trubody score is associated with greater risk, therefore a clinician may initiate surveillance echocardiography, which could lead to earlier identification of myocardial depression and associated sequelae, such as intra-cardiac thrombus.

6.4 Limitations and strengths of predictive model

This predictive model has limitations. It was developed from a small sample size, reflecting difficulties in obtaining a sufficient sample from a single-operator study. Additionally, the odds ratios and statistical significance of each variable as a stand-alone predictor is unknown. Furthermore, explanatory variables were collected at a mean duration of 13 hours following AICU admission, and the effect of collection time on model performance is unknown.

Variables included in the model represent readily available clinical and haemodynamic data. Whilst this follows the recommended approach[137], it does preclude early inclusion of potentially useful variables, such as novel biomarkers.

The use of canonical correlation precluded elucidation of a single, independent variable that was a predictor of the development of myocardial depression. The model does, however, provide a foundation for future work to clarify the precise relationship between explanatory variables and the development of myocardial depression.

The strengths of the model lie in the consistent definitions and prospectively defined data collection rules, the routine availability of explanatory variables and the generalisable population from which it was drawn.

Variables were prospectively defined and were collected according to rules of the study data dictionary. Inconsistency in variable definitions has been identified as an impediment to predictive model generalisability[192], therefore, where necessary, variable definitions were sourced from highly cited publications from leading journals.

None of the articles identified from the literature review into prediction of myocardial depression in critically ill sub-populations (section 1.3.8) discussed data collection rules. This lack of transparency in collection rules hampers the reproducibility of their findings.

A strength of this predictive modelling lies in the routine availability of the data, collected to prospectively defined data collection rules, incorporating accepted definitions.

The mean time to collection of variables was 13 hours since admission to AICU. What effect the time of collection has on the reliability of predictive model remains unknown. Modelling at different time points since admission to AICU was not attempted due to the sample size, nevertheless, the merits of the exercise would be questionable as defining the onset of critical illness remains notoriously difficult and would not account for mitigating circumstances such as delayed admission to AICU.

The ambiguity of the effect of the time of recording on predictive variable measures is not new. For example, a study by Post[42] (literature review 2, section 1.3.8) used B-type natriuretic peptide (BNP) to predict the development of septic myocardial depression in AICU patients (n = 93), and reported that a BNP level >154 pg/mL on day five was most useful in prediction. It was not, however, reported when the sampling occurred or the potential effect of diurnal variability[193] on the reliability of the predictive model.

The work of Post[42] is merely one example of a predictive model on AICU patients that has encountered the difficulty of estimating the effect of time on the measurement of explanatory variables. Whilst the effect of time of observation on the prediction of myocardial depression may be elucidated with a greater sample size, it would not overcome the difficult in defining the onset of critical illness.

Finally, whilst the sample size of the development population is comparatively small (n = 112), all reasonable attempts were made to increase the size of the development cohort, including accessing retrospective data (ELF 2). Consequently, the ELF dataset is one of the largest from a single centre. Furthermore, the inclusion criteria of the ELF studies were kept broad, with minimal exclusion criteria to maximise generalisability of the study population; with the exception of elective admissions to AICU, as it was felt these patients do not represent a similar cohort to emergency admissions. As discussed in the previous section on explanatory variables, the age and gender composition of the development cohort is similar to the AICU case-mix reported by the Intensive Care National Audit and Research Centre[97–99].

As a pilot, the prediction of myocardial depression in the general adult population experiencing critical illness, was a success. This exploratory work demonstrates that the incidence of myocardial depression in this population is sufficient to facilitate development of a predictive model, and has identified explanatory variables of interest. The threshold to minimise the false negatives has been determined and through the creation of the Trubody score, a clinically useful and intuitive tool has been developed to assess risk of myocardial depression using routinely available observations. Key areas of future work and lessons learned from this process are discussed in the following section.

6.5 Future work

Many of the challenges presented by the dataset stem from the sample size. The incidence of myocardial depression reported in the ELF studies was between 16 – 34%. Despite this, the practicalities of identifying a substantial number of patients with myocardial depression from a single centre presents challenges. Whilst echocardiography is being increasingly adopted in critical care units, particularly in Europe, in the UK daily transthoracic echocardiography has not yet become part of routine assessment. Consequently, tracking changes in LV systolic function over time, and establishing the development of myocardial depression remains labour-intensive.

The creation of a registry of patients with myocardial depression would allow more reliable estimates of the incidence, time course and sequelae to be determined. Furthermore, collection of basic haemodynamic, demographic and clinical data would facilitate expansion of available candidate variables.

Whilst useful explanatory variables have been identified from this work, an increased sample size would potentially mitigate the effect, and therefore some of the problems, of collinearity between explanatory variables. A greater sample size could facilitate the identification of useful individual explanatory variables and reliably estimate their effect size.

This project has demonstrated that the prediction of myocardial depression in patients experiencing critical illness is feasible, and whilst this has identified some

useful explanatory variables, they represent routinely collected clinical and haemodynamic data. An area of future investigation would be the role of plasma catecholamines as predictors of myocardial depression. As discussed in the introductory chapter (section 1.2.1.1), elevated plasma catecholamines have been proposed as a common pathophysiological mechanism in the development of myocardial depression. Consequently, these may be promising novel predictors.

The next step logical step in the current work would be to validate the effectiveness of the Trubody score and the predictive model. The intent was to construct the model from the ELF 1 and 2 studies and validate this on the ELF 3 population, however the number of participants with myocardial depression was insufficient for this purpose[137]. Nevertheless, the routine availability of the explanatory variables, and the potential for the Trubody score to be integrated into a patient clinical information system, means the validation process will not be too onerous and with increasing adoption of echocardiography in critical care units makes this the next logical step in this area of research.

The ability to identify patients at risk of myocardial depression within the first 24 hours of AICU admission could result in greater identification of this process, thereby facilitating the tracking the clinical course and expanding the body of evidence on the outcomes of this condition.

6.6 Summary

This work has addressed a key research question and has demonstrated that it is possible to predict the development of myocardial depression using routinely collected clinical and haemodynamic variables available within the first 24 hours of admission to AICU.

A total of 112 participants from the three ELF studies were included in the development population. Whilst this is a small sample size, all attempts were made to increase the size, including identification of retrospective data (ELF 2). A total of 27 participants in the development cohort demonstrated myocardial depression.

Preliminary work identified collinearity amongst explanatory variables. Consequently, canonical correlation was used to express the explanatory variables as a factor. The list of available candidate explanatory variables was not exhaustive, but represented routinely collected data.

Five variables were identified as useful explanatory variables. Systolic blood pressure, heart rate, sinus rhythm, cardiovascular organ dysfunction, and severe sepsis contribute to the prediction of myocardial depression. These variables were collected according to a prospectively defined data collection dictionary.

These variables were expressed as a factor that was then used as an explanatory variable in a binary regression generalised linear model. This model was statistically significant ($p < 0.05$) and demonstrated modest discriminating ability (AUROC 0.69). Model diagnostics were then performed as per the

recommendations of Collett[163] for modelling binary data, which demonstrated a well-fitting model. The threshold of Pr ≥0.25 was then determined as the cut off that minimised the number of false negatives. Finally, the creation of the Trubody score allows for the calculation of risk of myocardial depression at the bedside.

The future work of this area of research will be to validate the model and associated scoring system and elucidate the precise predictive ability of the explanatory variables in the model. A potential novel and promising predictor may be plasma catecholamines, as they form part of a proposed common pathophysiological mechanism of reversible cardiomyopathies[66].

Chapter VII: Conclusion

7.0 Overview

This chapter revisits the justification for the research, the key findings and their theoretical implications, the limitations of the work and areas for future research.

7.1 Study rationale

The ELF studies had two aims: to characterise epidemiological features of myocardial depression and to determine if myocardial depression can be predicted using routinely collected variables available within the first 24 hours of AICU admission.

The development of myocardial depression has been associated with a host of adverse sequelae, including arrhythmias, intra-cardiac thrombus, left ventricular outflow tract obstruction and shock.

Traditionally, the features of myocardial depression have been described by the concomitant disease process e.g. septic myocardial depression. This approach has overlooked the striking overlap in the presentation, time course, pattern of wall motion abnormalities and elevation of biomarkers amongst commonly described manifestations.

The precise aetiology is unknown, but one theory suggests that excessive sympathetic activity, as a result of physiological stress, drives cardiac myocyte injury via a cyclic-AMP mediated calcium overload. This theory is supported by the

histological feature of contraction band necrosis, which is consistent with catecholamine excess, identified in patients with sub-types of myocardial depression.

Increasingly, reversible myocardial depression has been considered to represent a spectrum, rather than separate disease processes. The existing literature is dominated by descriptions of the epidemiological features in sub-populations of critical illness. It is unknown if these findings are generalisable to the broader population of critically ill patients.

Few studies have been undertaken to describe the epidemiological features in the general population of adults experiencing critical illness. These studies have tended to be small and excluded patients with pre-existing cardiac disease, which is often poorly defined. Exclusion of patients with pre-existing cardiac disease hampers generalisability and is problematic, as it has been reported that up to 30% of AICU patients exhibit occult cardiac disease.

Furthermore, significant methodological limitations in the existing literature have been identified. Many studies have used a threshold, rather than change in LVEF, to define myocardial depression, which presents problems. Firstly, patients with chronically reduced LVEF may be inappropriately classified as demonstrating myocardial depression, therefore confounding the reported incidence. Finally it is unknown if the thresholds of LVEF used in the studies are relevant in the critically ill patients.

In the studies that have described changes in LVEF over time, few have reported intra- and inter-observer variability data, thus the reliability of the measurements, and therefore, results, are unknown.

Consequently, a number of key epidemiological features of myocardial depression remain unclear in the general population of adults experiencing critical illness. Furthermore, no study has, to the best of my knowledge, been undertaken predictive modelling to identify risk factors for the development of myocardial depression in this population.

Given the adverse sequelae that have been described in sub-populations of patients experiencing critical illness, and the absence of robust evidence of the epidemiology in the general critically ill population, the ELF studies were designed to answer the following research questions:

- What is the incidence of LV systolic RMD occurring in the general AICU?
- What is the natural history of LV systolic RMD occurring in the general AICU?
    - When does myocardial depression occur during AICU admission?
    - What is the decline in LVEF?
    - What proportion of patients demonstrate recovery?
    - What is the degree of recovery in LVEF?
- Can we predict the development of LV systolic myocardial depression using routinely collected variables within the first 24 hours of AICU admission?
- Can we predict the recovery of LV systolic myocardial depression?

7.2 Key findings

The incidence of myocardial depression was between 16.3 – 34.0%, which occurred at around three to four days following admission to AICU. An additional latent myocardial depression was observed in nine participants in ELF 1 and eight in ELF 2, occurring around three weeks following discharge from AICU. The median decline in LVEF at the onset of depression was between 6.5 – 14.7%, progressing to between 10 – 17.5% at the nadir. Between 43.7 – 71.4% of participants demonstrated some degree of recovery of LVEF during the study period, with the median improvement in LVEF between 13.3 – 20.2%.

The development of myocardial depression can be predicted by systolic blood pressure, heart rate, sinus rhythm, cardiovascular organ dysfunction and severe sepsis, expressed as a factor. The presence of severe sepsis and extreme blood pressures, are associated with increased risk. Increases in heart rate and the presence of sinus rhythm are associated with decreased risk of development.

Predicting recovery from myocardial depression was unfeasible in the current study, as the number of participants demonstrating recovery in the ELF studies was too low.

7.3 Theoretical implications

Prior to the ELF studies, the incidence of myocardial depression in the general critically ill population had been reported to be between 6 – 95% i.e. it is unclear. The incidence reported in the ELF studies is similar to the findings of Park[60], who

reported the incidence to be 28%. Park[60] and colleagues recruited patients from a medical AICU, therefore, the slightly higher overall incidence in the ELF studies could potentially be attributed to the inclusion of surgical patients.

The ELF studies have identified that myocardial depression is not uncommon, and is not limited to certain sub-populations of critical illness. This is consistent with the theory that the physiological stress of critical illness is sufficient to induce myocardial depression.

The ELF studies provide a description of the onset of myocardial depression occurring during critical illness. This has scarcely been previously reported, with only two studies previously describing the development of myocardial depression occurring beyond day one of AICU admission. This was observed in up to one third of patients, typically occurring during days two to three of AICU admission.

The majority of the existing literature uses a threshold to classify patients as demonstrating myocardial depression on day one of AICU admission, these patients are then observed over time. This is a flawed approach as it makes the assumption that myocardial depression is exhibited at day one, and, by using a threshold rather than a change in LVEF, it assumes a decreased LVEF is attributable to myocardial depression. This may inadvertently include patients with a chronically reduced LVEF. Attempts at excluding patients with pre-existing cardiovascular disease are fraught with difficulty as firstly, pre-existing cardiovascular disease is not synonymous with impaired LV systolic function, and also occult cardiovascular disease has been demonstrated to occur in up to one third of AICU patients.

The onset of myocardial depression occurred between days three to four during the ELF studies. This was consistent in both prospective and retrospective datasets, which indicates that this finding was not purely a function of the timing of assessments set by study protocol. This delayed onset is an interesting observation, which may potentially be explained by catecholamine exposure. As mentioned earlier, a proposed mechanism of myocardial depression is catecholamine excess. The physiological stress of critical illness[66], coupled with catecholamine administration in 80% of participants with myocardial depression may result in cardiotoxic effects, which are both dose and time dependent[79].

The decline in LVEF occurring during myocardial depression had not been previously quantified. The ELF studies provide a novel description to the extent of LV systolic dysfunction observed during myocardial depression. The absolute drop in LVEF to the nadir was substantial (between 10 – 17.5%) and demonstrates that the impairment of systolic function is considerable and extends far beyond the intra-observer reliability of the researcher.

The literature on the recovery from myocardial depression is inconclusive, with the incidence ranging from 0 – 100%. Similarly, in the ELF studies the results are unclear, with the incidence of recovery falling between 43.7 – 71.4%. In those that recovered, the increases in LVEF (13.3 – 20.2%) are in the vicinity of improvements reported by others (19%[35] and 26%[71]). Unfortunately, too few participants recovered to facilitate predictive modelling to identify features to predict recovery. The source of this heterogeneity in recovery remains

undetermined, nevertheless, this indicates that myocardial depression occurring during critical illness is not a benign process and warrants further investigation.

Predictive modelling identified five explanatory variables associated with the development of myocardial depression. Heart rate, systolic blood pressure, and the presence or absence of sinus rhythm, severe sepsis and cardiovascular organ dysfunction are useful to determine risk of developing myocardial depression. In this model, the variables are expressed as an explanatory factor. Consequently, the precise risk associated with each individual variable on the development of myocardial depression remains unquantified. Nevertheless, these useful explanatory variables have been identified and form a foundation for future work. Prediction of myocardial depression in the general AICU has not been attempted before, thus this work represents a promising proof-of-concept.

7.4 Limitations

Whilst this research has provided a comprehensive description of the epidemiological features and identified a method to assess risk of the development of myocardial depression, this work has a number of limitations that must be considered.

Firstly, the sample size of the ELF studies was small, and participants were recruited from a single centre. Furthermore, to facilitate assessment of changes in LV systolic function over time, participants were admitted to AICU for longer periods, thus the ELF studies reflect a selected population.

Additionally, LVEF was calculated using linear measurements, which were performed by a relatively inexperienced operator who was not blinded to prior results.

Predictive modelling using traditional techniques was hampered by multicollinearity between explanatory variables, which may have been avoided by a larger sample size. Alternative techniques were used, which precluded the estimation of odds ratios for individual explanatory variables. The final model had a modest discriminating ability, but is yet to be externally validated.

Nevertheless, the findings of the ELF studies, combined with the aforementioned limitations, focus the direction of future work.

7.5 Future work

There are two main areas of future work that warrant further investigation, epidemiology and aetiology.

Firstly, whilst the ELF studies have provided a foundation to describe some of the epidemiological features of myocardial depression in critical illness, others remain unclear. Future work should focus on characterising the incidence of recovery and identify features that may differentiate between those that do and do not recover.

Future projects can incorporate findings from the ELF studies, e.g. time to depression, into their design so that timing of study assessments are evidence based, rather than arbitrary.

Furthermore, the precise nature of the explanatory variables on the development of myocardial depression should be elucidated. The ELF studies have identified variables that are associated with the outcome, but were underpowered to elicit their direct effect.

An exciting area of future work is exploring the relationship between endogenous and exogenous catecholamines and the development of myocardial depression. Whilst the cardiotoxic effects of catecholamines is known, and their use essential in critical care units, investigating the effect of different therapeutic doses of catecholamines on the risk of myocardial depression is a promising and novel area of research.

Furthermore, elevated endogenous plasma catecholamines have been identified in a few small studies of sub-populations of patients with myocardial depression. It would be interesting to identify if patients that develop myocardial depression exhibit higher levels of endogenous catecholamines in the early stages of critical illness, as this may be useful to differentiate at risk patients. However, it is currently impossible to biochemically differentiate between endogenous and exogenous catecholamines. Furthermore, given the labour-intensive specimen handling process and multiple confounders of assay results, careful thought must be given to study design.

Whilst echocardiography provides a non-invasive assessment of LV systolic function with minimal risk or burden to the patient, it is unable to fully characterise the myocardium. Additionally, the architecture of the right ventricle precludes

thorough assessment by echocardiography. Cardiac magnetic resonance imaging, however, is able to provide a comprehensive assessment of tissue, volumes and function of the entire heart. This method has been employed in sub-populations of critically ill patients demonstrating myocardial depression, which has demonstrated myocardial oedema. Future work should utilise this modality in the broader population of critically ill patients, to characterise the myocardium and therefore potentially confirm the finding of myocardial oedema. This may add evidence to the argument that myocardial depression represents a continuum, rather than separate disease processes. This area is the focus of post-doctoral research.

7.6 Summary

The ELF studies have provided a comprehensive description of myocardial depression occurring in the general population of adults experiencing critical illness. Furthermore, they have identified variables associated with the development of myocardial depression and harnessed this information to provide a bedside assessment of risk. Whilst these studies have limitations, they have identified important and novel areas of future work that will further characterise the epidemiological features and aetiology of this condition.

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Appendices

Appendix 1: Mayo Clinic criteria Takotsubo's cardiomyopathy

Mayo Clinic diagnostic criteria for Takotsubo's cardiomyopathy[57]. All four criteria must be met for the diagnosis to be made.

1	Transient hypokinesis, akinesis or dyskinesis of the mid-LV segments with or without apical involvement; the regional wall motion abnormalities (RWMA) extend beyond a single epicardial vascular distribution
2	Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3	New electrocardiographic abnormalities (ST segment elevation and/or T wave inversion) or modest elevation in cardiac troponin
4	Absence of pheochromocytoma or myocarditis

Appendix 2: CASP checklist for all papers in literature review 1

1. Bailen

Reversible myocardial dysfunction, a possible complication in critically ill patients without heart disease
Bailen, Journal of Critical Care, 2003

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Description of reversible myocardial depression in critically ill patients without a history of cardiovascular disease

---

2. Was the cohort recruited in an acceptable way? ☐ Yes ☑ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Excluding patients with sepsis could significantly compromise generalisability of the findings. Furthermore, only patients who had an echocardiogram for a clinical indication were included in the study.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Clear inclusion criteria. Exclusion criteria were detailed, although specific definitions (e.g. sepsis) were not provided.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Echocardiography was measured in a standardised way, with a mean of three ejection measurements taken.
Regional wall motion scores were recorded according to accepted guidelines.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

5. (a) Have the authors identified all important confounding factors?

☐ Yes ☐ Can't tell ☑ No

Large intervals between echocardiograms (timing: 1st 24 hours, 1 week, between weeks 2-3, one month, between 3-6 months) could potential result in myocardial depression being undetected as it may develop, and resolve, during an imaging interval.

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: The author has recognised that the reported incidence of this study is not generalisable.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☑ Yes ☐ Can't tell ☐ No

25 of 33 patients

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

All patients demonstrated RWMA. Initial median LVEF was 34 (range 16-48%), which improved to 60 (range 50-73%) by 3-6 months following AICU admission. RWMA resolved with improvement in LVEF.

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8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

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9. Do you believe the results?

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

☐ Yes ☐ Can't tell ☑ No

I don't believe this study can make reliable estimates of the incidence. It does, however, demonstrate reversible myocardial depression in critical illness.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☐ Yes ☑ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Provides increased awareness that reversible myocardial dysfunction can occur during critical illness. Although the incidence remains yet to be elucidated.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

Increasing recognition of reversible myocardial dysfunction occurring during critical illness.

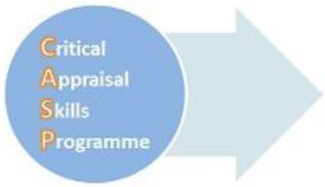
---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Increased awareness.



Isolated and reversible impairment of ventricular relaxation in patients with septic shock
Bouhemad et al, Critical Care Medicine, 2008

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Explore the relationship between troponin-I and reversible diastolic function in septic shock

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Recruited from a surgical intensive care unit. Clear inclusion and exclusion criteria, although excluded patients with a history of "cardiac disease" although this is not defined. Also excluded patients not in sinus rhythm.

Sepsis/septic shock defined using accepted definitions

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Very comprehensive approach to standardising therapies across patients. Very clear process.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Blinded echo reader. Measurements taken at end-expiration over 5 cardiac cycles. LV systolic dysfunction was defined as a FAC <50%, which is accepted.

5. (a) Have the authors identified all important confounding factors?

☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: Very comprehensive approach to minimise variability in patient management, which could have potentially affected echo values (adequate fluid resuscitation etc).

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☐ Yes ☑ Can't tell ☐ No

Unclear the exact number of patients at each time point

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

Following patients until day ten of AICU stay or cessation of vasoactive support, whichever earliest.

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

11/54 patients demonstrated systolic dysfunction, defined as a FAC <50%. The mean FAC at day 1 was 34% +/- 11%, which progressively normalised to a mean of 50 +/- 11% at the final study (mean: day 7). Changes in FAC were not statistically correlated with changes in troponin-I.
Furthermore, reversible diastolic dysfunction was associated with transient increases in troponin-I, tumor necrosis factor alpha, IL-8 and IL-10, in 20% of patients with septic shock.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Thorough and methodical approach.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Yes, transparent approach. Although the incidence was slightly lower (20.3%) than what has been reported in other studies, this may be due to excluding patients with cardiac disease and those not in sinus rhythm.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

Fairly consistent with other studies from similar populations

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Provides a description of the incidence and time course of reversible myocardial depression in septic shock. These changes were not associated with changes in troponin-I.

Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis
Charpentier et al, Critical Care Medicine, 2004

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

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- **Will the results help locally?** **(Section C)**

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Investigate the role of B-type natriuretic peptide as a marker of myocardial depression in severe sepsis in critically ill patients.

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Clear inclusion and exclusion criteria. Generalisable cohort, although reservations about excluding patients with chronic hypertension - this is a common pre-existing medical condition amongst AICU patients.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Used accepted definitions of sepsis.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Echocardiography measures interpreted by a blinded operator.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

5. (a) Have the authors identified all important confounding factors?

☐ Yes ☐ Can't tell ☑ No

Intra/inter observer variability not discussed. Observed changes in LV systolic function could potentially due to measurement error.

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☐ Yes ☐ Can't tell ☑ No

List: Inter/intra observer variability of echocardiography should be reported.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☐ Yes ☐ Can't tell ☑ No

Data for 34 patients available for D2, whereas only 16 available at D8.

(b) Was the follow up of subjects long enough?

☐ Yes ☐ Can't tell ☑ No

Ideally, follow up for those demonstrating persisting impairment at day eight, as delayed recovery of myocardial depression has been observed.

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

On day 2 of AICU stay, 15 patients had a fractional area change (measure of LV systolic function) <50% (mean 38.6 (SD +/- 2.4)), in the five patients with follow up data at day 8, this had risen to a mean of 61.6% (SD +/- 0.9). Higher BNP levels were observed in patients with myocardial depression between AICU days 2-4.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

The standard deviations around the reported fractional area change is low.

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Yes, although the inter/intra observer variability should be reported to demonstrate the changes observed in FAC are beyond measurement error.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

Incidence is consistent with literature of myocardial depression in sepsis

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Raised awareness that increased BNP levels may be associated with development of myocardial depression

Cardiac morphological and functional changes during early septic shock: A transesophageal echocardiographic study
Etchecopar-Chevreuil et al, Intensive Care Medicine, 2008

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Characterise the cardiac morphological and functional changes that occur during early septic shock

---

2. Was the cohort recruited in an acceptable way? ☐ Yes ☑ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Appears to have used a definition of septic shock that is similar to, but not the same as accepted guidelines.
Excluded patients with "previous cardiac disease", but this is not defined, nor described how this was identified. Excluded patients that are not in sinus rhythm.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Well described definition of sepsis. Patients treated according to directive of consultant.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Cut offs for LV dysfunction are defined, although are different to accepted thresholds of the British Society of Echocardiography and the European Association of Echocardiography.
Blinding of echocardiographer not reported.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

5. (a) Have the authors identified all important confounding factors?

☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: Reported intra and inter-observer variability of echocardiographers.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

< 24 hours, cessation of vasoactive support and again at 28 days following AICU discharge in those with persisting dysfunction.

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

16 patients (46%) had depressed LVEF at day 1. LVEF depression had completely resolved in 12 patients at the cessation of vasoactive support (day n), and the remaining four patients recovered by day 28. Diastolic dysfunction was present in 7 patients on day 1, which resolved by day n.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Slightly higher incidence could be accounted by the inclusion criteria.
Pattern and resolution of myocardial depression consistent with the literature.

(C) Will the results help locally?

10. Can the results be applied to the local population?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Whilst the definition of septic shock is slightly different to accepted definitions, the results are consistent with the literature. Myocardial depression is not uncommon in patients with septic shock and the majority of patients resolve their systolic dysfunction during AICU.

---

11. Do the results of this study fit with other available evidence?

☑ Yes ☐ Can't tell ☐ No

Yes. Higher incidence may be due to differences in definition used in sepsis.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Supporting evidence for the incidence and time course of myocardial depression in septic shock.
Reservations regarding the definition of septic shock used and the non-standard echocardiography parameters.

Persistent Preload Defect in Severe Sepsis Despite Fluid Loading
Jardin et al, Chest, 1999

12 questions to help you make sense of cohort study

How to use this appraisal tool

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These checklists were designed to be used as educational tools as part of a workshop setting

There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Investigate rate of recovery from septic shock in patients with suspected LV dysfunction

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Specific inclusion criteria - vasoactive support for >24 hours, absence of cardiopulmonary disease, identification of causative bacterial agent

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Sepsis was defined using an accepted definition.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Standardised procedure for review of echocardiographic images. Observer blinded to the final outcome.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

5. (a) Have the authors identified all important confounding factors?

☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: Protocolised haemodynamic management

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☐ Yes ☐ Can't tell ☑ No

144 patients enrolled, 54 excluded due to poor echo windows, 56 patients (62%) died in AICU, very limited complete dataset. High mortality known in sepsis.

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

In those that survived, they were followed to the end of AICU stay.

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

In survivors (n = 34), ejection fraction demonstrated statistically significant improvement between day one of AICU admission and AICU discharge. No change observed in non-survivors

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Consistent with other studies.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Although older study, some changes in clinical practice are to be expected.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

Observed recovery of LVEF and high mortality associated with sepsis are consistent.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Survival benefit of initially depressed ejection fraction and then recovery prompts further investigation.

Diastolic dysfunction and mortality in severe sepsis and septic shock
Landesberg et al, European Heart Journal, 2012

12 questions to help you make sense of cohort study

How to use this appraisal tool

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Effect of diastolic dysfunction on mortality in septic shock.

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Population, site, recruitment window well defined

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Excluded potential confounders and defined sepsis.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Defined process for collecting echocardiographic parameters. Blinded, independent echo reader.

5. (a) Have the authors identified all important confounding factors? ☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ☑ Yes ☐ Can't tell ☐ No

List:

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough? ☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough? ☐ Yes ☐ Can't tell ☑ No

Echocardiography studies were undertaken on day 1 and day 2 of AICU admission. This is insufficient to capture changes over time.

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

61/262 demonstrated systolic dysfunction. No changes in any recorded echocardiographic parameter between day 1 and day 2. Patients with systolic or diastolic dysfunction had higher BNP and troponin-T.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

---

9. Do you believe the results?

☐ Yes ☑ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Insufficient capture period to determine changes in systolic or diastolic function over time

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Reported incidence of LV systolic myocardial depression is inkeeping with other studies.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

The incidence of myocardial depression observed in sepsis is similar to other studies, but the timing of echocardiography precludes description of recovery.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Additional evidence establishing the incidence of myocardial depression in sepsis.

Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock
McLean et al, Critical Care Medicine, 2007

12 questions to help you make sense of cohort study

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(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Investigate the role of BNP in predicting outcomes in AICU patients with severe sepsis/septic shock

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Accepted definition of sepsis. Recruited from a mixed medical and surgical, general AICU.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Used accepted definitions of sepsis. Enrolled all patients that were suspected of having sepsis, and then later excluded patients from the analysis if this diagnosis was not confirmed.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Accepted assessment method for echocardiography measures. Echocardiographer not blinded to outcome

5. (a) Have the authors identified all important confounding factors?

☐ Yes ☐ Can't tell ☑ No

Study looked at BNP levels, but did not exclude patients with pre-exisiting conditions known to elevate BNP.

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☐ Yes ☐ Can't tell ☑ No

List: Did not exclude patients with pre-existing conditions known to elevate BNP.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

Day ten of AICU admission, or AICU discharge, whichever earlier. This is a reasonable follow up period to capture reversible changes.

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

7/40 patients demonstrated reversible myocardial depression. None of these patients had a history of chronic cardiac dysfunction. 100% of patients recovered their LVEF to >55% at an average of 4.7 +/- 2 days since AICU admission.
There were no differences in mortality, length of stay and admission BNP levels.
BNP levels were elevated in sepsis, regardless of cardiac function, mortality or length of stay

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

---

9. Do you believe the results?

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

☑ Yes ☐ Can't tell ☐ No

This study is well designed. Although patients that may have chronically elevated BNP were not excluded, this makes the results more generalisable because, from a practical perspective, it is difficult to identify all possible conditions that may increase BNP.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Very similar setting, easily to identify cohort.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

BNP has previously been trialled as a prognosticator for septic myocardial depression, with little success.
The incidence of reversible myocardial depression is lower (17.5%) than what has been previously described in sepsis (approximately 1/3 affected)

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Identified that BNP levels cannot discriminate between those with myocardial depression and those without.
Identified that reversible myocardial depression in sepsis takes around 5 days from AICU admission to recover. Recovery was observed in 100% of patients

B-type natriuretic peptide release and left ventricular filling pressure assessed by echocardiographic study after subarachnoid hemorrhage: a prospective study in non-cardiac patients
Meaudre et al, Critical Care, 2009

12 questions to help you make sense of cohort study

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Quantify the incidence, time course, and recovery patterns of BNP and LV filling pressures by using serial echocardiographic measurements during the first week after aneurysm rupture.

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Clear inclusion and exclusion criteria, although excluded patients from analysis who died before day 7 ?bias
Managed by standard protocol

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☐ Yes ☑ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Comprehensive interviews with NOK to ensure SAH occurred within 48 hours of AICU admission. Patients treated according to protocol/treating physician.
Excluded patients not in sinus rhythm, but this is a significant as arrhythmia is not uncommon after neurological insult.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Performed by an experienced, blinded, cardiologist. Measurements performed according to accepted guidelines. LVEF <50% defined as abnormal.

5. (a) Have the authors identified all important confounding factors? ☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ☑ Yes ☐ Can't tell ☐ No

List: Excluded patients with pre-existing conditions known to cause an elevated BNP

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough? ☐ Yes ☑ Can't tell ☐ No

(b) Was the follow up of subjects long enough? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

No patients had a LVEF <50% during the study period. BNP increased following SAH, and returns to baseline in approximately one week. Increase in BNP is not associated with increased LV filling pressures.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

---

9. Do you believe the results?

☐ Yes ☑ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Excluded patients not in sinus rhythm, but this is a significant as arrhythmia is not uncommon after neurological insult.
Over half the patients that were admitted to the unit were ineligible ?generalisability
Furthermore, excluded patients with hypertension, however hypertension is common amongst patients with SAH.
I am suspicious that not a single patient had a LVEF <50%. Intra/inter observer variability is not reported.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☐ Yes ☐ Can't tell ☑ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Not a generalisable cohort

---

11. Do the results of this study fit with other available evidence? ☐ Yes ☐ Can't tell ☑ No

Did not observe myocardial depression following SAH.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Nil, without further evidence.

N-terminal pro-brain natriuretic peptide as an early prognostic factor in cancer patients developing septic shock
Mokart et al, Critical Care, 2007

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(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Identify the role of N-terminal pro-BNP as an early prognostic factor of AICU patients with cancer and septic shock

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Sepsis defined using accepted guidelines. Excluded patients with conditions known to increase N-terminal pro-BNP levels. Consecutive enrollment undertaken. Excluded patients with a LVEF <45% at AICU admission

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Sepsis was well defined, using an accepted definition.
Excluded patients with pre-existing conditions associated with increased N-terminal pro-BNP levels.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Biomarker testing procedure well described. Although samples not necessarily taken at the same time as echocardiography was performed.
Echocardiography was performed in an accepted manner. LV systolic dysfunction defined as LVEF < 45%, which has been used in other studies. Echocardiographer not blinded to the outcome.

5. (a) Have the authors identified all important confounding factors?

☐ Yes ☐ Can't tell ☑ No

Many patients (n = 28, 65%) were recently treated with anthracyclins, which can be cardiotoxic

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: Anthracyclin therapy was compared between survivors and non-survivors (not significant)

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☑ Yes ☐ Can't tell ☐ No

88% received daily echo during AICU stay

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

AICU mortality is independently associated with N-terminal pro-BNP levels at day 2 (Odds ratio: 1.2, 95% CI 1.004 - 1.32, p = 0.022). A N-terminal pro-BNP level >6,624 pg/ml predicted AICU mortality with a sensitivity of 86% and a specificity of 77%. 45 patients had echocardiography. 18 demonstrated new LV systolic dysfunction, 18 demonstrated new LV diastolic dysfunction and 17 demonstrated RV dysfunction. Cardiac function was normal in 11.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

The lower bound of the confidence interval for N-terminal pro-BNP levels at day 2 are extremely close to not significant.

---

9. Do you believe the results?

☐ Yes ☑ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

A small study. I believe the results about new onset cardiac dysfunction in patients with sepsis, but I have my reservations about the role of N-terminal pro-BNP as a predictor. I would need to see these results replicated.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

The incidence of myocardial depression in cancer patients with severe sepsis can be carried forward.
Reservations about N-terminal pro-BNP results mentioned above.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

The reported incidence of LV systolic dysfunction in sepsis is around 30%, the reported incidence of this study was 40%. It is plausible that prior treatment with cardiotoxic chemotherapy may account for the increased incidence.
The time-course of LV systolic dysfunction was not described in the paper. The authors have not responded to this request.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

No direct implications for clinical practice. The work with N-terminal pro-BNP needs to be replicated.
More evidence regarding the incidence of myocardial depression in sepsis.

Cardiac and central vascular functional alterations in the acute phase of aneurysmal subarachnoid hemorrhage
Papanikolaou, Critical Care Medicine, 2012

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of
- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

To investigate aortic functional alterations in the acute phase of aneurysmal subarachnoid hemorrhage and to evaluate the relationship between potential cardiovascular alterations and delayed cerebral infarctions or poor Glasgow Outcome Scale score at discharge from critical care unit

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:
- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Appropriate site and justified inclusion and exclusion criteria.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Radiological confirmation of SAH, excluding patients with mycotic aneurysms, brain trauma, cardiac disease, aortic aneursym, obstructive artery disease, chronic renal insufficiency and diabetes mellitus.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Echocardiography performed before surgical intervention and 21 days post initial bleed. Echocardiography performed using accepted techniques. Reported by a blinded observer. Neurological outcomes predefined

5. (a) Have the authors identified all important confounding factors?

☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: Excluded patients with pre-existing cardiac disease. These patients, however, could still demonstrate myocardial depression.
Compared differences between groups of those who were excluded from the study and those that were included, with no significant differences.
Recruitment sites were compared and no significant differences were found in clinical or echo data.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☐ Yes ☑ Can't tell ☐ No

Not explicitly stated

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

21 days is a reasonable time frame to capture recovery following SAH

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

12 (32.4%) patients had a RWMA and LVEF <50%, and additional two patients had RWMA, but a preserved ejection fraction. RWMA pattern did not follow typical normal coronary artery distribution. Increasing severity of SAH (as assessed by Hunt&Hess scores) was associated with a worse LVEF.
LVEF improved between acute SAH and stable state (p <=0.005). LVEF changes were more marked in patients with RWMA in >1 area (10.2% vs 2.4% +/- 1.8%, p = 0.002)
Pulse-wave velocity/LVEF ratio was the only independent predictor for delayed cerebral infarctions.

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Well conducted study

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Results are broadly generalisable, specific study exclusions may hamper applicability.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

The reported incidence and recovery of LV systolic function is consistent with the literature.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Increased recognition of cardiac sequelae following SAH. Further evidence to support the incidence of reversible myocardial depression to be around 30%.

Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU
Park et al, Chest, 2005

12 questions to help you make sense of cohort study

How to use this appraisal tool

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- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Frequency and outcomes of left ventricular apical ballooning in medical ICU patients admitted with non-cardiac illnesses

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Clearly defined population. Although patients with a "history of any cardiac disease" were excluded - these methods/criteria were not defined. Surgical patients not included.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Exposure - admitted to AICU for non-cardiac medical illness.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Blinded observers reading echos. Although definition of impairment was apical ballooning in addition to LV EF <50% - no justification

5. (a) Have the authors identified all important confounding factors?

☑ Yes ☐ Can't tell ☐ No

Attempted to ensure fluid resuscitated. The definition/approach of "prior cardiac history" is vague and could potentially exclude a large number of patients/hamper generalisability. Doesn't address occult disease.

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: Attempted to address pre-existing cardiac disease, but probably done inadequately.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☐ Yes ☐ Can't tell ☑ No

One third of patients died in AICU,

(b) Was the follow up of subjects long enough?

☐ Yes ☑ Can't tell ☐ No

Follow up interval not standard: range 2 - 25 days. This may have lead to inadequate capture of recovery

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

LVAB observed in 26 (28%) of patients admitted to AICU with a non-cardiac medical illness. LVAB was more common in patients with sepsis. Normalisation of LV function occurred in 20 of 26 at around one week from AICU admission.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Consistent with other studies in AICU sub-populations

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

? Applicability outside their specific cohort.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☐ Yes ☑ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Need to consider those with surgical conditions and those with pre-existing cardiovascular disease.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

Similar to those seen in sepsis subpopulations, which is unsurprising as this cohort is sepsis-dominant.

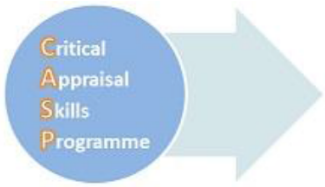
---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Interesting observations, would like to see the results replicated in patients with pre-existing cardiac disease. I have reservations about the generalisability to the broader AICU.



Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. Pulido et al, Mayo Clinic proceedings, 2012

12 questions to help you make sense of cohort study

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(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Determine the frequency and spectrum of myocardial dysfunction in patients with severe sepsis and septic shock using transthoracic echocardiography and to evaluate the impact of the myocardial dysfunction types on mortality.

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Clear and justified inclusion and exclusion criteria.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Used accepted definition of sepsis

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Echocardiography parameters measured in accepted manner. Interpretation not blinded. Discrepancies agreed by consensus

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Used accepted definition of sepsis

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Echocardiography parameters measured in accepted manner. Interpretation not blinded. Discrepancies agreed by consensus

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

5. (a) Have the authors identified all important confounding factors? ☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ☑ Yes ☐ Can't tell ☐ No

List:

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough? ☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

LV systolic dysfunction (LVEF <50%) was present in 29 patients (27%) on day 1. There was a significant increase in LVEF between day 1 and day 5/AICU discharge (LVEF 42% +/- 15% vs 61%+/- 9%; P<0.001). 20 patients had complete resolution of myocardial function, seven improved and only one did improve demonstrated any change in function on follow up.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Done well. Consistent with existing literature. .

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Generalisable. Similar cohorts.

---

11. Do the results of this study fit with other available evidence? ☑ Yes ☐ Can't tell ☐ No

Yes, consistent with expected incidence of myocardial depression in sepsis.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Increased recognition that septic myocardial depression is common.

Reversible Myocardial Contraction Abnormalities in Patients With an Acute Noncardiac Illness
Sharkey et al, Chest, 1998

12 questions to help you make sense of cohort study

How to use this appraisal tool

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue?

☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Retrospective analysis of reversible contraction abnormalities in non-cardiac patients

---

2. Was the cohort recruited in an acceptable way?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Well defined inclusion criteria, but potential selection bias as patients were identified following cardiology referral

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☐ Yes ☑ Can't tell ☐ No

Patients met specific inclusion criteria, but a selection bias is potentially introduced by identifying patients by cardiology referral.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Blinded echocardiographer reporting results

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

5. (a) Have the authors identified all important confounding factors? ☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ☑ Yes ☐ Can't tell ☐ No

List: Recognised the limitations of retrospective data.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough? ☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough? ☑ Yes ☐ Can't tell ☐ No

Followed all patients

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

All 22 patients had an anterior RWMA, which progressively normalised in 16 patients. Only one patient had significant coronary artery disease on coronary angiography. All patients demonstrated non-specific ECG changes.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptors

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comprehensive description of retrospective data. Given the potential selection bias, guarded generalisability.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☐ Yes ☑ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Small retrospective, selective study

---

11. Do the results of this study fit with other available evidence? ☐ Yes ☑ Can't tell ☐ No

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

No direct implications for clinical practice, but adds supporting evidence that reversible contraction abnormalities can occur in patients with critical, non-cardiac illness in the absence of obstructive coronary artery disease.

Left ventricular fraction after severe trauma
Smail et al, Intensive Care Medicine, 1996

12 questions to help you make sense of cohort study

How to use this appraisal tool

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Evaluate cardiac function in early stages of severe trauma

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Well defined population, although only studied patients if they felt mechanical ventilation was to last >48 hours - how was this judgement made?

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☐ Yes ☑ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Enrolled following trauma, but trauma is not defined, only a mean injury severity score for the cohort is reported.

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

All patients were fluid resuscitated before echocardiography.
Echocardiographer blinded to other measurements.

5. (a) Have the authors identified all important confounding factors? ☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ☑ Yes ☐ Can't tell ☐ No

List: Considered and addressed potential myocardial contusion secondary to trauma.

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough? ☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
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- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
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- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

All patients (n = 7) had a depressed LV systolic function, as measured by fractional area change (FAC), at the first assessment. There was a statistically significant improvement in FAC observed at day 2.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

---

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Very, very small study, but well. Clinical practice has changed since 1996, but the physiological stress to induce a transient myocardial depression has been proposed before.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

It could, in so far as to consider myocardial depression as a cause of haemodynamic instability in patients with trauma.

---

11. Do the results of this study fit with other available evidence? ☐ Yes ☑ Can't tell ☐ No

Very little evidence about myocardial depression in trauma.

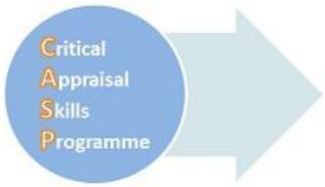
---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Recognition that severe trauma can induce transient myocardial depression. The pattern and time course is similar to other sub-populations experiencing myocardial depression.



Relation of Elevation in Cardiac Troponin I to Clinical Severity, Cardiac Dysfunction, and Pulmonary Congestion in Patients With Subarachnoid Hemorrhage
Tanabe et al, American Journal of Cardiology, 2008

12 questions to help you make sense of cohort study

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There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

To test the hypothesis that increases in troponin-I in patients with SAH were related to severity of the clinical neurologic condition, cardiac function, and occurrence of acute pulmonary congestion.

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Appropriate recruitment site. Identified patients with a radiological confirmation of non-traumatic SAH, with a Fisher score >= 2 and/or a Hunt&Hess score >=3

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Radiological confirmation of SAH, specific severity sub-group, details of therapy outlined. Patients treated according to usual clinical practice.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

---

4. Was the outcome accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

Echocardiography data collected using accepted techniques. Blinded echocardiogram reader.

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

5. (a) Have the authors identified all important confounding factors? ☑ Yes ☐ Can't tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ☑ Yes ☐ Can't tell ☐ No

List:

Identified patients with pre-existing coronary artery disease (n = 7,7%)

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough? ☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough? ☑ Yes ☐ Can't tell ☐ No

Between days 5- 10 is appropriate

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

17 patients demonstrated RWMA, during the study period 4/17 patients normalised their RWMA scores, 8 patients improved and 5 had worsening. RWMA tended to be anteriorally/ anterior-septally. Changes in ejection fraction were not reported. Overall, a positive troponin-I was not associated with an abnormal ejection fraction, although highly positive troponin-I (>1.0 ng/ml) was associated with neurological severity, slight depression of ejection fraction, pulmonary congestion, and longer intensive care unit stay.

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

Descriptive study

9. Do you believe the results?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

The RWMA changes observed following SAH are well described.

(C) Will the results help locally?

10. Can the results be applied to the local population? ☐ Yes ☑ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

The reported incidence of RWMA in this study is lower than similar studies. This could potentially be due to the first echocardiogram occurring up to 72 hours since bleeding onset, it is possible that milder cases that quickly recovered could have been missed by this approach.

---

11. Do the results of this study fit with other available evidence? ☐ Yes ☐ Can't tell ☑ No

Lower incidence than previously reported, potential explanation detailed above.

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Interesting descriptive study, no direct implications for clinical practice without further evidence.

Actual incidence of global left ventricular hypokinesia in adult septic shock
Vieillard-Baron et al, Critical Care Medicine, 2008

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

Establish the incidence of global ventricular hypokinesia in septic shock

---

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Consistent approach. Required the patient receive mechanical ventilation and be treated for septic shock --> specific criteria.

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias?

☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

Consistent approach to inclusion criteria. Exposure: septic shock. Accepted definition used.

Excluded patients with cardiac failure

---

4. Was the outcome accurately measured to minimise bias?

☐ Yes ☐ Can't tell ☑ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Outcome: LVEF <45%.
Echocardiographers not blinded.

Inter-observer variability up to 10% - ? what patients demonstrated an improvement above and beyond what could possibly be measurement variation?

5. (a) Have the authors identified all important confounding factors?

☑ Yes ☐ Can't tell ☐ No

Excluded patients who died before day three - could potentially under-report the incidence because patients who died were not included in the analysis

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?

☑ Yes ☐ Can't tell ☐ No

List: Fluid responsiveness assessed. Considered patients with AF

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough?

☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough?

☑ Yes ☐ Can't tell ☐ No

Full recovery observed by cessation of vasoactive drugs

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

Incidence of LV hypokinesis 60%, the majority of patients display this on admission, but a smaller number develop this later in their clinical course. Full recovery by weaning of vasoactives.

---

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

---

9. Do you believe the results?

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

☐ Yes ☑ Can't tell ☐ No

The present study reports an incidence that is much much greater than similar literature

(C) Will the results help locally?

10. Can the results be applied to the local population? ☐ Yes ☑ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

Reservations about reproducibility and generalisability. Very select population.

---

11. Do the results of this study fit with other available evidence? ☐ Yes ☐ Can't tell ☑ No

Incidence far greater than previously reported

---

12. What are the implications of this study for practice?

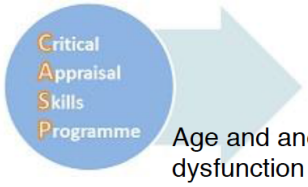
HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Interesting observations. Unlikely to change clinical practice until results are replicated. Hypothesis generating, as the authors discuss that patients who developed myocardial depression after initiation of noradrenaline ?noradrenaline induced cardiomyopathy

Appendix 3: CASP checklist for all papers in literature review 2

1. Khush



Age and aneurysm position predict patterns of left ventricular dysfunction after subarachnoid hemorrhage. Khush et al Journal of the American Society of Echocardiography, 2005

11 questions to help you evaluate a clinical prediction rule

How to use this appraisal tool

Three broad issues need to be considered when appraising any study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 11 questions on the following pages are designed to help you think about these issues systematically.
The first three questions are screening questions and can be answered quickly. Only if you can answer "yes" to all three is it likely to be worthwhile continuing with the rest of the questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

(A) Are the results of the study valid?

Screening Questions

1. Is the CPR clearly defined?

☑ Yes ☐ Can't tell ☐ No

HINT:

- The type of patients to whom the CPR will be applied is clearly defined?
- The variables included in the rule are clearly defined?
- Is the outcome relevant and is it clinically reasonable? (The outcome can be expressed as a probablility or as course of action)

Inclusion and exclusion criteria well defined. Development population generalisable. Interesting outcome (? prediction of apical sparing vs apical affected variants of RWMA post subarachnoid haemorrhage), but ?usefulness.

---

2. The population from which the rule was derived included an appropriate spectrum of patients?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Is it adequate the way the patients were selected?
- The spectrum of patient to whom the rule will apply is well represented?

Population dominated by women, as expected. Full range of severity of subarachnoid haemorrrhages included in the population. 67 patients in the sample.

3. Was the rule validated in a different group of patients?

☐ Yes ☐ Can't tell ☑ No

HINT:

- It is not good enough that the rule had a good performance on the patient group used to derive it. The rule should be validated in a set of patients different from those who served to derive the rule
- The validation was done in a group of patients similar to the one used to derive it

Not validated

Is it worth continuing?

Detailed questions

4. Were the predictor variables and the outcome evaluated in a blinded fashion?

☐ Yes ☑ Can't tell ☐ No

Not detailed.

HINT: Did

- People evaluating the outcome know the predictor variables?
- People evaluating the predictor variables know the outcome

5. Were the predictor variables and the outcome evaluates in the whole sample selected initially?

☑ Yes ☐ Can't tell ☐ No

Detailed number of patients (n = 6) that did not meet apical sparing or apical affected RWMA criteria, but did not describe if these were then excluded.

HINT:

- Are exclusions and drop outs well described and do the authors discuss the reasons for them?
- Sometimes the outcome cannot be measured in the same way in all patients

---

6. Are the statistical methods used to construct and validate the rule clearly described?

☑ Yes ☐ Can't tell ☐ No

This was done very well. The process is transparent. The selection of variables from univariate analysis, the stepwise forward, multiple regression were all detailed.

HINT:

- Were all important variables included and the positivity criteria explained?
- The statistical method is adequately described?
- Was the reliability of the rule considered?

(B) What are the results?

7. Can the performance of the rule be calculated?

	Outcome +	Outcome -
Rule +	a	b
Rule -	c	d

HINT:

- Performance results can be presented as: Sens, Sp, + LR, -LR, ROC curve, calibration curves etc.

Model performance was not assessed

- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- LR+ = sens/(1-sp)
- LR- = (1-sens)/sp

---

8. How precise was the estimate of the treatment effect?

Did they try to refine the rule with other variables to see whether the precision could be improved or the rule simplified?

The model was not refined. There were FAR too many candidate predictors trialled in model development (n = 19), for only 67 patients with the outcome.

HINT: Think about

- The sample size and the number of Variables included in the CPR
- Is the rule robust? Has there been Any attempt to refine it?

(C) Will the results help locally? / Are the findings applicable to the scenario?

9. Would the prediction rule be reliable and and the results interpretable if used for your patient?

☐ Yes ☐ Can't tell ☑ No

I doubt it would be reliable as the results are not validated. The development population is generalisable, but in it's current form, it is not useful.

HINT: Consider

- Is your setting too different from that of the study?

---

10. Is the rule acceptable in your case?

☐ Yes ☐ Can't tell ☑ No

It is unvalidated. Furthermore, I wonder the clinical utility of prediction of RWMA pattern - this could easily and quickly be confirmed by echocardiography.

HINT: Consider

- The ease of use and the availability of the rule and the costs
- If the rule is reasonable from a clinical point of view

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her?

❒ Yes ❒ Can't tell ☑ No

I don't think this is a useful rule.

HINT: Consider

- In addition to your opinion, might there be studies analysing the impact (in monetary terms or health results) of the rule?
- If nothing will change, the rule is at best useless in terms of benefit to the patients.
- How the initial estimation has changed after applying the rule, and the effect it has had on the action threshold.

2. Kothavale

Predictors of left ventricular regional wall motion abnormalities after subarachnoid hemorrhage
Kothavale et al, Neurocritical care, 2006

11 questions to help you evaluate a clinical prediction rule

How to use this appraisal tool

Three broad issues need to be considered when appraising any study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 11 questions on the following pages are designed to help you think about these issues systematically.
The first three questions are screening questions and can be answered quickly. Only if you can answer "yes" to all three is it likely to be worthwhile continuing with the rest of the questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

(A) Are the results of the study valid?

Screening Questions

1. Is the CPR clearly defined?

☑ Yes ☐ Can't tell ☐ No

HINT:

- The type of patients to whom the CPR will be applied is clearly defined?
- The variables included in the rule are clearly defined?
- Is the outcome relevant and is it clinically reasonable? (The outcome can be expressed as a probablility or as course of action)

Well defined development population. Variables are clear. The outcome is clinically useful.

---

2. The population from which the rule was derived included an appropriate spectrum of patients?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Is it adequate the way the patients were selected?
- The spectrum of patient to whom the rule will apply is well represented?

Appropriate, well defined and generalisable.

3. Was the rule validated in a different group of patients?

☐ Yes ☐ Can't tell ☑ No

HINT:

- It is not good enough that the rule had a good performance on the patient group used to derive it. The rule should be validated in a set of patients different from those who served to derive the rule
- The validation was done in a group of patients similar to the one used to derive it

The rule was not validated.

Is it worth continuing?

Detailed questions

4. Were the predictor variables and the outcome evaluated in a blinded fashion?

☑ Yes ☐ Can't tell ☐ No

HINT: Did

- People evaluating the outcome know the predictor variables?
- People evaluating the predictor variables know the outcome

This was done well. Echocardiography staff (who determined the outcome variable) were blinded to other variables.

5. Were the predictor variables and the outcome evaluates in the whole sample selected initially?

☑ Yes ☐ Can't tell ☐ No

Transparent in the number of patients with the outcome, the number of patient deaths and completeness of data.

HINT:

- Are exclusions and drop outs well described and do the authors discuss the reasons for them?
- Sometimes the outcome cannot be measured in the same way in all patients

---

6. Are the statistical methods used to construct and validate the rule clearly described?

☑ Yes ☐ Can't tell ☐ No

This was done well. Univariate analysis was undertaken, and significant variables ($p < 0.10$) were then trialled with multivariate analysis.

HINT:

- Were all important variables included and the positivity criteria explained?
- The statistical method is adequately described?
- Was the reliability of the rule considered?

(B) What are the results?

7. Can the performance of the rule be calculated?

	Outcome +	Outcome -
Rule +	a	b
Rule -	c	d

HINT:

- Performance results can be presented as: Sens, Sp, + LR, -LR, ROC curve, calibration curves etc.

The sensitivity of a troponin I > 1.0ug/L in predicting RWMA on the concurrent echocardiogram was 30% (95% CI 23-38%), specificity 95% (95% CI 93- 97%)

- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- LR+ = sens/(1-sp)
- LR- = (1-sens)/sp

---

8. How precise was the estimate of the treatment effect?

Did they try to refine the rule with other variables to see whether the precision could be improved or the rule simplified?

The rule was not refined. Upper limit of appropriate number of candidate variables. At risk of overfitting.

HINT: Think about

- The sample size and the number of Variables included in the CPR
- Is the rule robust? Has there been Any attempt to refine it?

(C) Will the results help locally? / Are the findings applicable to the scenario?

9. Would the prediction rule be reliable and and the results interpretable if used for your patient?

☐ Yes ☑ Can't tell ☐ No

Setting would be similar, but this rule needs to be validated.

HINT: Consider

- Is your setting too different from that of the study?

---

10. Is the rule acceptable in your case?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- The ease of use and the availability of the rule and the costs
- If the rule is reasonable from a clinical point of view

Reasonable from a clinical perspective, readily available input variables, however needs to be validated.

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her?

❒ Yes ☑ Can't tell ❒ No

Uncertain with the current available information

HINT: Consider

- In addition to your opinion, might there be studies analysing the impact (in monetary terms or health results) of the rule?
- If nothing will change, the rule is at best useless in terms of benefit to the patients.
- How the initial estimation has changed after applying the rule, and the effect it has had on the action threshold.

Cardiac Injury after Subarachnoid Hemorrhage Is Independent of the Type of Aneurysm Therapy
Miss et al, Neurosurgery, 2004

11 questions to help you evaluate a clinical prediction rule

How to use this appraisal tool

Three broad issues need to be considered when appraising any study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 11 questions on the following pages are designed to help you think about these issues systematically.
The first three questions are screening questions and can be answered quickly. Only if you can answer "yes" to all three is it likely to be worthwhile continuing with the rest of the questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

(A) Are the results of the study valid?

Screening Questions

1. Is the CPR clearly defined?

☑ Yes ☐ Can't tell ☐ No

HINT:

- The type of patients to whom the CPR will be applied is clearly defined?
- The variables included in the rule are clearly defined?
- Is the outcome relevant and is it clinically reasonable? (The outcome can be expressed as a probablility or as course of action)

Clear development population of patients with subarachnoid haemorrhage. Clinically reasonable outcome. Variables well defined.

---

2. The population from which the rule was derived included an appropriate spectrum of patients?

☑ Yes ☐ Can't tell ☐ No

Classified based on aneurysm treatment method.

HINT: Consider

- Is it adequate the way the patients were selected?
- The spectrum of patient to whom the rule will apply is well represented?

3. Was the rule validated in a different group of patients?

☐ Yes ☐ Can't tell ☑ No

The study was not validated.

HINT:

- It is not good enough that the rule had a good performance on the patient group used to derive it. The rule should be validated in a set of patients different from those who served to derive the rule
- The validation was done in a group of patients similar to the one used to derive it

Is it worth continuing?

Detailed questions

4. Were the predictor variables and the outcome evaluated in a blinded fashion?

☑ Yes ☐ Can't tell ☐ No

The outcome variable was assessed in a blinded fashion.

HINT: Did

- People evaluating the outcome know the predictor variables?
- People evaluating the predictor variables know the outcome

5. Were the predictor variables and the outcome evaluates in the whole sample selected initially?

☑ Yes ☐ Can't tell ☐ No

Clear that only data occurring AFTER the therapy included in the study.

HINT:

- Are exclusions and drop outs well described and do the authors discuss the reasons for them?
- Sometimes the outcome cannot be measured in the same way in all patients

---

6. Are the statistical methods used to construct and validate the rule clearly described?

☐ Yes ☐ Can't tell ☑ No

Type of analysis described, but model building procedure and thresholds for inclusion of variables were omitted.
Model performance was not considered.

HINT:

- Were all important variables included and the positivity criteria explained?
- The statistical method is adequately described?
- Was the reliability of the rule considered?

(B) What are the results?

7. Can the performance of the rule be calculated?

HINT:

- Performance results can be presented as: Sens, Sp, + LR, -LR, ROC curve, calibration curves etc.

	Outcome +	Outcome -
Rule +	a	b
Rule -	c	d

Model performance cannot be calculated

- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- LR+ = sens/(1-sp)
- LR- = (1-sens)/sp

---

8. How precise was the estimate of the treatment effect?

Did they try to refine the rule with other variables to see whether the precision could be improved or the rule simplified?

HINT: Think about

- The sample size and the number of Variables included in the CPR
- Is the rule robust? Has there been Any attempt to refine it?

Adjustment for demographic and clinical factors did not change the effect of therapy choice.
"Haemodynamic data were averaged among all echocardiographic studies for each group" - this was not justified.
Did not elucidate a difference between therapies and development of cardiac sequelae.

(C) Will the results help locally? / Are the findings applicable to the scenario?

9. Would the prediction rule be reliable and and the results interpretable if used for your patient?

☐ Yes ☑ Can't tell ☐ No

This has not been validated and I am concerned about the lack of transparency of statistical methods.

HINT: Consider

- Is your setting too different from that of the study?

---

10. Is the rule acceptable in your case?

☐ Yes ☐ Can't tell ☑ No

HINT: Consider

- The ease of use and the availability of the rule and the costs
- If the rule is reasonable from a clinical point of view

The question is worth asking, but I don't feel this was answered in the correct way.

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her?

❒ Yes ❒ Can't tell ☑ No

I would be reluctant to use this without further evidence.

HINT: Consider

- In addition to your opinion, might there be studies analysing the impact (in monetary terms or health results) of the rule?
- If nothing will change, the rule is at best useless in terms of benefit to the patients.
- How the initial estimation has changed after applying the rule, and the effect it has had on the action threshold.

B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients
Post et al, Critical Care Medicine, 2008

11 questions to help you evaluate a clinical prediction rule

How to use this appraisal tool

Three broad issues need to be considered when appraising any study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 11 questions on the following pages are designed to help you think about these issues systematically.
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These checklists were designed to be used as educational tools as part of a workshop setting

(A) Are the results of the study valid?

Screening Questions

1. Is the CPR clearly defined?

☑ Yes ☐ Can't tell ☐ No

HINT:

- The type of patients to whom the CPR will be applied is clearly defined?
- The variables included in the rule are clearly defined?
- Is the outcome relevant and is it clinically reasonable? (The outcome can be expressed as a probablility or as course of action)

Yes, patients with severe sepsis. Predictor variable (B-type natriuretic peptide) well defined. Prediction of septic myocardial depression is relevant.

---

2. The population from which the rule was derived included an appropriate spectrum of patients?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Is it adequate the way the patients were selected?
- The spectrum of patient to whom the rule will apply is well represented?

Appropriate and justified selection within the bounds of their inclusion and exclusion criteria. Although, excluded patients that died before day 5, thus potentially excluding sicker patients.

3. Was the rule validated in a different group of patients?

☐ Yes ☐ Can't tell ☑ No

HINT:

- It is not good enough that the rule had a good performance on the patient group used to derive it. The rule should be validated in a set of patients different from those who served to derive the rule
- The validation was done in a group of patients similar to the one used to derive it

The rule was not validated

Is it worth continuing?

Detailed questions

4. Were the predictor variables and the outcome evaluated in a blinded fashion?

☐ Yes ☑ Can't tell ☐ No

HINT: Did

- People evaluating the outcome know the predictor variables?
- People evaluating the predictor variables know the outcome

This information was not documented

5. Were the predictor variables and the outcome evaluates in the whole sample selected initially?

☑ Yes ☐ Can't tell ☐ No

HINT:

- Are exclusions and drop outs well described and do the authors discuss the reasons for them?
- Sometimes the outcome cannot be measured in the same way in all patients

Exclusion criteria inadequately described. States excluded patients with "known history of cardiac disease" but this is not defined, nor documented how this data were sourced. Excluded patients that died before day five of AICU - but does not adequately describe this population nor how this may affect generalisability.

---

6. Are the statistical methods used to construct and validate the rule clearly described?

☑ Yes ☐ Can't tell ☐ No

HINT:

- Were all important variables included and the positivity criteria explained?
- The statistical method is adequately described?
- Was the reliability of the rule considered?

Well described

(B) What are the results?

7. Can the performance of the rule be calculated?

	Outcome +	Outcome -
Rule +	a	b
Rule -	c	d

HINT:

- Performance results can be presented as: Sens, Sp, + LR, -LR, ROC curve, calibration curves etc.

ROC AUC 0.955 for BNP >153 pg/mL on day five
95% CI: 0.89-0.98

- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- LR+ = sens/(1-sp)
- LR- = (1-sens)/sp

---

8. How precise was the estimate of the treatment effect?

Did they try to refine the rule with other variables to see whether the precision could be improved or the rule simplified?

The rule was not refined. The aim was to determine if BNP, as a sole explanatory variable, could be used to predict the development of septic myocardial depression.
Adequate number of explanatory variables (one) for the size of the dataset.

HINT: Think about

- The sample size and the number of Variables included in the CPR
- Is the rule robust? Has there been Any attempt to refine it?

(C) Will the results help locally? / Are the findings applicable to the scenario?

9. Would the prediction rule be reliable and and the results interpretable if used for your patient?

☐ Yes ☐ Can't tell ☑ No

HINT: Consider

- Is your setting too different from that of the study?

The rule is novel, however, the utility is questionable. If the BNP level is > 154 pg/mL on day five of AICU, then it is highly sensitive and specific for acquiring septic myocardial depression - which is ostensibly useful, however the majority of admissions to AICU stay less than 5 days.

---

10. Is the rule acceptable in your case?

☐ Yes ☐ Can't tell ☑ No

HINT: Consider

- The ease of use and the availability of the rule and the costs
- If the rule is reasonable from a clinical point of view

Easy to use, availability of predictor variable is good but minority of AICU admissions stay until day 5.

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her?

❒ Yes ☑ Can't tell ❒ No

HINT: Consider

- In addition to your opinion, might there be studies analysing the impact (in monetary terms or health results) of the rule?
- If nothing will change, the rule is at best useless in terms of benefit to the patients.
- How the initial estimation has changed after applying the rule, and the effect it has had on the action threshold.

If may do, if I suspected myocardial depression and BNP was something that was regularly ordered in our unit. I do, however, question the utility of the rule for the vast majority of patients. Given that echocardiography is essentially free, once the cost of the infrastructure has been outlaid, I doubt this rule has any economic impact.

Relation of Elevation in Cardiac Troponin I to Clinical Severity, Cardiac Dysfunction, and Pulmonary Congestion in Patients With Subarachnoid Hemorrhage
Tanabe et al, American Journal of Cardiology, 2006

11 questions to help you evaluate a clinical prediction rule

How to use this appraisal tool

Three broad issues need to be considered when appraising any study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 11 questions on the following pages are designed to help you think about these issues systematically.
The first three questions are screening questions and can be answered quickly. Only if you can answer "yes" to all three is it likely to be worthwhile continuing with the rest of the questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

(A) Are the results of the study valid?

Screening Questions

1. Is the CPR clearly defined?

☑ Yes ☐ Can't tell ☐ No

HINT:

- The type of patients to whom the CPR will be applied is clearly defined?
- The variables included in the rule are clearly defined?
- Is the outcome relevant and is it clinically reasonable? (The outcome can be expressed as a probablility or as course of action)

Adequate detail provided. Reasonable clinical question. Clear population.

---

2. The population from which the rule was derived included an appropriate spectrum of patients?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Is it adequate the way the patients were selected?
- The spectrum of patient to whom the rule will apply is well represented?

Reasonable and justified approach to patient selection. Expected gender split. Good representation of severity of SAH.

3. Was the rule validated in a different group of patients?

☐ Yes ☐ Can't tell ☑ No

HINT:

- It is not good enough that the rule had a good performance on the patient group used to derive it. The rule should be validated in a set of patients different from those who served to derive the rule
- The validation was done in a group of patients similar to the one used to derive it

The model was not validated.

Is it worth continuing?

Detailed questions

4. Were the predictor variables and the outcome evaluated in a blinded fashion?

☑ Yes ☐ Can't tell ☐ No

Blinded outcome.

HINT: Did

- People evaluating the outcome know the predictor variables?
- People evaluating the predictor variables know the outcome

5. Were the predictor variables and the outcome evaluates in the whole sample selected initially?

☑ Yes ☐ Can't tell ☐ No

Transparent about data completeness.

HINT:

- Are exclusions and drop outs well described and do the authors discuss the reasons for them?
- Sometimes the outcome cannot be measured in the same way in all patients

---

6. Are the statistical methods used to construct and validate the rule clearly described?

☑ Yes ☐ Can't tell ☐ No

Clearly described.

HINT:

- Were all important variables included and the positivity criteria explained?
- The statistical method is adequately described?
- Was the reliability of the rule considered?

(B) What are the results?

7. Can the performance of the rule be calculated?

HINT:

- Performance results can be presented as: Sens, Sp, + LR, -LR, ROC curve, calibration curves etc.

ROC AUC 0.889 for troponin-I > 1.31 ng/ml to predict RWMA in patients with SAH. Sensitivity 76% specificity 91%

	Outcome +	Outcome -
Rule +	a	b
Rule -	c	d

- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- LR+ = sens/(1-sp)
- LR- = (1-sens)/sp

---

8. How precise was the estimate of the treatment effect?

Did they try to refine the rule with other variables to see whether the precision could be improved or the rule simplified?

HINT: Think about

- The sample size and the number of Variables included in the CPR
- Is the rule robust? Has there been Any attempt to refine it?

Appropriate events per variable. Rule not refined

(C) Will the results help locally? / Are the findings applicable to the scenario?

9. Would the prediction rule be reliable and and the results interpretable if used for your patient?

☑ Yes ☐ Can't tell ☐ No

Once validated, this could be a useful tool. Generalisability study population and routinely collected data.

HINT: Consider

- Is your setting too different from that of the study?

---

10. Is the rule acceptable in your case?

☑ Yes ☐ Can't tell ☐ No

Potentially very useful, needs validation.

HINT: Consider

- The ease of use and the availability of the rule and the costs
- If the rule is reasonable from a clinical point of view

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her?

HINT: Consider

- In addition to your opinion, might there be studies analysing the impact (in monetary terms or health results) of the rule?
- If nothing will change, the rule is at best useless in terms of benefit to the patients.
- How the initial estimation has changed after applying the rule, and the effect it has had on the action threshold.

❒ Yes ☑ Can't tell ❒ No

In the current form, no. It is promising work and needs validation.

Predictors of neurocardiogenic injury after subarachnoid hemorrhage.
Tung et al, Stroke, 2004

11 questions to help you evaluate a clinical prediction rule

How to use this appraisal tool

Three broad issues need to be considered when appraising any study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 11 questions on the following pages are designed to help you think about these issues systematically.
The first three questions are screening questions and can be answered quickly. Only if you can answer "yes" to all three is it likely to be worthwhile continuing with the rest of the questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

(A) Are the results of the study valid?

Screening Questions

1. Is the CPR clearly defined?

☑ Yes ☐ Can't tell ☐ No

HINT:

- The type of patients to whom the CPR will be applied is clearly defined?
- The variables included in the rule are clearly defined?
- Is the outcome relevant and is it clinically reasonable? (The outcome can be expressed as a probablility or as course of action)

Well defined variables and study population. Reasonable and well justified outcome

---

2. The population from which the rule was derived included an appropriate spectrum of patients?

☑ Yes ☐ Can't tell ☐ No

Well defined, generalisable, study population. Reasonable spread of severity of subarachnoid haemorrhages.

HINT: Consider

- Is it adequate the way the patients were selected?
- The spectrum of patient to whom the rule will apply is well represented?

3. Was the rule validated in a different group of patients?

☐ Yes ☐ Can't tell ☑ No

The rule has not yet been validated.

HINT:

- It is not good enough that the rule had a good performance on the patient group used to derive it. The rule should be validated in a set of patients different from those who served to derive the rule
- The validation was done in a group of patients similar to the one used to derive it

Is it worth continuing?

Detailed questions

4. Were the predictor variables and the outcome evaluated in a blinded fashion?

☐ Yes ☑ Can't tell ☐ No

Not described

HINT: Did

- People evaluating the outcome know the predictor variables?
- People evaluating the predictor variables know the outcome

5. Were the predictor variables and the outcome evaluates in the whole sample selected initially?

☐ Yes ☑ Can't tell ☐ No

Not described, although inferred complete dataset.

HINT:

- Are exclusions and drop outs well described and do the authors discuss the reasons for them?
- Sometimes the outcome cannot be measured in the same way in all patients

---

6. Are the statistical methods used to construct and validate the rule clearly described?

☐ Yes ☐ Can't tell ☑ No

Univariate and multivariate results provided. Details of model construction process omitted. Model performance and validation not undertaken.

HINT:

- Were all important variables included and the positivity criteria explained?
- The statistical method is adequately described?
- Was the reliability of the rule considered?

(B) What are the results?

7. Can the performance of the rule be calculated?

HINT:

- Performance results can be presented as: Sens, Sp, + LR, -LR, ROC curve, calibration curves etc.

	Outcome +	Outcome -
Rule +	a	b
Rule -	c	d

Not provided

- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- LR+ = sens/(1-sp)
- LR- = (1-sens)/sp

---

8. How precise was the estimate of the treatment effect?

Did they try to refine the rule with other variables to see whether the precision could be improved or the rule simplified?

HINT: Think about

- The sample size and the number of Variables included in the CPR
- Is the rule robust? Has there been Any attempt to refine it?

The rule was not refined.
Adequate number of events per variable.
Precision of rule not quantified

(C) Will the results help locally? / Are the findings applicable to the scenario?

9. Would the prediction rule be reliable and and the results interpretable if used for your patient?

☐ Yes ☐ Can't tell ☑ No

The performance and model validity has not been tested. It this form it is not useful.

HINT: Consider

- Is your setting too different from that of the study?

---

10. Is the rule acceptable in your case?

☐ Yes ☐ Can't tell ☑ No

HINT: Consider

- The ease of use and the availability of the rule and the costs
- If the rule is reasonable from a clinical point of view

This is reasonable from a clinical perspective but the model performance and validity has not yet been assessed. This represents preliminary work.

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her?

❒ Yes ❒ Can't tell ☑ No

This work has the potential to be useful, but in it's current form, it does not represent a clinically useful tool.

HINT: Consider

- In addition to your opinion, might there be studies analysing the impact (in monetary terms or health results) of the rule?
- If nothing will change, the rule is at best useless in terms of benefit to the patients.
- How the initial estimation has changed after applying the rule, and the effect it has had on the action threshold.

7. Park

Park, Chest, 2005
Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU

11 questions to help you evaluate a clinical prediction rule

How to use this appraisal tool

Three broad issues need to be considered when appraising any study:

- **Are the results of the study valid? (Section A)**
- **What are the results? (Section B)**
- **Will the results help locally? (Section C)**

The 11 questions on the following pages are designed to help you think about these issues systematically.
The first three questions are screening questions and can be answered quickly. Only if you can answer "yes" to all three is it likely to be worthwhile continuing with the rest of the questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

(A) Are the results of the study valid?

Screening Questions

1. Is the CPR clearly defined?

☑ Yes ☐ Can't tell ☐ No

HINT:

- The type of patients to whom the CPR will be applied is clearly defined?
- The variables included in the rule are clearly defined?
- Is the outcome relevant and is it clinically reasonable? (The outcome can be expressed as a probablility or as course of action)

General medical AICU

---

2. The population from which the rule was derived included an appropriate spectrum of patients?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Is it adequate the way the patients were selected?
- The spectrum of patient to whom the rule will apply is well represented?

Not applicable for surgical patients
Excluded patients with pre-existing cardiovascular disease

3. Was the rule validated in a different group of patients?

☐ Yes ☐ Can't tell ☑ No

HINT:

- It is not good enough that the rule had a good performance on the patient group used to derive it. The rule should be validated in a set of patients different from those who served to derive the rule
- The validation was done in a group of patients similar to the one used to derive it

Not validated

Is it worth continuing?

Detailed questions

4. Were the predictor variables and the outcome evaluated in a blinded fashion?

☐ Yes ☑ Can't tell ☐ No

HINT: Did

- People evaluating the outcome know the predictor variables?
- People evaluating the predictor variables know the outcome

Not specified

5. Were the predictor variables and the outcome evaluates in the whole sample selected initially?

☐ Yes ☐ Can't tell ☑ No

HINT:

- Are exclusions and drop outs well described and do the authors discuss the reasons for them?
- Sometimes the outcome cannot be measured in the same way in all patients

Not prospectively defined.
Exclusions not well defined

---

6. Are the statistical methods used to construct and validate the rule clearly described?

☑ Yes ☐ Can't tell ☐ No

HINT:

- Were all important variables included and the positivity criteria explained?
- The statistical method is adequately described?
- Was the reliability of the rule considered?

Unclear. The collection rules are not clearly defined. The statistical method was well described. Input variable justification not clear.

(B) What are the results?

7. Can the performance of the rule be calculated?

HINT:

- Performance results can be presented as: Sens, Sp, + LR, -LR, ROC curve, calibration curves etc.

	Outcome +	Outcome -
Rule +	a	b
Rule -	c	d

Model performance not discussed

- Sensitivity = a/(a+c)
- Specificity = d/(b+d)
- LR+ = sens/(1-sp)
- LR- = (1-sens)/sp

---

8. How precise was the estimate of the treatment effect?

Did they try to refine the rule with other variables to see whether the precision could be improved or the rule simplified?

HINT: Think about

- The sample size and the number of Variables included in the CPR
- Is the rule robust? Has there been Any attempt to refine it?

26 patients with the outcome, five variables trialled. Therefore at risk of overfitting the model. Only one variable, sepsis, was useful on multivariate analysis.
Sepsis OR 9.2 95% CI 2.36 - 35.69 p <0.001

(C) Will the results help locally? / Are the findings applicable to the scenario?

9. Would the prediction rule be reliable and and the results interpretable if used for your patient?

☐ Yes ☑ Can't tell ☐ No

Seems reasonable, but very large CI and a select population.

HINT: Consider

- Is your setting too different from that of the study?

---

10. Is the rule acceptable in your case?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- The ease of use and the availability of the rule and the costs
- If the rule is reasonable from a clinical point of view

Requires validation.

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her?

❐ Yes ❐ Can't tell ☑ No

Not without validation.

HINT: Consider

- In addition to your opinion, might there be studies analysing the impact (in monetary terms or health results) of the rule?
- If nothing will change, the rule is at best useless in terms of benefit to the patients.
- How the initial estimation has changed after applying the rule, and the effect it has had on the action threshold.

Appendix 4: Study protocols

1. ELF 1

Note: Ethics amendment was undertaken to abandon the 12 month follow up assessment

Date and Version No: **28/6/11 Version 1**

Study Title: Observational study to assess the incidence and reversibility of acute left ventricular myocardial dysfunction in critically ill adults

Ethics Ref:

Date and Version No: 28/6/11 Version 1

Chief Investigator: **Dr Duncan Young**
Consultant and Senior Clinical Lecturer
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Investigators: **Dr Andrew Jacques**
Specialist Trainee Year 6
Intensive Care Medicine
Adult Intensive Care Unit
John Radcliffe Hospital

Sponsor: **University of Oxford**

Funder (if applicable):

Signatures & dates:

Table of Contents

1. SYNOPSIS

Study Title	Observational study to assess the incidence and reversibility of acute left ventricular myocardial dysfunction in critically ill adults
Study Design	Observational study
Study Participants	Critically ill patients in adult general intensive care
Planned Sample Size	150
Follow-up duration	12 months
Planned Study Period	24 months
Primary Objective	To determine the incidence and prevalence of acute left ventricular myocardial dysfunction in critically ill adults.
Secondary Objectives	In those participants who develop acute left ventricular dysfunction, what recovery occurs at three and twelve months after ICU admission? In those participants who develop acute left ventricular dysfunction is the duration of mechanical ventilation longer than a matched group of patients without acute left ventricular dysfunction? In those participants who develop acute left ventricular dysfunction is the duration of care on an intensive care unit longer than a matched group of patients without acute left ventricular dysfunction? In those participants who develop acute left ventricular dysfunction is the incidence of acute dysrhythmias occurring during their intensive care unit stay greater than a matched group of patients without acute left ventricular dysfunction? In those participants who develop acute left ventricular dysfunction is the use of inotropes and vasoactive drugs greater than a matched group of patients without acute left ventricular dysfunction?
Intervention (s)	Observational study only. Transthoracic echocardiogram to assess left ventricular function performed on days 1, again once between days 3&5 and again once between days 5&7 after intensive care unit admission. Participants with evidence of acute left ventricular dysfunction will have repeat echocadiograms at 1 week after ICU discharge, and at three months and twelve months after their admission to the intensive care unit.

2. BACKGROUND AND RATIONALE

Acute left ventricular dysfunction (LVD) has been shown to occur in up to one third of critically ill patients. The reported incidence is increasing, partially secondary to increased screening and clinical suspicion. LVD may be secondary to ischaemia as a result of coronary artery disease, due to trauma or as part of the systemic response to critical illness.[1]

Assessment of LVD is important as decreased cardiac contractility is a common cause of haemodynamic instability in critically ill patients treated on intensive care units (ICUs).[2] Assessment of ventricular function by clinical examination or invasive haemodynamic monitoring is necessarily indirect and often poorly correlated with transthoracic or transoesophageal ultrasound imaging.[3] Echocardiography can non-invasively provide diagnostic information on both the structure and function of the heart, both globally and at chamber/wall level.[4] Transthoracic echocardiography (TTE) has been shown to be an excellent tool for the assessment of ventricular function generally and in critically ill patients.[3] Adequate or good images in intensive care patients, many of who are mechanically ventilated, can be obtained in over three quarters of patients, with some studies showing adequate images in up to 84 to 98% of patients.[5,6] In addition, after brief formal training it has been demonstrated that intensivists can perform and interpret echocardiograms with accuracy.[7]

Possible complications of LVD include; thrombosis formation and embolisation, increased length of stay and morbidity, shock, increased incidence of arrhythmias and precipitation of acute respiratory failure and other organ failures. Thus diagnosis of LVD may lead to a change in management or an alteration in the level of vigilence. To avoid these complications a number of direct treatments for LVD have been proposed, including anticoagulation, recruiting stunned myocardium using inotropes and using dobutamine even in the absence of shock. Prevention of LVD has been proposed using beta-blocking drugs or angiotensin converting enzyme inhibitors (ACE-i) .[8]

Reversible myocardial dysfunction (RMD) has been well described and documented in the context of ischaemic heart disease, and classically is described as myocardial “stunning” representing persistent post-ischaemic myocardial dysfunction despite restoration of normal flow and myocardial hibernation, representing impaired left ventricular function secondary to reduced coronary blood flow which may be improved following revascularisation of a residual stenosis.[9]

Stress cardiomyopathy or Takotsubo cardiomyopathy, as originally described in Japan, is a highly characteristic but uncommon cause of RMD in critically ill patients and is thought to occur secondary to excessive use of exogenous catecholamines, or excessive endogenous production. It typically affects women within the 62-75 year old age range and has a very distinctive pattern of regional wall motion abnormality with akinesis of the mid and apical segments of the left ventricle and a hypercontractile base. This leads to the classical appearance of ballooning of the ventricular apex.[1]

However, LVD and RMD have been described in ICU patients with no prior history of ischaemic heart disease and who do not meet the criteria for stress cardiomyopathy. This

was initially observed in patients with sepsis, but has now been more widely observed in the ICU setting, in a range of pathologies including respiratory failure, trauma, acute pancreatitis, anaphylaxis, hypo- and hyperthyroidism, hypo- and hyperthermia and in patients with phaeochromocytomas. A variety of mechanisms have been proposed to account for RMD in the absence of ischaemic heart disease, including tissue hypoxia, reperfusion phenomenon, as a result of the "systemic inflammatory response syndrome" (SIRS), catecholamine excess, a direct cytotoxic mediator and genetic predisposition. The pathogenesis of RMD is probably multifactorial and dependent on the initiating stimulus.[8]

One of the first studies to show a RMD in septic patients was a landmark paper in 1984 by Parker showing that, contrary to popular belief of a hyperdynamic state in sepsis, a significant proportion of patients exhibited a reversible reduction in ventricular ejection fraction (determined with radionucleotide imaging).[10] Furthermore, surprisingly, he showed that patients with normal ventricular ejection fractions had worse outcomes. He observed ventricular dilatation in those with low ejection fractions which he postulated to be protective. Subsequent follow up studies have failed to observe this ventricular dilatation.[11] In addition despite initial evidence from other researchers to support an improved outcome of septic patients with impaired ejection fractions, the same study group have now shown this not to be the case.[12]

In addition to sepsis, RMD, has been shown to occur in a wide range of other critical illnesses. Sharkey and colleagues describe RMD occurring in a retrospective study of 22 patients with a range of pathologies including head injury, sepsis, acute pulmonary disease, drug overdose, metabolic abnormalities and following surgery.[13] They showed a median initial left ventricular function score of 3.0 (indicating a moderate decrease in left ventricular function), with severe dysfunction in almost a third of the patients. In 15 patients the left ventricular dysfunction was secondary to anterior-apical regional wall motion abnormality. In the remaining 7, basal hypokinesia contributed to the global left ventricular dysfunction. Repeat echocardiography at discharge from ICU after a median stay of 7 days showed significant improvement. Eight patients were followed up six months after hospital discharge which demonstrated normal wall motion in 5 patients, improved in 2 and unchanged wall motion in 1 patient. Thirteen patients in this study underwent cardiac catheterisation, coronary arteries were normal in 10, but 3 showed significant coronary artery disease. Although all patients in the study were admitted to critical care with non-cardiac illnesses, no comment is made of previous history of ischaemic heart disease.

In order to attempt to quantify the incidence of RMD in patients without heart disease Bailen and colleagues conducted a prospective descriptive study.[14] They looked at critically ill patients who underwent echocardiography for: 1) electrocardiographic changes, 2) signs of cardiac insufficiency, 3) persistent arrhythmias or 4) for any other condition where the intensivist treating the patient believed echocardiography might be beneficial. Patients with known chronic or acute heart disease were excluded, as were patients with a critical illness known to be associated with LVD. This included patients with myocarditis, sepsis and septic shock, postpartum cardiomyopathy, following cardiac arrest and following thoracic trauma. Of 1778 patients admitted to the ICU over the study period, 574 underwent echocardiographic examination. Of these 43 (7.5% of the total population) demonstrated LVD. The majority of the patients, as in Sharkey's study, demonstrated apical dysfunction, with basal dysfunction occurring in only 20%. 37% showed a compensatory increase with a hyperkinetic basal wall, despite overall reduced ventricular function. Echocardiographic examinations were repeated in 33 survivors within the first week, in the second or third week, after one month and after 3-6 months. A statistically significant and progressive improvement

in left ventricular function (LVF) was observed over time. This was matched by improvements in apical segmental contractility scores.

Though this was a large study, it was over a decade ago, and could not have estimated the incidence of RMD, as the entry criteria excluded some individuals who if studied would have demonstrated acute LVD. In addition the study only identified patients who had LVD on admission, and not those who developed LVD during their ICU stay. Studies looking at LVD in sepsis have shown that whilst 39% have LVD on admission, 21% more developed LVD despite an initially normal LVF.[12] The incidence of LVD is lower than other studies, the relevance of this is difficult to determine as the case mix in the study is poorly described.

Summary

We know LVD occurs in the adult general intensive care unit in patients with no prior history of cardiac dysfunction. Previous studies estimate an incidence of 7.5-20% in this population. We know that often this LVD may partially or fully resolve. In some patients left ventricular function may be normal on admission to ICU and subsequently deteriorate. There is mixed evidence as to the influence of LVD on outcome with some studies showing an association with increased mortality and others not.

Value of the study:

LVD and its reversibility have been well described in the context of sepsis, however, there are few good quality studies investigating the incidence in general ICU patients with other critical illnesses. In addition studies looking at all patients in ICU with no cardiac history have only looked for the presence of LVD on admission and then serially followed those with LVD on admission over time. The aim of this study would be to examine for LVD on three occasions in the first week and then serially follow those with evidence of LVD. This would lead to a greater understanding of the incidence of LVD in adult critically ill patients, the time course of any reversibility and which patients are at risk of developing LVD.

There are no risks to study participants in receiving a transthoracic echocardiogram. Potential benefits to participants include more frequent transthoracic echocardiogram examination than would be performed as part of standard care, thus allowing increased detection of cardiac abnormalities. In addition participants will receive three additional visits following ICU discharge where potential medical problems may be highlighted, and/or questions regarding their illness/ICU stay can be answered.

The population to be studied will be adult patients admitted as an emergency to the general intensive care unit who require mechanical ventilation. Patients with a prior history of cardiac disease or cardiac failure or admission to intensive care as a result of cardiac disease will be excluded.

3. OBJECTIVES

3.1 Primary Objective

To determine the incidence and prevalence of acute left ventricular myocardial dysfunction in critically ill adults.

3.2 Secondary Objectives

In those participants who develop acute left ventricular dysfunction, what recovery occurs at three and twelve months after ICU admission?

In those participants who develop acute left ventricular dysfunction is the duration of mechanical ventilation longer than a matched group of patients without acute left ventricular dysfunction?

In those participants who develop acute left ventricular dysfunction is the duration of care on an intensive care unit longer than a matched group of patients without acute left ventricular dysfunction?

In those participants who develop acute left ventricular dysfunction is the incidence of acute dysrhythmias occurring during their intensive care unit stay greater than a matched group of patients without acute left ventricular dysfunction?

In those participants who develop acute left ventricular dysfunction is the use of inotropes and vasoactive drugs greater than a matched group of patients without acute left ventricular dysfunction?

4. STUDY DESIGN

4.1 Summary of Study Design

This is an observational study involving additional transthoracic echocardiograms above those needed for patient care.
The duration of the study for participants will be either 7 days for those with normal ventricular function as assessed on three occasions within the first week of intensive care admission or 12 months for those with evidence of left ventricular dysfunction and entered into the extended follow-up. All participants will receive a transthoracic echocardiogram on day 1, once again between days 3&5 and once again between days 5&7 following intensive care unit admission. Those entered into the extended echocardiographic follow-up will receive an additional three echocardiograms, one at 1 week following discharge from the intensive care unit, one at three months after the original admission to the intensive care unit and one at twelve months after the original admission to the intensive care unit. Each transthoracic echocardiogram study lasts approximately 20 minutes. Patients with no evidence of left ventricular dysfunction will not receive long term follow up but will have their vital status recorded at three and twelve months.
There is no clear consensus on the optimum measures of left ventricular systolic and diastolic dysfunction determined from transthoracic echocardiographic images. Prior to the study a systematic review will be undertaken to identify and determine the measurement properties and practical utility of all described measures. “Conventional” measures to determine left ventricular ejection fraction, as well as techniques to quantify wall motion abnormalities, Doppler based techniques and speckle tracking will be reviewed. It is likely a panel of measurements will be used in the study.

Whichever measures are finally used will be reported as incidence and prevalence in the population studied, and time dependent changes in the absolute measures and fractional measures. To determine possible associations between LVD and morbidity such as duration of mechanical ventilation patients will be matched 1:2 with patients of the same age, sex and broad diagnostic category, and also matched on initial severity of illness measured using the APACHE II or ICNARC score.

4.2 Primary and Secondary Endpoints/Outcome Measures

The primary outcome measure will be the incidence of acute left ventricular dysfunction observed in the first seven days of critical illness in patients admitted to the adult general intensive care unit as an emergency.

Secondary outcome measures

- In those participants who develop acute left ventricular dysfunction during the first seven days of their intensive care unit stay, repeat measures of left ventricular function will be obtained following discharge from the intensive care unit to assess for improvement and therefore reversibility. These assessments will occur one week following discharge from the intensive care unit, and three and twelve months after admission to the intensive care unit.
- Those participants who develop acute left ventricular dysfunction will be compared with an age, sex, diagnosis and severity matched cohort without ventricular dysfunction to look for associations between left ventricular function and duration of mechanical ventilation, duration of intensive care unit stay, and the incidence of cardiac dysrhythmias and vasoactive/inotropic drug use whilst in the intensive care unit.
- Mortality to one year following intensive care admission will be compared between those who develop left ventricular dysfunction within the first seven days of study participation to those without, assessed using Kaplan-Meier curves.

4.3 Study Participants

4.3.1 Overall Description of Study Participants

Participants who are admitted to the adult general intensive care unit at the John Radcliffe Hospital as an emergency.

4.3.2 Inclusion Criteria

- Patient admitted to the adult general intensive care unit as an emergency
- Male or female, aged 16 years or above.
- Assent provided by personal or professional consultee whilst participant lacks capacity
- Following return of capacity participant is willing and able to give informed consent for ongoing participation in the study and use of data already obtained

4.3.3 Exclusion Criteria

The participant may not enter the study if any of the following apply:

- Admission to intensive care as a result of a cardiac arrest

- History of chronic cardiac failure from any cause
- Disease/condition making transthoracic echocardiogram impossible, unreliable or contraindicated (eg surgical emphysema, burns, chest wall surgery)

4.4 Study Procedures

All study assessments will comprise of a transthoracic echocardiogram and review of case notes.
Transthoracic echocardiography will be performed according to guidelines published by the British Society of Echocardiography.[15] All echocardiograms will be recorded electronically to allow intra- and inter-rater concordance to be estimated.

4.4.1 Informed Consent

Informed consent will be obtained by the chief investigator or his delegates. It is anticipated study participants will lack capacity to consent to study entry, however, they may regain capacity during the study. Consent will be sought from the personal consultee (usually the next of kin) by arranging a meeting as soon as is convenient after identifying a potential participant, explaining the study and providing written information. If or when participants regain capacity they will be visited by the chief investigator or his delegates and consent will be sought for use of data already obtained and for ongoing participation in the study. Written information will be provided. Where a personal consultee is unavailable the Trust-appointed professional consultee will be used.

4.4.2 Study Assessments

All patients admitted to the adult general intensive care unit of the John Radcliffe Hospital will be screened for potential eligibility to the study. Patients who have been admitted as an emergency and do not meet any of the exclusion criteria will be identified as potential participants. Following consent participants will receive their first visit as soon after gaining consent as practically possible, but within a minimum of 24 hours.

Assessment 1 (Day 1 following ICU admission)

Data recorded will include:

Patient identifiers and demographics

Admission date and time

Admitting diagnosis

APACHE II score

ICNARC score

Spontaneous or positive pressure assisted ventilation

If assisted, duration of positive pressure assisted ventilation

Global haemodynamic variables

Inotrope and vasopressor requirements

Physiological data required to categorise patients into the SIRS/Sepsis/Severe Sepsis grading

The examination will comprise of a transthoracic echocardiogram performed as per standard BSE guidelines, with all images recorded electronically with associated ECG traces.

Assessment 2 (between days 3&5 following ICU admission)

Data recorded as above except the APACHE II and ICNARC scores will be replaced by sequential organ failure assessment scores (SOFA).

Repeat transthoracic echocardiogram as per assessment 1.

Assessment 3 (between days 5&7 following ICU admission)

As assessment 2

Assessment 4 (1 week post ICU discharge)

Data recorded will include

Organ severity score (SOFA)

Intensive care unit discharge date

Total duration of positive pressure assisted ventilation whilst in the intensive care unit

Presence of any cardiac rhythm other than sinus rhythm since the preceding visit

Repeat transthoracic echocardiogram as per previous assessments.

Assessment 5 and 6 (3 and 12 months post admission to ICU)

Data recorded will include

Hospital discharge date

Current cardiac rhythm

Mean arterial blood pressure

Repeat transthoracic echocardiogram as per previous assessments.

Three and twelve month assessments will take place in the ICU follow up clinic in the outpatients department of the John Radcliffe hospital.

4.5 Definition of End of Study

The end of study is the date of the last assessment of the last participant. It is anticipated this will be within 25 months of entry of the first participant.

4.6 Interventions

Interventions performed on study participants will be a transthoracic echocardiogram performed on day 1 following ICU admission, once again between days 3&5 and once again between days 5&7 following ICU admission. Those participants identified as having evidence of left ventricular dysfunction on any occasion within the first seven days will receive three additional echocardiograms. These will be at 1 week following intensive care unit discharge, then at three and twelve months following intensive care unit admission.

5. Safety reporting

All echocardiographic examinations with any abnormality will be reported to the relevant clinician or general practitioner.

6. STATISTICS

6.1 The Number of Participants

The estimated number of participants receiving one or more echocardiograms is 150, based on the admission rates and diagnoses of patients admitted to the John Radcliffe Hospital's adult intensive care unit in the year ending April 2011

6.2 Analysis of Endpoints

Whichever measures are finally used will be reported as incidence and prevalence in the population studied, and time dependent changes in the absolute measures and fractional measures. To determine possible associations between LVD and morbidity such as duration of mechanical ventilation patients will be matched 1:2 with patients of the same age, sex and broad diagnostic category, and also matched on initial severity of illness measured using the APACHE II or ICNARC score.

7. ETHICS

The major ethical issue is common to all studies in critically ill patients, that patients cannot usually initially give consent. This study uses similar consenting procedures to all recent studies in this patient group.

7.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so, which will be after the last follow up and data cleaning.

7.2 Data Handling and Record Keeping

All study data will be entered on an "Access" relational database customised for the study. One table in this database will link the patient's identifiers to a unique study number used as an index in all other tables, allowing simple anonymisation of the data when required. The database will be held on secure servers with appropriate back up.

8. FINANCING AND INSURANCE

The University of Oxford will carry insurance for this study.

9. REFERENCES

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2. ELF 2

Date and Version No: **June 2013 v.1**

Study Title: Retrospective analysis of the natural history of acute reversible myocardial dysfunction in the critically ill

Ethics Ref: 13/SC/0399

Date and Version No: June 13 2013

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Sponsor: University of Oxford

Signatures:

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1. SYNOPSIS

Study Title	Retrospective analysis of the natural history of reversible myocardial dysfunction in the critically ill
Study Design	Retrospective study
Study Participants	Patients admitted to an Intensive Care Unit (ICU)
Number of Participants	75 (approx.)
Planned Study Period	2 years
Primary Objective	Determine the natural history of acute reversible myocardial dysfunction in the critically ill.
Secondary Objectives	To determine if participants demonstrating acute, reversible myocardial dysfunction require greater duration or requirements of vasopressor/inotropic support than those who do not demonstrate dysfunction To determine if participants demonstrating acute, reversible myocardial dysfunction have worse mortality outcomes than those who do not demonstrate dysfunction To determine if participants demonstrating acute, reversible myocardial dysfunction have elevated cardiac biomarkers during the duration of cardiac impairment To determine if acute, reversible myocardial dysfunction is more common in certain sub-populations of critical illness To determine if participants demonstrating acute, reversible myocardial dysfunction have a longer duration of mechanical ventilation than those who do not demonstrate dysfunction
Intervention (s)	This is a retrospective analysis of pre-existing medical records that were collected as part of routine clinical care.

2. ABBREVIATIONS

CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
NIGB	National Information Governance Board
OUH	Oxford University Hospitals
R&D	NHS Trust R&D Department
REC	Research Ethics Committee

3. BACKGROUND AND RATIONALE

Acute left ventricular dysfunction (LVD) has been demonstrated to affect up to one third of critically ill adults [1, 2]. There has been a reported increase in the incidence of this disease, which may be attributed to greater clinical suspicion and screening [1, 3-5]. Left ventricular dysfunction has been demonstrated in the setting of trauma, may occur secondary to ischaemia in the setting of coronary artery disease or develop as part of the systemic response to critical illness [6].

Recognised types of reversible myocardial dysfunction include hibernating myocardium and myocardial "stunning". These have been well described in the context of ischaemic heart disease with "stunning" representing persisting post ischaemic myocardial dysfunction despite restoration of coronary blood flow and hibernation representing impaired left ventricular function secondary to chronically reduced coronary blood flow, that may benefit from revascularisation [7].

Whilst the phenomena of reversible myocardial dysfunction has been extensively described in patients with ischaemic heart disease, it has also been reported in patients with critical illness such as neurological insults such as subarachnoid haemorrhage, acute severe respiratory failure and in trauma [5, 7]. Some studies [2, 5, 8-11] have demonstrated that acute left ventricular dysfunction can reverse over time however differing research methods mean that the natural history of this condition in the critically ill remains unknown.

Numerous theories have been proffered to explain the aetiology of reversible myocardial dysfunction in the critically ill. A large number of mechanisms and mediators such as reperfusion phenomenon, hypoxia, catecholamine excess, tumour necrosis factor alpha, nitric oxide and prostanoids have been postulated but the pathogenesis still remains largely unknown [7, 12].

Acute left ventricular dysfunction is important clinically as it is a common cause of haemodynamic instability in the critically ill [3, 13]. A review by Bailen and colleagues has suggested that occult ventricular dysfunction in the critically ill may play a role in progression towards cardio-respiratory failure [7]. Understanding the natural history of reversible myocardial dysfunction may ameliorate patient outcome by equipping the

clinician with information that may influence the decision to initiate or continue pharmacological or mechanical therapies.

Whilst some studies have been undertaken on reversible myocardial dysfunction in patients with sepsis, it is unknown if these results are generalisable to patients with other conditions. Furthermore, studies of reversible myocardial dysfunction in patients with sepsis are known to have significant limitations. These limitations have stemmed from differing methodologies in defining, assessing and tracking the time course of the dysfunction and thus natural history of the illness has not been fully elucidated. Additionally, significant patient selection bias is seen in numerous studies.

Transthoracic echocardiography has the ability to non-invasively provide diagnostic information regarding both cardiac structure and function [13]. Whilst serial echocardiography is able to measure variables such as change in ejection fraction over time, the unknown natural time course of reversible acute left ventricular dysfunction means that the ideal intervals for capturing these changes remains unknown.

This study aims to undertake a retrospective analysis of existing clinical data to characterise the time course of reversible myocardial dysfunction. Given the absence of knowledge of the natural history of this condition in the general critically ill population, this study will provide important information to guide the establishment of a prospective study in the future.

Summary

Acute left ventricular dysfunction occurs in the adult general intensive care population in patients with no prior history of cardiac dysfunction. We know that some patients experience reversible myocardial dysfunction in the course of critical illness but the time course during which this develops and remits has not been fully elucidated.

4. OBJECTIVES

4.1 Primary Objective

Determine the natural history of acute reversible myocardial dysfunction in the critically ill.

4.2 Secondary Objectives

To determine if participants demonstrating acute, reversible myocardial dysfunction require greater duration or requirements of vasopressor/inotropic support than those who do not demonstrate dysfunction

To determine if participants demonstrating acute, reversible myocardial dysfunction have worse mortality outcomes than those who do not demonstrate dysfunction

To determine if participants demonstrating acute, reversible myocardial dysfunction have elevated cardiac biomarkers during the duration of cardiac impairment

To determine if acute, reversible myocardial dysfunction is more common in certain sub-populations of critical illness

To determine if participants demonstrating acute, reversible myocardial dysfunction have a longer duration of mechanical ventilation than those who do not demonstrate dysfunction

5. STUDY DESIGN

5.1 Summary of Study Design

This study is a retrospective analysis of patients admitted to Intensive Care who received serial echocardiographic assessments during their admission. Echocardiographic measures will be linked to data pertaining to participants ICU stay to address primary and secondary outcomes.

Patient hospital numbers of all admissions to Intensive Care Units at Oxford University Hospitals (OUH) between 1/1/2008 and 1/6/2013 will be extracted from the local ICU patient database, CareVue. These hospital numbers will be run against the database (Xcelera) housing all echocardiographic images for OUH. This will identify patients who have had serial echocardiograms whilst in the ICU and are therefore eligible for enrolment. Clinical information relating to hospital admission of patients eligible for enrolment will then be extracted from CareVue and combined with local submission data for the Intensive Care National Audit and Research Centre. These data will be linked with the echocardiograms images. Following data linkage, all data will be anonymised.

This will allow characterisation of the time course of reversible myocardial dysfunction and facilitate investigation of its relationship to clinical outcomes.

National Information Governance Board approvals are being sought to gain permission to link existing patient data that was collected for clinical care purposes.

5.2 Primary and Secondary Endpoints/Outcome Measures

Changes in cardiac function over time, as demonstrated by echocardiography, will be assessed through clinically accepted measures. This will be related to haemodynamic data recorded at the time of assessment.

Requirements of vasopressor and inotropic therapy will be compared between participants demonstrating reversible myocardial dysfunction and those who do not. Measures will include, but are not limited to, infusion rates and vasopressor/inotropic free days.

Survival to ICU discharge, day 28 and 90 mortality outcomes will be compared between participants demonstrating reversible myocardial dysfunction and those that do not.

Comparisons will be made between participants demonstrating reversible myocardial dysfunction in regards to levels of cardiac biomarkers. Comparisons will include, but are not limited to, peak levels and duration of elevation.

Analysis of the admission diagnoses and past medical history of participants of demonstrating acute, reversible myocardial dysfunction may indicate if this phenomenon is more common in particular disease states.

Comparisons will be made between participants who demonstrate acute, reversible myocardial dysfunction and those who do not, to assess if patients demonstrating myocardial dysfunction have a longer duration of mechanical ventilation.

5.3 Study Participants

5.3.1 Overall Description of Study Participants

- Patients admitted to Oxford University Hospitals Intensive Care Units who have had serial echocardiography assessments.

5.3.2 Inclusion Criteria

- All adult patients who have undergone serial echocardiographic studies, that allow for the assessment of ventricular function, whilst admitted to an ICU at Oxford University Hospitals between 1/1/2008 and 1/6/2013.

5.3.3 Exclusion Criteria

- Aged <16 years
- < 2 echocardiographic assessments performed during ICU admission

5.4 Study Procedures

This is a retrospective study. No patients will be contacted. An application is in progress to obtain NIGB approval for the use of patient data without their consent.

Subject to NIGB approval the following process will be undertaken:

- Extraction of patient identifiers (name, date of birth, hospital number) of admissions to Intensive Care Units at OUH from 1/1/2008-1/6/2013 from the source database
- Extracted patient identifiers run against database housing echocardiographic images
- Identification of patients eligible for enrolment
- Extraction of clinical data from CareVue and local ICNARC databases of patients eligible for enrolment
- Data linkage between echocardiographic images and clinical data
- Anonymisation of data
- Analysis of data to address primary and secondary objectives

5.4.1 Informed Consent

Informed consent will not be sought for the use of medical records. An application to the National Information Governance Board (NIGB) is in process to use confidential medical records.

5.5 Definition of End of Study

The study will end at the conclusion of data analysis.

6. STATISTICS AND ANALYSIS

6.1 Number of Participants

Approximately 75 participants will be enrolled. This number is an estimate based on internal audit data.

6.2 Analysis of Endpoints

If there are data for all participants at all time points, changes in ejection fraction between the echocardiograms will be tested using ANOVA. However, it is unlikely this will occur, in which case "t" tests will be used with appropriate correction for multiple tests.

The patients will be divided into two groups, those who recover their ejection fraction and those that do not. Explanatory variables will be compared between the groups using parametric or non-parametric tests as appropriate.

7. ETHICS

7.1 Participant Confidentiality

All data will be from a single institution. All patients admitted to Oxford University Hospitals have access to information regarding the use of patient information, stating that subject to approval, may be used for research.

The proposed identifiers for use in this study are name, date of birth and hospital number. The hospital number will be primary identifier, with name and date of birth used as secondary identifiers. Access to identifiable data will be restricted to the immediate research team, Dr Duncan Young and Dr Victoria Trubody.

Once the relevant patient information has been identified and retrieved from each data source (CareVue, ICNARC, Xcelera), information will anonymised and given a unique linkage key. This anonymised information will be kept in a secure database and held in accordance with the Data Protection Act 1998. The linkage file that contains the unique linkage key and corresponding patient identifiers will be stored on a separate secure research server, which is password protected and housed behind secure, swipe access doors, with access restricted to Dr Duncan Young and Dr Victoria Trubody. All staff have undertaken Good Clinical Practice training and are bound by NHS confidentiality agreements.

It is anticipated that the retrieval and anonymisation process will take up to 9 months. The linkage file will be retained on the secure server until project completion.

7.2 Other Ethical Considerations

Patients admitted to Intensive Care have a high mortality, even following discharge from Intensive Care and hospital. Attempting to gain retrospective consent from relatives in this context is likely to cause considerable distress and would be unfeasible with the available resources. Enrolling only participants who were able to provide informed consent would introduce considerable recruitment bias.

8. DATA HANDLING AND RECORD KEEPING

All NHS computers used by the research team to access and analyse the data will be password protected at turn on, will be kept in a secure area in Oxford University Hospitals, and have hardware data encryption to standards required by the NHS.

All university computers used by the research team to access and analyse the data will be password protected at turn on, will be kept in a secure area in the Kadoorie Centre, and have hardware data encryption to standards required by the NHS.

The linkage key for patient anonymisation will be kept on a secure, password protected server with access restricted to Drs Young and Trubody.

No paper records containing identifiable information will be kept.

9. INSURANCE

9.1 Insurance

The University of Oxford will carry insurance for this study.

10. REFERENCES

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3. ELF 3

Note: Approvals were sought to undertake plasma catecholamine sampling and cardiac magnetic resonance imaging on a selected sub-population of ELF 3 participants. This, however, was not feasible.

Date and Version No: Version 1.1, 2nd July 2014

Study Title: Evaluation of the time course of acute reversible myocardial dysfunction in the general adult intensive care population

Short title: Reversible myocardial dysfunction in the critically ill

Ethics Ref: 14/SC/0305

Date and Version No: Version 1.1, 2nd July 2014

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Funder: University of Oxford

Conflicts of interest None declared

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1. SYNOPSIS

Study Title	Evaluation of the time course of acute reversible myocardial dysfunction in the general adult intensive care population	
Study Design	Observational study	
Study Participants	Patients treated on general adult intensive care (ICU)	
Number of Participants	60	
Planned Study Period	13 months	
	Objective(s)	Outcome measure(s)
Primary	To determine the time course of acute reversible myocardial dysfunction in the general ICU population	description of acute reversible myocardial dysfunction in patients admitted to adult general Intensive Care Unit, as determined by echocardiography and CMRI.
Secondary	In those patients who develop acute myocardial dysfunction what degree of reversibility is observed during their stay in ICU and the three months following ICU discharge? Do patients who develop acute reversible myocardial dysfunction have higher total inotrope/vasopressor requirements than those who do not develop the condition?	Echocardiography and cardiac magnetic resonance imaging will be used to track the reversibility and time course of cardiac function during ICU and the recovery period, to three months following ICU discharge. Medical records will be used to determine if participants who demonstrated acute, reversible myocardial dysfunction required a longer duration or higher total doses of invasive therapies (vasopressors, inotropes and mechanical ventilation) in

		comparison with those who did not demonstrate impairment.
	Do patients who develop acute reversible myocardial dysfunction require a greater duration of mechanical ventilation than those who do not develop the condition?	Medical records will be used to determine if participants who demonstrated acute, reversible myocardial dysfunction required a longer duration of mechanical ventilation than those who did not demonstrate impairment
	Do patients who have acute reversible myocardial dysfunction during their ICU stay, as demonstrated by echocardiogram, have continuing demonstrable myocardial dysfunction after Intensive Care discharge, as demonstrated with cardiac magnetic resonance imaging?	Two cardiac magnetic resonance imaging studies will be used to determine residual or persisting impairment in survivors of critical illness who demonstrate myocardial dysfunction on echocardiography.
	Do patients who develop acute, reversible myocardial dysfunction have a longer duration of ICU therapy than those who do not?	Medical records will also determine if participants who develop acute reversible myocardial dysfunction have a longer duration of ICU admission compared with those without the condition.
	Do patients who develop acute, reversible myocardial dysfunction have elevated levels of endogenous catecholamines than those who do not develop the condition?	Circulating catecholamine levels will be used to determine if participants who demonstrate reversible myocardial dysfunction have elevated plasma concentrations
Intervention (s)	This is an observational study. Participants will receive serial echocardiograms in addition to usual care during their ICU stay. In selected	

	hospital inpatient participants demonstrating myocardial impairment and not on vasopressors, a blood sample (1mL) will be drawn at the time of assessment to determine circulating catecholamine levels. Participants demonstrating impaired myocardial function during their ICU stay will have a final echocardiogram performed at three months following ICU discharge. After ICU discharge, selected patients deemed safe for MRI imaging, who additionally consent to CMRI, will receive CMRI at >10 days following ICU discharge and again at three months following discharge.

2. ABBREVIATIONS

ALVD	Acute left ventricular dysfunction
APACHE	Acute Physiology and Chronic Health Evaluation
CMRI	Cardiac Magnetic Resonance Imaging
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
LVEF	Left Ventricular Ejection Fraction
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
TTE	Transthoracic Echocardiography

3. BACKGROUND AND RATIONALE

Acute left ventricular dysfunction (ALVD) has been demonstrated to affect up to one third of critically ill adults [1, 2]. There has been a reported increase in the incidence of this disease, which may be attributed to greater clinical suspicion and screening [3-6]. Left ventricular dysfunction has been demonstrated in the setting of trauma, may occur secondary to ischaemia in the setting of coronary artery disease, or develop as part of the systemic response to critical illness [6]. Detection of acute left ventricular dysfunction has important clinical applications as it has been identified as a common cause of haemodynamic instability in the critically ill [7]. Some studies [2, 5, 7-9] have demonstrated that acute left ventricular dysfunction can resolve over time, however differing research methods mean these results should be interpreted with caution.

Recognised types of reversible myocardial dysfunction include "hibernating" myocardium and myocardial "stunning". These have been well described in the context of ischaemic heart disease with "stunning" representing persisting post ischaemic myocardial dysfunction despite restoration of coronary blood flow and "hibernation" representing impaired left ventricular function, secondary to chronically reduced coronary blood flow, that may benefit from revascularisation [10]. Whilst the phenomena of reversible myocardial dysfunction has been extensively described in patients with ischaemic heart disease, it has also been demonstrated in patients with critical illness such as anaphylaxis, neurological insults such as subarachnoid haemorrhage, acute severe respiratory failure, after major surgery and in trauma [5, 11].

Acute left ventricular dysfunction has been reported to affect the general ICU patients with no prior history of ischaemic heart disease. In addition, these patients have not met the criteria for other cardiomyopathies seen in the critically ill such as Takotsubo cardiomyopathy [6]. It is not a newly recognised phenomenon, in 1984 Parker and colleagues described reversible, acute left ventricular dysfunction in a landmark paper. In this study, a significant proportion of patients with septic shock exhibited a reversible reduction in ejection fraction demonstrated with radionuclide cineventriculography [12]. However, investigating the condition has become considerably easier with advances in echocardiography and other imaging techniques.

Numerous theories have been proffered to explain the aetiology of acute, reversible left ventricular dysfunction in the critically ill. A large number of mechanisms and mediators such as reperfusion phenomenon, hypoxia, catecholamine excess, excess tumour

necrosis factor α, nitric oxide and prostanoids have been postulated but the pathogenesis still remains largely unknown [10, 11].

Elevated plasma catecholamine levels have been demonstrated in a number of reversible cardiomyopathies, such as Takotsubos and in neurological insults [13, 14]. Furthermore, case series have reported reversible myocardial dysfunction induced through exogenous catecholamine administration [15]. Some studies have undertaken cardiac biopsies [14, 16], which have demonstrated contraction band necrosis, a hallmark of elevated catecholamines. In our study, we wish to investigate whether the reversible myocardial dysfunction observed in critical illness is also associated with elevated endogenous catecholamine levels. This has potential implications for the management of reversible myocardial dysfunction occurring in the critically ill, as it has been suggested that cardiomyopathies associated with elevated catecholamines should avoid administration of exogenous catecholamines and instigate mechanical therapies e.g. intra-aortic balloon pump.

Acute left ventricular dysfunction is not a benign condition as there are significant complications associated with its development. Acute left ventricular dysfunction is important clinically as it is a common cause of haemodynamic instability in the critically ill [17, 18]. A review by Bailen and colleagues has suggested that occult ventricular dysfunction in the critically ill may be a subtle manifestation of organ failure [10]. Consequently, greater detection of acute, reversible, left ventricular dysfunction can potentially ameliorate patient outcomes by enhanced detection of associated complications such as hypoxia, arrhythmia, shock, pulmonary oedema and previously unexplained hypotension [10].

Limitations in prior studies have stemmed from differing methodologies in defining, assessing and tracking the time course of the dysfunction and thus incidence and natural history of the illness has not been fully elucidated. Significant patient selection bias is seen in numerous studies. Examples of selection bias encountered included, but not limited to, excluding or enrolling patients based up requiring vasoactive support [19] mechanical ventilation [20] or admission with a diagnosis known to be associated with myocardial dysfunction e.g. sepsis [5]. Studies have also excluded patients with “history of heart disease” but have not elaborated how this was defined or how the data were collected [5, 17].

Differing approaches in defining cardiac impairment has resulted in the need for caution when applying results to clinical practice. The definition of significantly impaired ejection fraction has differed greatly between studies, with no apparent "gold standard" for defining impairment. Commonly, ejection fraction limits for defining "impaired" ejection fraction range from 30-55% [2, 17, 19-23].

Acute left ventricular dysfunction observed in the critically ill has been demonstrated to resolve over time [5, 7, 12, 20]. Studies in the septic population have demonstrated progressive normalisation of acute left ventricular dysfunction occurring between seven and ten days following the onset of sepsis with significant changes demonstrated between ICU admission and discharge [12, 19]. In the non-septic general critically ill population, the pattern of progressive normalisation during the course of critical illness has been reported in a small number of studies [5, 7]. The description of the time-course of reversible myocardial dysfunction remains unknown.

Echocardiography allows non-invasive, real-time assessment of myocardial function at the bedside. Undertaking serial echocardiographic studies allows for the description of the time course of reversible myocardial dysfunction in the critically ill. This tool is increasingly adopted in the assessment of critically ill patients and has been safely used in this environment for over a decade [24]. Whilst there are a number of imaging techniques available for the assessment of myocardial function, echocardiography is the most appropriate in the critical care environment as it is non-invasive, performed quickly and without the need to transport patients.

Cardiac magnetic resonance imaging is considered by some to be the "gold standard" in cardiac imaging owing to its high spatial resolution and accurate determination of left ventricular ejection fraction (LVEF) [25, 26]. In addition to the information obtained by transthoracic echocardiography, this study aims to utilise the high spatial resolution provided by CMRI in order to detect subtle changes in myocardial function that occur during recovery from critical illness. This will provide comprehensive information on the time course and nature of reversible myocardial dysfunction in the critically ill.

Cardiac magnetic resonance imaging does not use ionising radiation, thus rendering it more favourable than computed tomography imaging techniques. There are, however, important safety considerations in utilising cardiac magnetic resonance imaging, these relate to the use of high-powered magnets. Safety protocols, however, are well established and implemented to mitigate risk to both the participant and operators.

Ideally, CMRI would be undertaken during ICU admission, however some of the therapies used to sustain and restore life in the ICU contraindicate MRI scanning. Consequently, the proposed timing of cardiac magnetic resonance imaging reflects the earliest, yet safest opportunity to conduct this investigation.

Summary

The incidence and natural history of acute, reversible, left ventricular dysfunction in the critically ill remains yet to be elucidated. It has been identified as a cause of haemodynamic instability and has been suggested that it is a subtle manifestation of organ failure. Elevated endogenous catecholamine levels have been observed in a number of reversible cardiomyopathies, it is unknown if this feature occurs during reversible myocardial dysfunction in patients experiencing critical illness.

Transthoracic echocardiography will be used to determine the time course of reversible myocardial dysfunction occurring during critical illness. Cardiac magnetic resonance imaging is considered the "gold standard" in the accurate determination of ejection fraction and can be utilised to provide detailed assessment in changes in cardiac function during recovery from critical illness. Plasma catecholamine levels will be tested to investigate if reversible myocardial dysfunction occurring in critical illness shares similarities with other known reversible cardiomyopathies. Greater understanding of the time course of acute, reversible, left ventricular dysfunction may lead to increased clinical suspicion and detection, which will allow greater tailoring of management and potentially ameliorate patient outcomes.

4. OBJECTIVES AND OUTCOME MEASURES

Primary Objective	Primary Outcome measure
To determine the time course of acute reversible myocardial dysfunction in the general ICU population	Description of acute reversible myocardial dysfunction in patients admitted to adult general Intensive Care Unit, as determined by echocardiography and CMRI.
Secondary Objectives	**Secondary Outcome measures**
In those patients who develop acute myocardial dysfunction what degree of reversibility is observed during their stay in ICU and the three months following ICU discharge?	Echocardiography and cardiac magnetic resonance imaging will be used to track the reversibility and time course of cardiac function during ICU and the recovery period, to three months following ICU discharge.
Do patients who develop acute reversible myocardial dysfunction have higher total inotrope/vasopressor requirements than those who do not develop the condition?	Medical records will be used to determine if participants who demonstrated acute, reversible myocardial dysfunction required a longer duration or higher total doses of invasive therapies (vasopressors, inotropes and mechanical ventilation) in comparison with those who did not demonstrate impairment.
Do patients who develop acute reversible myocardial dysfunction require a greater duration of mechanical ventilation than those who do not develop the condition?	Medical records will be used to determine if participants who demonstrated acute, reversible myocardial dysfunction required a longer duration of mechanical ventilation than those who did not demonstrate impairment

Do patients who have acute reversible myocardial dysfunction during their ICU stay, as demonstrated by echocardiogram, have continuing demonstrable myocardial dysfunction after Intensive Care discharge, as demonstrated with cardiac magnetic resonance imaging?	Two cardiac magnetic resonance imaging studies will be used to determine residual or persisting impairment in survivors of critical illness who demonstrate myocardial dysfunction on echocardiography.
Do patients who develop acute, reversible myocardial dysfunction have a longer duration of ICU therapy than those who do not?	Medical records will also determine if participants who develop acute reversible myocardial dysfunction have a longer duration of ICU admission compared with those without the condition.
Do patients who develop acute, reversible myocardial dysfunction have elevated levels of endogenous catecholamines than those who do not develop the condition?	Circulating catecholamine levels will be used to determine if participants who demonstrate reversible myocardial dysfunction have elevated plasma concentrations

5. STUDY DESIGN

This is an observational study involving additional cardiac imaging above that needed for standard patient care. Participants will be involved in the study for up to three months after their enrolment.

There are two parts in this study. All 60 participants will participate in part 1 of the study. Following obtaining informed consent/assent, daily echocardiography will be undertaken on participants during their ICU admission to assess for evidence of impaired myocardial function. Participants not demonstrating any evidence of impaired myocardial function after the first three days of ICU admission will conclude their participation in the study. Participants who demonstrate impaired myocardial

dysfunction during the first three days of ICU admission will continue to receive daily transthoracic echocardiograms until day ten or ICU discharge, whichever is earlier. In participants not receiving vasopressors (for a full drug list please see study SOP), a blood sample (1mL) will be drawn daily at the time of each echocardiography to test for circulating catecholamines (noradrenaline, adrenaline and dopamine). Samples will be taken from pre-existing vascular access devices where possible.

For the part 2, we would like to invite up to 20 participants from Part 1 who demonstrate impaired myocardial dysfunction during ICU admission. They will receive a CMRI scan at the earliest, safest, opportunity once they have been deemed clinically stable. These participants will undergo an additional, separate, informed consent procedure. Repeat echocardiography and blood sampling will occur at the time of CMRI. A final assessment consisting of echocardiography and CMRI will be conducted in these participants at three months following ICU discharge.

6. PARTICIPANT IDENTIFICATION

6.1 Study Participants

Patients treated on the general adult Intensive Care Units at the John Radcliffe Hospital who are admitted to ICU as an emergency.

6.2 Inclusion Criteria

- Adult patients 16 years or older treated on the adult general ICU with medical staff committed to continuing treatment.
- ICU length of stay ≥ 72 hours

6.3 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria are met:

- Aged under 16 years
- ICU length of stay <72 hours
- Condition rendering future CMRI unsafe or unreliable
- Condition rendering transthoracic echocardiography unreliable
- Admission to the Intensive Care Unit as a result of cardiac arrest
- Cardiac arrest during admission to the Intensive Care Unit
- Planned, elective admissions to the Intensive Care Unit
- Limitations in treatment
- Limitations in the use of English
- Prisoners

- Known presence of phaeochromocytoma

7. STUDY PROCEDURES

Please refer to APPENDIX A for the overview of study procedures.

7.1 Recruitment

All patients admitted the general adult Intensive Care Units at the John Radcliffe Hospital site will be screened for study eligibility. Patients who have been admitted as an emergency and do not meet any of the exclusion criteria will be flagged as potential participants (screened) by the clinical team.

Clinical staff will ask patients or their representative (consultee) if it is acceptable to them for a member of the research team to speak with them to discuss the project, stressing that it is a voluntary process and will not affect clinical care. This will occur during the first 24 hours of ICU admission.

The research team will then have an obligation-free discussion about the project and give the patient/consultee as long as they need to consider the project and read the written information. If consent/favourable opinion is obtained, the patient will be enrolled in the study. The research team will be available on the ICU for the participant/consultee to ask questions and give their decision about joining the study. Participants/consultees may also give their decision to the clinical team (to be relayed to the research team) should they prefer.

Following obtaining informed consent/consultee favourable opinion, participants are enrolled in the study.

7.2 Informed Consent

For part 1, Informed consent will be obtained by the chief investigator or her delegates, using the patient consent form. It is anticipated study participants will lack capacity to consent to study entry, however, they may regain capacity during the study. Favourable opinion will be sought from the personal consultee (usually the next of kin) by arranging a meeting as soon as is convenient after identifying a potential participant, explaining the study and providing written information (consultee declaration). If or when participants regain capacity they will be visited by the chief investigator or her delegates and consent will be sought for use of data already obtained and for ongoing participation in the study (retrospective patient consent). Written information will be provided. Where a personal consultee is unavailable a Trust-

employed professional consultee will be used. If a participant loses capacity, consultee opinion will be sought for continuing involvement in echocardiography and blood sampling.

In the Part 2, participants that demonstrate impaired myocardial function with echocardiography will be considered for cardiac magnetic resonance imaging. Selected participants that are able to provide consent and meet the stringent safety criteria will be invited to undertake this imaging. Informed consent will be obtained by the chief investigator or her appropriately trained delegates (CMRI patient consent). Prior to approaching a patient, the research team will discuss with the clinical team if there are any concerns about capacity. Given the rigorous safety checks that must be performed prior to CMRI, it is not appropriate for consultee opinion to be given. All research staff will have undertaken Good Clinical Practice training.

7.3 Part-1 of the study

Echocardiography

All study assessments will comprise of a transthoracic echocardiogram and review of case notes.

Transthoracic echocardiography will be performed according to guidelines published by the British Society of Echocardiography. All echocardiograms will be recorded electronically to allow intra- and inter-rater concordance to be estimated.

Procedure:

- Identification of eligible patients through discussions with clinical staff
- Discuss study with patient or consultee
- Obtain informed consent or favourable opinion following assessment of capacity
- Undertake daily transthoracic echocardiography during the first three days of ICU admission. If there is no evidence of myocardial dysfunction, the participant will conclude their involvement at the completion of the third scan. If there is evidence of impairment, daily scans will continue to ICU discharge or day ten of ICU stay, whichever is earliest.
- Participants demonstrating myocardial dysfunction will also receive a final scan during their ICU follow up clinic appointment.

Blood sample for plasma catecholamines

Circulating catecholamines will be tested at the time of echocardiography/ CMRI occurring in the hospital setting. All participants demonstrating dysfunction who are not receiving vasopressors will be tested. Where possible, blood samples (1mL) will be

drawn from pre-existing vascular access. Standard techniques will be used for blood sampling and processing of specimens. No genetic testing will be done.

7.4 Part-2 of the study

Cardiac Magnetic Resonance Imaging

All CMRI studies will be performed according to established, current protocols of the University of Oxford Acute Vascular Imaging Centre by appropriately trained operators. The cardiac magnetic resonance imaging machine used will be a 3 Tesla Siemens.

First CMRI scan

- When the patient is deemed clinically stable by the treating team, magnet safety clearance will be confirmed. Following approval from the clinical team, participants will then be accompanied to the CMRI unit and throughout the entire imaging session by an appropriately trained doctor
- In patients with adequate renal function (eGFR >30 ml/min/1.73m^2), an intravenous cannula will be inserted (as necessary) for gadolinium administration, with gadolinium administered at the appropriate dose. Participants who do not have an eGFR >30 ml/min/1.73m^2, as determined by a blood sample taken within 1 week of imaging, will not receive gadolinium.
- During the CMRI, electrocardiographic and respiratory gating will be performed according to standard procedures.
- CMRI sequencing performed according to local protocols.

Second CMRI scan (during follow up visit to clinic)

- At three months following ICU discharge a repeat CMRI will be performed in participants who demonstrated impaired myocardial function during initial imaging. This will be undertaken at the time of ICU follow up clinic wherever possible, following repeat safety clearance. This visit will last for up to 90 minutes. In patients with adequate renal function (eGFR >30 ml/min/1.73m^2), an intravenous cannula will be inserted (as necessary) for gadolinium administration, with gadolinium administered at the appropriate dose. Participants who do not have an eGFR >30 ml/min/1.73m^2, as determined by a blood sample taken at the point of care, will not receive gadolinium.

7.5 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

Data of excluded participants will be reviewed on a case-by-case basis to determine if it will be included in the final analysis, this will be determined by the reason for discontinuation. The reason for withdrawal will be recorded in the CRF.

7.6 Definition of End of Study

The end of the study is the date of the last assessment of the last participant. It is anticipated that this will be 12 months after the enrolment of the first participant.

8. INTERVENTIONS

8.1 Echocardiography

Participants will receive daily transthoracic echocardiographs during the first three days of their ICU admission. If there is any evidence of myocardial dysfunction, daily echocardiograms will be performed until day ten or ICU discharge, whichever is earlier. If no evidence of myocardial dysfunction is detected in the first three days then these participants will conclude their involvement in the study.

Participants will undergo transthoracic echocardiography (TTE) within 24 hours of ICU admission. Each examination is undertaken at the bedside and lasts approximately 20 minutes. All participants will receive daily transthoracic echocardiography for three days. Participants who demonstrate myocardial dysfunction during this period will continue to receive daily echocardiograms until ICU discharge or day ten of ICU stay, whichever is earlier. Participants who do not demonstrate impaired myocardial dysfunction in the first three days of ICU stay will be excluded from further imaging. All participants demonstrating impaired myocardial function during ICU admission will

receive a final TTE during their outpatient clinical appointment, three months following ICU discharge.

In a subset of participants who are selected for cardiac magnetic resonance imaging (detailed below), a repeat echocardiogram will occur just prior to CMRI studies.

8.2 Blood sample for plasma catecholamine

Whilst in hospital, plasma catecholamine sampling will occur at the time of cardiac assessment in participants demonstrating impaired myocardial function. Blood samples will be collected and handled according to standard laboratory and hospital protocols.

8.3 Cardiac Magnetic Resonance Imaging

Participants will be selected following further screening of existing study (echocardiographic imaging) participants and discussion with the treating clinical team. Importantly, participants will only be eligible for the study provided they are deemed medically stable, are able to provide informed, written consent, and met the stringent safety procedures of the magnetic resonance imaging unit. Participants will undergo cardiac magnetic resonance imaging whilst still an inpatient at the John Radcliffe Hospital. Participants will be invited back for repeat CMRI and echocardiogram to coincide with their three month ICU follow up appointment.

Participants identified as having impaired myocardial function by echocardiography will be screened for eligibility for undertaking CMRI studies. Only participants who are able to give informed consent, and meet the magnet safety criteria will be eligible. The timing and procedure of CMRI studies has been described elsewhere.

9. SAFETY

9.1 Echocardiography

Echocardiography utilises the properties of ultrasound to construct images, without the need for ionising radiation. Transthoracic echocardiography is a non-invasive investigation with no known risks. Any abnormality detected during imaging will be referred to an experienced echocardiographer for review and appropriate onward referral if required.

9.2 Blood sampling

Catecholamine testing requires 1mL of blood to be drawn per assessment. This is a marginal amount, and even with repeated testing, will not compromise the participant.

Where possible, blood samples will be drawn from pre-existing vascular access devices. Given how commonly these devices are used in ICU, the number of participants requiring blood to be drawn via a new skin puncture is felt to be low. Potential risks to participant include infection and bleeding, although with appropriately trained staff following hospital protocols, this is minimal.

9.3 Cardiac Magnetic Resonance Imaging

Magnetic Field

Magnetic Resonance Imaging (MRI) utilises the magnetic properties of positively charged hydrogen protons in the body, and their behaviour in the presence of a magnetic field and radiofrequency pulse, to produce detailed soft tissue images.

Magnetic resonance imaging devices generate a strong magnetic field that has the potential to cause injury if ferromagnetic objects enter its field. Additionally, the magnetic field generated has the ability to interact with implanted medical devices or metallic foreign bodies. Consequently, there are strict, well established protocols to minimise risk to the participants and operators.

At the time of recruitment, potential participants will be shown the safety screening document. If there is any doubt about a participant's eligibility, then senior staff will be consulted for advice before the subject is enrolled.

On the day of the scan, participants will screened again outside of the controlled area (magnet field), with a verbal interview and safety screening document. If there is any concern that the subject may not be safe to scan, the scan will not proceed and the relevant senior staff consulted before the subject enters the controlled area. Prior to entry to the magnet room, the participant will be independently checked by two research staff to ensure that they have removed all metallic belongings. This procedure will be repeated every time a subject is scanned.

Gadolinium Administration

Gadolinium is a contrast agent commonly used in cardiac magnetic resonance imaging and is considered safe. Occasionally it may cause itching, nausea and a mild headache. Rarely (<1 in 1000), it may induce a more severe allergic reason. The administration of Gadolinium has been associated with nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment. In keep with local and international guidance, patients with an eGFR <30ml/min/1.73m^2 will not be eligible for Gadolinium administration, and this part of the CMR study will be omitted. Gadolinium will be

administered through an intravenous cannula, if the participant does not have existing vascular access, this will be sited by the medical officer at the time of study, using standard techniques.

Local policy will accept eGFR lab results within one week of CMRI study date. All patients admitted to Intensive Care will have the eGFR calculated during their admission. Point of care eGFR testing is available at the AVIC unit site and all participants will have their eGFR determined prior to CMR study commencement.

All research personnel involved in this study will receive comprehensive magnet safety training prior to the enrolment of the first participant.

The University of Oxford Acute Vascular Imaging Centre is equipped with standard resuscitation equipment and defibrillator.

MRI scanning is non-invasive and has no significant adverse health effects when conducted properly. All persons entering the scanning room are screened for ferromagnetic materials or other factors that may cause risk in the presence of a strong magnetic field. All MRI scanners used in this study are equipped with hardware and software safety features to prevent delivery of unsafe levels of radiofrequency energy and nerve stimulation from magnetic field switching. These systems are within UK safety guidelines for scanning human subjects.

Operators conducting the MRI scans receive annual training in MRI safety and basic life support specific to the environment. The scanner creates significant noise during the scan, which is minimised using earplugs and headphones. Verbal contact will be maintained between the investigators and the participants at all times, and a call button will be given to subjects to enable them to stop the scan at any time.

Participants who experience claustrophobia or any discomfort will be free to stop the study at any time.

9.4 Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation

- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.5 Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant would be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs would be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form.

10. STATISTICS AND ANALYSIS

10.1 Number of Participants

Sixty patients will be enrolled to undertake comprehensive echocardiographic studies during their duration of their ICU admission. This figure takes into consideration the high mortality (12-14%) associated with critical illness. A selection of these participants who have demonstrated impaired myocardial function, who meet the safety criteria, will undergo cardiac magnetic resonance imaging.

Up to 20 participants will be enrolled for serial CMRI studies. Interim analysis for any evidence of reversible myocardial dysfunction will be performed at the conclusion of the final study of the tenth patient.

10.2 Analysis of Endpoints

The primary endpoint will be characterisation of the time course of reversible myocardial dysfunction, as calculated using accepted measures, using echocardiography and cardiac magnetic resonance imaging.

Secondary outcomes:

- Exploratory parametric and non-parametric tests will be used as appropriate to address secondary outcomes.

11. ETHICS AND REGULATORY CONSIDERATIONS

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

11.5 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. In this instance, it will be after the last visit of the last enrolled participant.

11.6 Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

11.7 Other Ethical Considerations

All researchers have appropriate training and experience in assessing capacity. Consent (or assent) will be sought prior to enrolment in the echocardiography arm of the study. Following completion of the echocardiographic studies, only patients who

are able to give informed consent will be eligible for the cardiac magnetic resonance imaging. Given the rigorous safety requirements that are needed before clearance is given to proceed with CMRI, it is not appropriate for consultee opinion to be asked to be obtained. Additionally, if a participant loses capacity whilst still undergoing CMRI safety checks, they will be excluded from the study and imaging will not proceed.

11.8 Procedure for Incidental Findings

There is a small possibility that echocardiography, plasma catecholamine sampling or cardiac magnetic resonance imaging may demonstrate an incidental finding (an abnormality not expected from the patients clinical presentation). Patients will be made aware that this is a possibility prior to enrolment, thus patients who would prefer not to become aware of such findings may opt not to participate in the study. Any suspected abnormality seen during imaging will be promptly referred to senior staff to determine if it is a true abnormality or an artefact, and the significance of the finding. Blood samples will be reanalysed to ensure it was not a spurious result.

Following confirmation of a true incidental finding (non artefactual), the treating clinical team will be informed and will guide management/action of the findings. The clinical team will be responsible for informing the participant of the findings.

There are established procedures within the University of Oxford Acute Vascular Imaging Centre for the management of incidental findings, which will be adhered to. These procedures aim to minimise the potential of distress to participants by ensuring prompt and thorough review of studies to discern if the finding is an artefact, normal variant or clinically significant abnormality and the most appropriate course of action. These standard operating procedures will be used in this study.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

13. DATA MANAGEMENT

13.1 Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13.2 Data Recording and Record Keeping

All study data will be stored on secure University of Oxford servers with appropriate access control, with secure server back-up. All paper based documentation will be kept in a locked filing cabinet in the Kadoorie Centre behind two access controlled doors. All electronic documentation will be kept as an Access database on a high compliance server with password protection. Data will be entered by the CI or her delegates. The participants will be identified by a study specific participants number and/or code in any database. All documentation will be archived in a secure off site facility for 15 years as per usual practice.

14. FINANCING AND INSURANCE

14.1 Funding

The study is funded by the Nuffield Department of Clinical Neurosciences, University of Oxford.

14.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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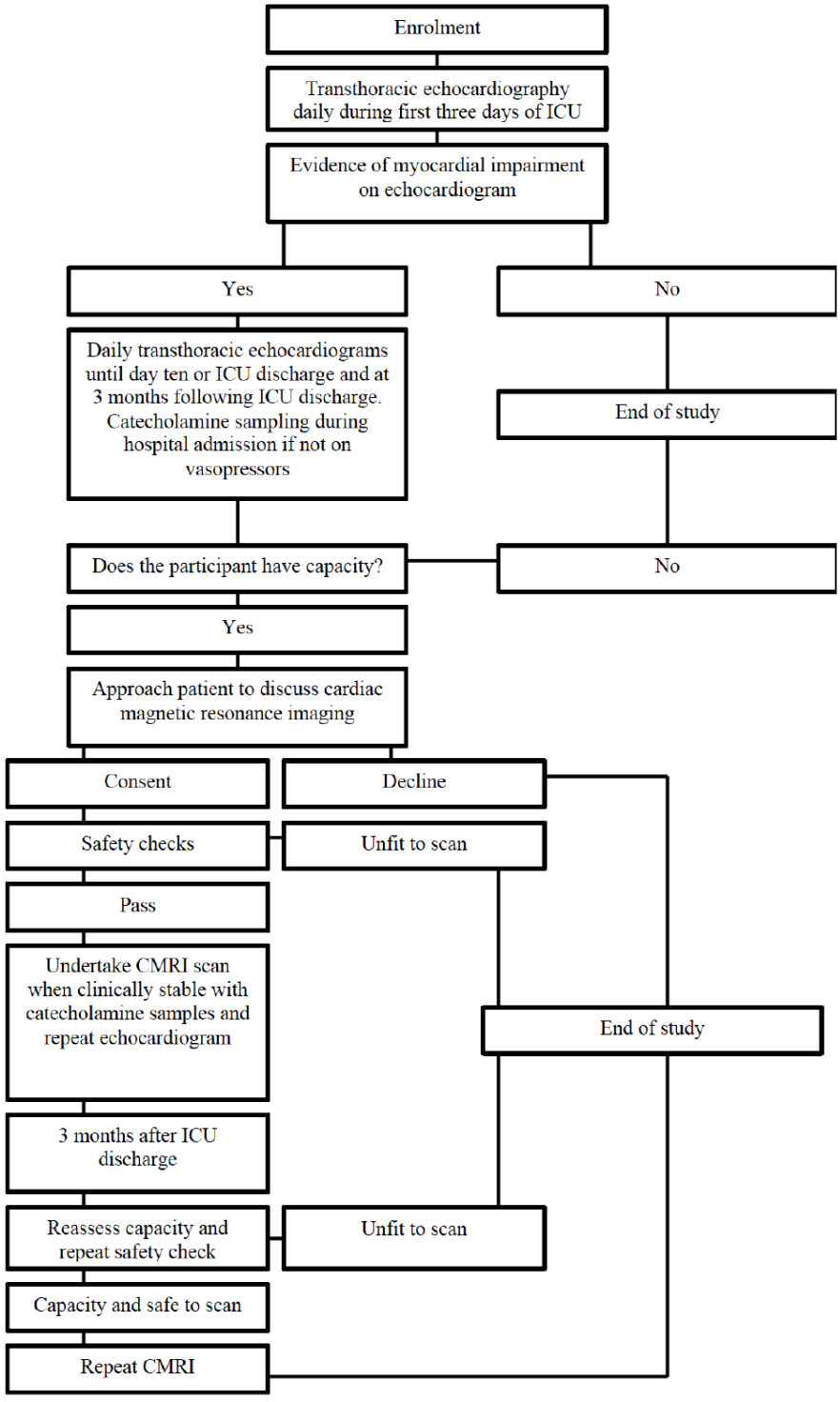
Table 1 – study flow chart



Appendix 5: Additional study documentation

Ethics committee correspondence: ELF 1

NHS
Health Research Authority
NRES Committee South Central - Oxford C
Room 002
TEDCO Business Centre
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 428 3564
Facsimile: 0191 428 3432

17 May 2012

Ms Julie Darbyshire
Research Manager
Nuffield Division of Anaesthetics
University of Oxford
John Radcliffe Hospital
Oxford
OX3 9DU

Dear Ms Darbyshire

Study title: **Observational study to assess the incidence and reversibility of acute left ventricular myocardial dysfunction in critically ill adults**
REC reference: **12/SC/0099**

Thank you for your letter of 10 May 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter	Julie Darbyshire (John Radcliffe Hospital)	26 January 2012
Evidence of insurance or indemnity	Dr Andrew Walden (University of Oxford)	17 January 2012
GP/Consultant Information Sheets	3 Month - Version 1.0	28 June 2011
GP/Consultant Information Sheets	12 Month - Version 1.0	28 June 2011
GP/Consultant Information Sheets	LVD - v1.0	30 October 2011
GP/Consultant Information Sheets	No LVD - v1.0	30 October 2011
Investigator CV	Dr John Duncan Young	
Letter from Sponsor	Mrs E Chick (University of Oxford)	26 January 2012
Participant Consent Form: (for Patients)	Version 1.3	04 April 2012
Participant Consent Form: (Consultee Assent Form)	Version 1.3	04 April 2012
Participant Information Sheet: (for Patients - Retrospective)	Version 1.2	24 January 2012
Participant Information Sheet: (for Patients)	Version 1.3	04 April 2012
Participant Information Sheet: (for Consultees)	Version 1.3	04 April 2012
Protocol	Version 1.2	24 January 2012
REC application	IRAS Version 3.4 80599/286487/1/432	06 February 2012
Response to Request for Further Information	Julie Darbyshire (University of Oxford)	10 May 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for

Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/SC/0099	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

L. Kirkbride (pp)

Professor Nigel Wellman
Chair

Email: laura.kirkbride@sotw.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Duncan Young*

Oxford University Hospitals NHS Trust

NHS
Health Research Authority

NRES Committee South Central - Oxford C
Bristol REC Centre
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421392
Facsimile: 0117 3420445

10 September 2013

Dr J Duncan Young
Consultant Intensivist and Senior Clinical Lecturer
Oxford University Hospitals NHS Trust
Kadoorie Centre, Level 3
John Radcliffe Hospital
Headley Way, Oxford
OX3 9DU

Dear Dr Young,

Study title:	**A retrospective analysis of the natural history of reversible myocardial dysfunction in critically ill patients**
REC reference:	**13/SC/0399**
IRAS project ID:	**134468**

The Research Ethics Committee reviewed the above application at the meeting held on 30 August 2013. Thank you and Dr Victoria Trubody for attending to discuss the application.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Ms Rae Granville, nrescommittee.southcentral-berkshire@nhs.net.

Ethical opinion

After the Committee's initial discussions you and Dr Victoria Trubody were invited to join the meeting to clarify the following issues:

1. The Committee questioned the sample size; it viewed the total number of 75 as rather small when the data was to be extracted from a database.

   You both explained that you were unsure resulting sample size, as the cross-referencing would reduce the number of prospective patients. You both informed the Committee that the figure of 75 was an estimate of the likely pool of available data.

2. The Committee queried if you had received a response from CAG (formally NIGB). You both replied that you had received a positive outcome that was subject to conditions: an approval letter from the REC, improved security arrangements, amendment of the PIS to clearly state that the patient had the option to say no, and more information on public engagement activities. The Committee queried if the project would have a website which would show project progress. You both confirmed this. You both offered a copy of the CAG letter for the Committee to review.

3. The Committee questioned what useful results would be provided by this study. It noted that the data would be extracted from Carevue; you would not be studying the patient notes and would miss patient's daily records recorded by the nurse etc.

   You both explained that Carevue is used on ICU and narrative information is not entered. There was no plan to use narrative data but to extract diagnostic, age, gender data. You both informed the Committee that no further data was required; only the data set that would provide progression of the patient's condition.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		09 July 2013
Investigator CV		13 April 2013
Letter from Sponsor		08 July 2013
Protocol	1.0	02 July 2013
REC application		08 July 2013
Referees or other scientific critique report		07 July 2013

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

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- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Ethics committee correspondence: ELF 3

NHS
Health Research Authority

NRES Committee South Central - Berkshire
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421389

25 June 2014

Dr Victoria Trubody
Clinical Research Fellow
Oxford University Hospitals NHS Trust
Kadoorie Centre, Level 3
John Radcliffe Hospital, Headley Way
Oxford
OX3 9DU

Dear Dr Trubody,

Study title:	**Evaluation of the time course of acute, reversible myocardial dysfunction in the general adult intensive care population**
REC reference:	**14/SC/0305**
IRAS project ID:	**134971**

The Research Ethics Committee reviewed the above application at the meeting held on 17 June 2014. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Ms Rae Granville, nrescommittee.southcentral-berkshire@nhs.net.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Mental Capacity Act 2005

I confirm that the Committee has approved this research project for the purposes of the Mental Capacity Act 2005. The Committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

1. Please add the following point to the consultee information sheet 'When the patient regains capacity they will be invited to consent retrospectively, at that point your services will no longer be required. You will be expected to discuss the study with the patient once they regain capacity'.
2. Advisory point: please add the list of excluded medications as a protocol appendix or make suitable references to the list in your standard operating procedures within the study protocol.
3. If this study is part of an educational project please add an opening sentence inviting the participant/consultee to help you with this study, making it clear that you are a student seeking an educational qualification.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on question 2 of the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee agreed that the scientific rationale for understanding cardiac impairment in critical illness was clearly outlined: the incidence and natural history is not fully understood, but previous studies have demonstrated its development and associated complications. Greater understanding and detection of cardiac dysfunction could potentially reduce these associated complications.

The Committee asked for further information on the scheduled review at a midway point, after three months. You answered some indicators would not show up in the scans and if patients were not responding you would have to reassess the study.

Recruitment arrangements and access to health information, and fair participant selection

The Committee asked you who you would normally appoint as a consultee; you explained that it would typically be the nearest relative or the person who identified themselves as the patient's next of kin according to standard records – you were conscious of risks of unsettling family dynamics. You were also clear that this person would be the most likely to visit frequently and could continue to be consulted as necessary.

The Committee questioned the indefinite period of time given for participants or consultees to decide whether they wished to participate. It requested clarification. You answered that ideally the patient would consent within twenty-four hours but sometimes this timing would not be appropriate; you were anxious to not put the patient or their consultee under any pressure. For this reason the recruitment timing was flexible for the patient. You added that you would make this more explicit in the PIS' if required.

The Committee queried the criteria and rationale for recruiting only twenty participants for the MRI part of the study. You replied the criteria set included the fact that all patients would have capacity to consent for themselves and do not have implanted defibrillators or any other MRI contra-indications. The decision on which of the first 20 to be recruited would be a combined decision with the patient's consultant. The Committee was content with this

response.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee pointed out that the information sheet does not suggest any personal benefit to participants, only potential future benefits to patients with critical illness due to improved detection of cardiac dysfunction and possible treatments. Whilst the proposal (B4-5 of the REC Form) suggests any cardiac pathology detected by the echocardiography could result in changed treatment and thus potential benefit. It queried how you would manage any abnormalities detected. You replied that the patient information sheet (PIS) did state that this study was for research purposes not diagnostic purposes. You added that the staff completing the scans were well qualified and would refer any participant for treatment if an abnormality was noted. The Committee pointed out that the proposal stated that the participant would benefit from the study. It requested clarification. You explained that any abnormality noted during the scan would be referred appropriately to a medical team who would complete the full battery of diagnostic scans.

The Committee commented that the risk to participants is negligible in the research phase involving participants unable to consent, and the research was not unduly invasive or restrictive. It agreed that the burdens and risks are clearly set out for the cardiac MRI phase, involving only participants able to give informed consent.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee reviewed the section on incidental findings. It questioned the process in place to deal with anomalies were discovered in patients unable to consent for themselves or those able to consent for themselves. The Committee agreed that the likelihood of discovery of incidental findings was higher in an intensive care setting. It queried if it would be acceptable for the patient or consultee to opt-out of the study until stabilisation occurred before discussing the issue. You answered that many patients had strong feelings in this area and that if the patient or consultee advised that the patient would be averse to the possibility the patient would not be enrolled in the study. It was clear to the Committee that no incapacitated patient would be recruited if there was evidence that they would not have consented to research with the potential of producing incidental findings of conditions with regard to which, they would prefer to remain ignorant.

The Committee noted that you would be using the participant date of birth and their initials as identifiers. It pointed out that the participant's anonymity could be jeopardised. It agreed that this was acceptable if the participant had consented to this anonymisation strategy.

The Committee was concerned that you would not be taking into account any myocardial dysfunction which had been present before the patient arrived at the ICU. The Committee questioned how you were intending to assess underlying dysfunction before the patient entered the ICU. You replied that it was difficult to assess patients who had dysfunction before entering ICU as they may have stabilised before entering the trial. You added that you intended to use the medical history of participants to gain a clearer picture.

The Committee requested that the medication exclusion list required expansion in the Protocol. You explained that the expanded list was in the study standard operating

procedures and agreed to add this exclusion list as a protocol appendix or reference the list from the study standard operating procedures in the protocol.

Informed consent process and the adequacy and completeness of participant information

Overall the Committee was impressed at the quality and detail of all participant and consultee information.

The Committee noted one minor issue. It noted that patient consent would be sought as soon as they gained capacity; it questioned whether the consultee would be required to discuss their involvement regarding joining the research, with the patient, at this point. You informed the Committee that this detail was on the consultee consent form. The Committee requested that it be added to the consultee PIS so that it was clearer.

Compliance with the Mental Capacity Act – the Committee agreed the following:

Relevance of the research to the impairing condition

The Committee agreed the research is connected with an impairing condition affecting persons lacking capacity or with the treatment of the condition.

Justification for including adults lacking capacity to meet the research objectives

The Committee agreed the research could not be carried out as effectively if it was confined to participants able to give consent.

Arrangements for appointing consultees

The Committee considered the arrangements set out in the application for appointing consultees under Section 32 of the Mental Capacity Act to advise on whether participants lacking capacity should take part and on what their wishes and feelings would be likely to be if they had capacity.

Balance between benefit and risk, burden and intrusion

After discussion, the Committee agreed that the research has the potential to benefit participants lacking capacity without imposing a disproportionate burden on them. Whilst the researcher had not identified the issue it was clear to the committee that participation could bring some benefit to patients in the form of diagnosis and treatment of cardiac pathology. The burdens involved in participation were minimal and amounted to little more than standard treatment.

Additional safeguards

The Committee was satisfied that reasonable arrangements would be in place to comply with the additional safeguards set out in Section 33 of the Mental Capacity Act.

Information for consultees

The Committee reviewed the information to be provided to consultees about the proposed research and their role and responsibilities as a consultee.

The Committee was satisfied that the information was adequate to enable consultees to give informed advice about the participation of persons lacking capacity. Overall the Committee was impressed at the quality and detail of all participant and consultee information.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		15 May 2014
Letter from funder [RMD in Critical Illness Funding Confirmation]		24 February 2014
Letter from sponsor		15 May 2014
Participant consent form [RMD in Critical Illness Consultee Retrospective Opinion]	1.0	07 February 2014
Participant consent form [RMD in Critical Illness Patient Consent CMRI]	1.0	07 February 2014
Participant consent form [RMD in Critical Illness Consultee Opinion]	1.0	07 February 2014
Participant consent form [RMD in Critical Illness Patient Consent]	1.0	07 February 2014
Participant information sheet (PIS) [RMD in Critical Illness Patient Information Sheet CMRI]	1.0	07 February 2014
Participant information sheet (PIS) [RMD in Critical Illness patient Information Prospective]	1.0	07 February 2014
Participant information sheet (PIS) [RMD in Critical Illness Patient Information Retrospective]	1.0	07 February 2014
Participant information sheet (PIS) [RMD in Critical Illness Consultee Information]	1.0	07 February 2014
REC Application Form		15 May 2014
Referee's report or other scientific critique report [RMD in Critical Illness Peer Review]		18 February 2014
Research protocol or project proposal [Reversible Myocardial Dysfunction in Critial Illness]	1.0	07 February 2014
Summary CV for Chief Investigator (CI) [Dr Victoria Trubody]		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- *Notifying substantial amendments*
- *Adding new sites and investigators*
- *Notification of serious breaches of the protocol*
- *Progress and safety reports*
- *Notifying the end of the study*

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

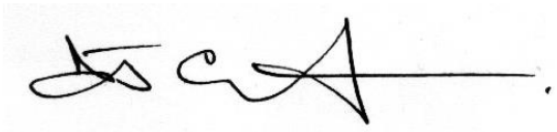
You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

14/SC/0305	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely,



Mr David Carpenter
Chair

E-mail: nrescommittee.southcentral-berkshire@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

After ethical review – guidance for researchers

Copy to: *Ms Heather House, Oxford University Hospitals NHS Trust*

NRES Committee South Central - Berkshire

Attendance at Committee meeting on 17 June 2014

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr David Carpenter	Social Scientist	Yes	
Dr Mike Emanuel	Pharmaceutical Consultant	Yes	
Mrs Liz Hunter	Retired Midwife and Clinical Governance Manager	Yes	
Mrs Vivienne Laurie	Barrister	Yes	
Dr Vandana Luthra	R&D Research Co-ordinator	Yes	
Mr Daniel Charles Mace	Retired Corporate Lawyer	Yes	
Mr Richard Merewood	Director	No	
Miss Victoria Mary Mills	Research Nurse	Yes	
Mr Neil Thomas O'Kane	Aviation Safety Consultant	Yes	
Dr Joanne Philpot	Consultant Paediatrician	Yes	
Dr Mike Proven	Co-ordinator for QA in Research	Yes	
Ms Ann Quinn	Head of the School of Health and Social Care	Yes	
Mr Donald Scott-Collett	Lead Pharmacist for Elderly Care, Neuro-rehabilitation, Dermatology and Clinical Governance	Yes	
Dr John Andrew Sutton	Medical Director	Yes	
Ms Susan Tonks	Senior Research Support Associate	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Rae Granville	REC Manager

ELF 3 Ethics committee correspondence: conditions met

NHS
Health Research Authority

NRES Committee South Central - Berkshire
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421389

09 July 2014

Dr Victoria Trubody
Clinical Research Fellow
Oxford University Hospitals NHS Trust
Kadoorie Centre, Level 3
John Radcliffe Hospital, Headley Way
Oxford
OX3 9DU

Dear Dr Trubody,

Study title: **Evaluation of the time course of acute, reversible myocardial dysfunction in the general adult intensive care population**
REC reference: **14/SC/0305**
IRAS project ID: **134971**

Thank you for your letter of 07 July 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 26 June 2014

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Participant information sheet (PIS) [Consultee Information]	1.1	07 July 2014
Research protocol or project proposal [RMD in critical illness protocol]	1.1	07 July 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper		15 May 2014
Letter from funder [RMD in Critical Illness Funding Confirmation]		24 February 2014
Letter from sponsor		15 May 2014

Participant consent form [RMD in Critical Illness Consultee Retrospective Opinion]	1.0	07 February 2014
Participant consent form [RMD in Critical Illness Consultee Opinion]	1.0	07 February 2014
Participant consent form [RMD in Critical Illness Patient Consent]	1.0	07 February 2014
Participant consent form [RMD in Critical Illness Patient Consent CMRI]	1.0	07 February 2014
Participant information sheet (PIS) [RMD in Critical Illness Patient Information Sheet CMRI]	1.0	07 February 2014
Participant information sheet (PIS) [RMD in Critical Illness Consultee Information]	1.0	07 February 2014
Participant information sheet (PIS) [RMD in Critical Illness Patient Information Retrospective]	1.0	07 February 2014
Participant information sheet (PIS) [Consultee Information]	1.1	07 July 2014
Participant information sheet (PIS) [RMD in Critical Illness patient Information Prospective]	1.0	07 February 2014
REC Application Form		15 May 2014
Referee's report or other scientific critique report [RMD in Critical Illness Peer Review]		18 February 2014
Research protocol or project proposal [Reversible Myocardial Dysfunction in Critical Illness]	1.0	07 February 2014
Research protocol or project proposal [RMD in critical illness protocol]	1.1	07 July 2014
Summary CV for Chief Investigator (CI) [Dr Victoria Trubody]		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/SC/0305	**Please quote this number on all correspondence**

Yours sincerely,

Ms Rae Granville
REC Manager

E-mail: nrescommittee.southcentral-berkshire@nhs.net

Copy to: *Ms Heather House, Oxford University Hospitals NHS Trust*

Oxford University Hospitals Research and Development correspondence

ELF 1

Oxford University Hospitals NHS
NHS Trust

HH/PT-JT/10154

Dr Andrew Jacques
ICU Registrar
Kadoorie Centre for Critical Care Research & Education
Level 3
John Radcliffe Hospital
Oxford OX3 9DU

From the R & D Lead
OUH Research & Development
Joint Research Office
Block 60, Churchill Hospital
Old Road, Headington
Oxford OX3 7LE

Tel: (01865)572236
Fax: (01865) (5)72242
Jenny.turner@ouh.nhs.uk
23 August 2012

Dear Dr Jacques

Re: Observational study to assess the incidence and reversibility of acute left ventricular myocardial dysfunction in critically ill adults

Research and Development Reference: 10154
Research Ethics Committee Reference: 12/SC/0099

Confirmation of Trust Management Approval

On behalf of the Oxford University Hospitals NHS Trust, I am pleased to confirm Trust Management Approval and Indemnity for the above research on the basis described in the application, protocol and other supporting documents.

Conditions of Approval

Your attention is drawn to the attached conditions of approval. Breach of these conditions may result in Trust Management Approval being revoked.

Ethics Correspondence

In order to facilitate good communications and avoid unnecessary delays please copy all correspondence with the Research Ethics Committee (REC) to R&D, providing copies of all relevant documents.

Research Sponsorship

It is noted that the University of Oxford has agreed to Sponsor this trial.

Site Specific Assessment

This Trust Management Approval letter also incorporates site specific assessment for the Oxford University Hospitals NHS Trust site

Approved Documents

Document Type	Version	Date
Covering letter	Julie Darbyshire	26 Jan 2012
Evidence of insurance or indemnity	Dr Andrew Walden	17 Jan 2012
GP/Consultant Information Sheets	3 Month. v1.0	28 June 2011
GP/Consultant Information Sheets	12 Month - v1.0	28 June 2011
GP/Consultant Information Sheets	LVD - v 1.0	28 June 2011
GP/Consultant Information Sheets	No LVD - v1.0	28 June 2011
Investigator CV	Dr Duncan Young	
Letter from Sponsor	Mrs E Chick	26 Jan 2012
Participant Consent Form: (Patients)	1.3	4 April 2012
Participant Consent Form: (Consultee Assent Form)	1.3	4 April 2012
Participant Information Sheet: (Patients - retrospective)	1.3	4 April 2012
Participant Information Sheet: (Patients)	1.3	4 April 2012
Participant Information Sheet: (Consultees)	1.3	4 April 2012
Protocol	1.2	24 Jan 2012
Response to request for further information	Julie Darbyshire	10 May 2012
REC Approval		17 May 2012

I wish you every success with the study.

Yours sincerely,

pp

Heather House
Research & Development Lead

Copy to:	Chief Investigator: Dr Duncan Young	By e-mail

ELF 2

Oxford University Hospitals NHS
NHS Trust

HH/TT/DF /8777
Dr Duncan J Young
Oxford University Hospitals NHS Trust
Kadoorie Centre for Critical Care Research and Education
Level 3, John Radcliffe Hospital, Headley Way
Oxford
OX3 9DU

29th December 2014

From the R & D Lead
OUH Research & Development
Joint Research Office
Block 60, Churchill Hospital
Old Road, Headington
Oxford OX3 7LE

Tel: (01865) (5)72386
Fax: (01865) (5)72242
james.church@ouh.nhs.uk

Dear Dr Duncan J Young,

Re: A retrospective analysis of the natural history of reversible myocardial dysfunction in critically ill patients
Research and Development Reference: 8777
Research Ethics Committee Reference: 13/SC/0399

Confirmation of Trust Management Approval
On behalf of the Oxford University Hospitals NHS Trust, I am pleased to confirm Trust Management Approval and Indemnity for the above research on the basis described in the application, protocol and other supporting documents.

Conditions of Approval
Your attention is drawn to the attached conditions of approval. Breach of these conditions may result in Trust Management Approval being revoked.

Recruitment

The agreed total recruitment target for your study at the OUH site is 75 participants by 1st August 2015 as specified in the SSI Form.

Your first participant recruitment target date is 24th February 2015.

To support OUH Trust and national recruitment targets, R&D will monitor and publish recruitment for your study: 1. Performance against the 70 calendar day period benchmark from the time of receipt of a valid research application in R&D to the date of recruitment of first participant to your study; and for interventional trials; 2. Recruiting planned participants to time and target. The R&D office will contact you to request recruitment progress against both targets. If you recruit your first participant into the study then please send the date to researchrecruitment@ouh.nhs.uk. If you miss this target you will be required to give reasons that can be reported to the DOH/NIHR.

Ethics Correspondence
In order to facilitate good communications and avoid unnecessary delays please copy all correspondence with the Research Ethics Committee (REC) to R&D, providing copies of all relevant documents.

Research Sponsorship

It is noted that University of Oxford has agreed to Sponsor this trial.

Site Specific Assessment

This Trust Management Approval letter also incorporates site specific assessment for the Oxford University Hospitals NHS Trust site.

Approved Documents

Document Type	Version	Date
Protocol	1	02/07/2013
Letter from Sponsor		08/07/2013
Investigator's CV	Dr Duncan J Young	
REC application		08/07/2013
REC Favourable Opinion		10/09/2013
NHS R&D Form		
NHS SSI Form	OUH NHS Trust	

I wish you every success with the study.

Yours sincerely,

Ms Heather House
Research and Development Lead

Copy to:	Sponsor	karl.shepherd@admin.ox.ac.uk
	OUH Study Finance	orh-tr.randdfdatabase@nhs.net

ELF 3

Oxford University Hospitals NHS
NHS Trust

HH/ JMC /DF/10652

Dr Victoria Trubody
Oxford University Hospitals NHS Trust
Kadoorie Centre, Level 3
John Radcliffe Hospital, Headley Way
Oxford
OX3 9DU

19th August 2014

From the R & D Lead
OUH Research & Development
Joint Research Office
Block 60, Churchill Hospital
Old Road, Headington
Oxford OX3 7LE

Tel: (01865) (5)74016
Fax: (01865) (5)72242
James.church@ouh.nhs.uk

Dear Dr Trubody,

Re: Description of the time course of acute, reversible myocardial dysfunction in the critically ill

Research and Development Reference: 10652
Research Ethics Committee Reference: 14/SC/0305

Confirmation of Trust Management Approval
On behalf of the Oxford University Hospitals NHS Trust, I am pleased to confirm Trust Management Approval and Indemnity for the above research on the basis described in the application, protocol and other supporting documents.

Conditions of Approval
Your attention is drawn to the attached conditions of approval. Breach of these conditions may result in Trust Management Approval being revoked.

Recruitment

The agreed total recruitment target for your study at the OUH site is 60 participants by 20th August 2015 as specified in the SSI form).

To support requirements of the OUH Trust and national recruitment targets, we will be monitoring and publishing outcomes of recruitment for your study. This will include reporting performance against the 70 calendar day period from the time of receipt of a valid research application in R&D to the time of recruitment of the first participant to your study.

Your first participant recruitment target date is 27th October 2014.
In the meantime, if you recruit your first participant into the study then please send the date to researchrecruitment@ouh.nhs.uk
The R&D office will contact you in due course by email to ask about the recruitment progress against this target.

Ethics Correspondence
In order to facilitate good communications and avoid unnecessary delays please copy all correspondence with the Research Ethics Committee (REC) to R&D, providing copies of all relevant documents.

Research Sponsorship

It is noted that University of Oxford has agreed to Sponsor this trial.

Site Specific Assessment

This Trust Management Approval letter also incorporates site specific assessment for the Oxford University Hospitals NHS Trust site.

Approved Documents

Document Type	Version	Date
Protocol	1.0	2nd July 2014
Participant Information Sheet: Prospective RMD	1.0	7th February 2014
Participant Information Sheet: Retrospective RMD	1.0	7th February 2014
Participant Information Sheet: CMRI RMD	1.0	7th February 2014
Participant Information Sheet: Consultee RMD	1.1	2nd July 2014
Consent Form: Patient RMD	1.0	7th February 2014
Consent Form: CMRI RMD	1.0	7th February 2014
Consent Form: Consultee RMD	1.0	7th February 2014
Consent Form: Prospective RMD	1.0	7th February 2014
Peer Review		
Letter from Funder		
Letter from Sponsor	Elaine Chick	15th May 2014
Insurance Certificate		
Investigator's CV	Victoria Trubody	
Investigator's CV	John Duncan Young	
REC Provisional Opinion		25th June 2014
REC Favourable Opinion		9th July 2014
NHS R&D Form		
NHS SSI Form	OUH NHS Trust	

I wish you every success with the study.

Yours sincerely,

Ms Heather House
Research and Development Lead

University sponsorship

ELF 1

RESEARCH SERVICES
Clinical Trials and Research Governance, Joint Research Office, Block 60,
Churchill Hospital, Headington, Oxford, OX3 7LE

UNIVERSITY OF OXFORD

To whom it may concern

26.01.12

Dear Sir/Madam,

Title: Observational study to assess the incidence and reversibility of acute left ventricular myocardial dysfunction in critically ill adults.

REC Code: 12/SC/0099

Lock Code: 80599/286487/1/432

The above study has been designed by Dr Duncan Young and colleagues at the University of Oxford and funded internally. I confirm that the University will accept the role of Research Sponsor of this Study and will comply with the requirements of the Department of Health Research Governance Framework for Health and Social Care 2005, in so far as these apply in the United Kingdom.

Indemnity and insurance arrangements have been put in place to cover the project, as outlined in the ethics application.

Sponsorship is confirmed subject to the condition that the following are sent to Clinical Trials and Research Governance for review prior to submission to the Research Ethics Committee. Failure to do so may compromise insurance cover for the project.

- Any substantial amendment
- Any extension to the study end date
- Addition of any new research site or patient identification centre

In addition annual progress reports must be copied to Clinical Trials and Research Governance.

Any communications relating to Research Sponsorship should be directed to the undersigned, whose contact details are given in this letter.

Yours faithfully

E. Chick

Mrs E Chick
Deputy Head, Clinical Trials and Research Governance

General Enquiries Tel: +44 (0)1865 572221 Direct Line Tel: +44 (0)1865 572222
Fax: +44 (0)1865 572228 Email: Elaine.chick@admin.ox.ac.uk Web: www.admin.ox.ac.uk/rso/

ELF 2

RESEARCH SERVICES
Clinical Trials and Research Governance
Joint Research Office
Block 60
Churchill Hospital
Headington
Oxford
OX3 7LE

UNIVERSITY OF OXFORD

CTRG Clinical Trials and Research Governance

08.07.13

Dear Sir/Madam,

Title: A retrospective analysis of the natural history of reversible myocardial dysfunction in critically ill patients.

REC Code: 13/SC/0399

Lock Code: 134468/474118/1/623

The above study has been designed by Dr Duncan Young and colleagues at the University of Oxford and funded internally by the department. I confirm that the University will accept the role of Research Sponsor of this Study and will comply with the requirements of the Department of Health Research Governance Framework for Health and Social Care 2005, in so far as these apply in the United Kingdom.

Insurance-provided indemnity arrangements are in place for the project, Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered :WD1200463

Sponsorship is confirmed subject to the condition that the following are sent to Clinical Trials and Research Governance for review prior to submission to the Research Ethics Committee. Failure to do so may compromise insurance cover for the project.

- Any substantial amendment
- Any extension to the study end date
- Addition of any new research site or patient identification centre

In addition, annual progress reports must be copied to Clinical Trials and Research Governance.

Any communications relating to Research Sponsorship should be directed to the undersigned, whose contact details are given in this letter.

Yours faithfully

E. Chick

Mrs E Chick
Deputy Head, Clinical Trials and Research Governance

General Enquiries Tel: +44 (0)1865 572221 · Direct Line Tel: +44 (0)1865 572222
Fax: +44 (0)1865 572228 · Email: Elaine.chick@admin.ox.ac.uk · Web: www.admin.ox.ac.uk/researchsupport/ctrg/

ELF 3

RESEARCH SERVICES
Clinical Trials and Research Governance
Joint Research Office
Block 60
Churchill Hospital
Headington
Oxford
OX3 7LE

15.05.14

Dear Sir/Madam,

Title: Reversible Myocardial Dysfunction in the Critically Ill

Pid: 10652

REC Code: 14/SC/0305

Lock Code: 134971/610219/1/956

The above study has been designed by Dr Victoria Trubody and colleagues at the University of Oxford and funded internally by the Department. I confirm that the University will accept the role of Research Sponsor of this Study and will comply with the requirements of the Department of Health Research Governance Framework for Health and Social Care 2005, in so far as these apply in the United Kingdom.

Insurance-provided indemnity arrangements are in place for the project, Newline Underwriting Management Ltd, at Lloyd's of London.

Sponsorship is confirmed subject to the condition that the following are sent to Clinical Trials and Research Governance for review prior to submission to the Research Ethics Committee. Failure to do so may compromise insurance cover for the project.

- Any substantial amendment
- Any extension to the study end date
- Addition of any new research site or patient identification centre

In addition, annual progress reports must be copied to Clinical Trials and Research Governance.

Any communications relating to Research Sponsorship should be directed to the undersigned, whose contact details are given in this letter.

Yours faithfully

E. Chick

Mrs E Chick
Deputy Head, Clinical Trials and Research Governance

General Enquiries Tel: +44 (0)1865 572221 · Direct Line Tel: +44 (0)1865 572222
Fax: +44 (0)1865 572228 · Email: Elaine.chick@admin.ox.ac.uk · Web: www.admin.ox.ac.uk/researchsupport/ctrg/

Health Research Authority

Confidentiality Advisory Group

Dr Duncan Young
Oxford University Hospitals NHS Trust
Kadoorie Centre, Level 3
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU

duncan.young@ndcn.ox.ac.uk

Skipton House
80 London Road
London
SE1 6LH

Tel: 020 797 22557
Email: HRA.CAG@nhs.net

24 October 2013

Dear Dr Young

Study title: **Retrospective analysis of reversible myocardial dysfunction in ICU**
CAG reference: **CAG 6-03(PR2)/2013**
IRAS Project ID: **134468/471913/4/214**

Thank you for your research application, submitted for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. This application was considered via the proportionate review process under criteria 4: *time limited access to undertake record linkage.*

Health Research Authority approval decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

1. The application is approved, subject to compliance with the standard and specific conditions of approval.

Context

Purpose of application

This research application from Oxford University Hospitals NHS Trust set out the purpose of a retrospective analysis of repeated heart ultrasound outcomes performed in general ICU population in order to characterise the natural history and outcomes of patients experiencing heart impairment. The study aims to develop a greater understanding about whether the condition affects wider critically ill patients. A recommendation for class 1, 4 and 6 support was requested in order for the research team within John Radcliffe Hospital to identify patients

who had serial heart ultrasounds whilst in the ICU and assess changes in heart function during the course of critical illness. Access was requested to the ICU patient monitoring database, local data collected for national ICU audit programme (ICNARC) and the heart ultrasound database. The ICU patient monitoring database would be extracted for all patients admitted to the ICU from January 2008 to June 2013 and linked to the ultrasound database. Where patients were identified as having serial ultrasounds clinical data would be extracted from the patient monitoring database and local ICNARC data.

Confidential patient information requested

Access was requested to name, date of birth, hospital number and gender.

CAG advice conclusion

In line with the considerations above, the CAG agreed that the minimum criteria under the Regulations appeared to have been met, and therefore advised recommending *conditional* support to the Health Research Authority, subject to compliance with the specific and standard conditions of support. Response to these conditions were received on the 3 September 2013 and are summarised below.

Specific conditions of support

1. Confirmation of a favourable opinion from a Research Ethics Committee. **Confirmed 10 September 2013.**

2. Confirmation of suitable security arrangements via IG Toolkit submission. **Confirmed 08 May 2013.**

3. Please amend the patient information materials to ensure that they give patients a clear opportunity and mechanism for objection if they do not wish their data to be included in the study. **It was confirmed that the patient information materials would be updated in December 2013. Please ensure that copies of the amended materials are submitted to CAG.**

4. Please ensure that information in relation to this specific activity is made available to living patients, in line with the fair processing requirements of the Data Protection Act 1998, for example through publication on the Trust website. **It was confirmed that information in relation to the study would be included on the OUH Trust website.**

5. Please provide more details concerning patient and public engagement with respect to this application, including more details in relation to attendees at the public meeting mentioned in the application. **Details were provided of the attendees at the public meeting in August 2011. It was also confirmed that the project would be brought to the attention of the local ICU patient group.**

As the above conditions have been accepted and/or met, this letter provides confirmation of final approval. I will arrange for the register of approved applications on the HRA website to be updated with this information.

Annual review

Please note that this approval is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is your responsibility to submit this report annually and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements. We are also streamlining the process to facilitate the service we provide to applicants. This means that annual reviews will be batched such that the approval will last until the last day of the

preceding month before the date of approval, and should be submitted 4 weeks before this date.

Please do not hesitate to contact me if you have any queries following this letter. I would be grateful if you could quote the above reference number in all future correspondence.

Reviewed documents

The documents reviewed by Members were:

Document	*Version*	*Date*
IRAS application form		03/07/2013
Protocol	1.0	03/07/2013
Patient information leaflet		24/07/2013
Completed query sheet		24/07/2013
Study flow chart		24/07/2013

Membership of the Group

The members of the Confidentiality Advisory Group who considered this item are listed below.

There were *no* declarations of interest in relation to this item.

With the Group's best wishes for the success of this project.

Yours sincerely

Claire Edgeworth
Deputy Confidentiality Advice Manager

Email: HRA.CAG@nhs.net

Enclosures: *List of Members who considered application*

Standard conditions of approval

Caldicott Guardian endorsement ELF 2

Oxford University Hospitals NHS
NHS Trust

Dr Christopher Bunch FRCP
Consultant Physician and Caldicott Guardian

Tel: 01865 221343
Fax: 01865 220069

Academic Street, Level 3
The John Radcliffe
Headley Way
Headington
Oxford
OX3 9DU

Confidentiality Advisory Group
Health Research Authority
Skipton House
80 London Road
London SE1 6LH

2nd July 2013

Dear Committee,

Research Project: A retrospective analysis of the natural history of reversible myocardial dysfunction in critically ill patients

I am writing concerning Duncan Young and Victoria Trubody's application for Section 251 support for the above project..

This project aims to characterize the incidence and recovery of heart function in patients experiencing critical illness. It is known that reversible heart impairment can occur in patients with certain types of critical illness, such as severe infections. Little is known about how this condition may affect other types of patients admitted to Intensive Care, and if the results seen in patients with infections are applicable to other groups. The results of this project will provide a greater understanding of the incidence and nature of acute heart impairment in critically ill patients, what effect it has on their illness and the degree of recovery of heart function following ICU discharge.

CAG permission is sought for the use of retrospective data without individual patient consent, and for the use of identifiers to match patients between different datasets. Investigation of other methods to obtain the necessary data to address the research question have been demonstrated to be impractical, in view of the low numbers of patients and the time period required to obtain a suitably large cohort for analysis. Retrospective consent is not practicable due to the time-span of data required and the high mortality of the target population.

Details of data storage and security have been addressed with all relevant groups, and are in keeping with the principles of research using patient confidential data. I am satisfied that their arrangements for information protection are of a high order.

Yours sincerely,

Christopher Bunch

UNIVERSITY OF OXFORD

Oxford Radcliffe Hospitals NHS
NHS Trust

University of Oxford CTRG/ Oxford Radcliffe Hospitals HNS Trust R&D Independent Peer Review Form

1. Full Project Title: (The project protocol should be attached to this form)		
Observational study to assess the incidence and reversibility of acute left ventricular myocardial dysfunction in critically ill adults		
2. Short Title:		
Observational study to assess the incidence and reversibility of acute left ventricular myocardial dysfunction in critically ill adults		
3. Investigators	**Name**	**Department**
(a) Chief Investigator (For ORH/OU sponsored studies)	Duncan Young	Adult Intensive Care, John Radcliffe hospital
(b) Principal Investigator (For External Sponsors)		
4. Application Details		
Funding Body	None	
Sponsor (if External)		

5. INDEPENDENT PEER REVIEW: Please comment on the following areas:	
Area Reviewed	**Comments**
(a) The originality of the research	While data exists on the presence of left ventricular dysfunction in ICU, this study's originality is in the systematic approach to patient population and the temporal trend in dysfunction.
(b) The study design	Well designed prospective, observational study where issues of potential selection bias have been addressed.
(c) The research methods - the appropriateness and achievability of the chosen methods and outcome measures in meeting the objectives of the study	Appropriate selection of patients to limit selection bias. Timing of Echocardiograms appropriate to level of resources and manpower available.

(d) Sampling – the appropriateness of the sampling methods and the inclusion/exclusion criteria	The sample size is an approximation to fit the resources and manpower available and looks like a realistic approximation of recruitment in the time available. A powered sample size is not necessary in this type of observational study
(e) Screening tools and questionnaires (where applicable) are these appropriate and have questionnaires been appropriately validated?	There are no screening tools or questionnaires necessary
(f) Appropriateness of data analysis methods and planned statistical tests	Matching of cases to control included in the data analysis. Precise nature of statistical tests will depend on measurements recorded from Echocardiogram
(g) Risks and benefits to participants	No direct risks from the Echocardiographic examinations. Potential benefit to patients from additional information given to treating clinicians
(h) Importance to patients/service users	The mortality rate in Critically ill patients on mechanical ventilation is high. Defining the morbidity from Left ventricular dysfunction may lead to interventions that improve morbidity and mortality in this patient group.
(i) Value for money	Very good
(j) Reputational risk to the University/NHSTrust	No reputational risk to the University or trust envisaged.

Reviewer details:	
Name	**Dr Andrew Walden**
Signature	
Date	**17/01/2012**
Position	**Consultant in Intensive Care Medicine, Royal Berks hospital, Reading**

Peer review ELF 2

University of Oxford CTRG/ Oxford Radcliffe Hospitals HNS Trust R&D Independent Peer Review Form

1. Full Project Title: (The project protocol should be attached to this form)		
A retrospective analysis of the natural history of reversible myocardial dysfunction in critically ill patients		
2. Short Title:		
NA		
3. Investigators	**Name**	**Department**
(a) Chief Investigator (For NHSTrust / University sponsored studies)	Dr Duncan Young	Adult Intensive Care Unit
(b) Principal Investigator (For External Sponsors)	NA	NA
4. Application Details		
Funding Body	Internal funding through the Kadoorie Research Centre	
Sponsor (if External)	NA	

5. INDEPENDENT PEER REVIEW: Please comment on the following areas:	
Area Reviewed	**Comments**
(a) The originality of the research	This remains an commonly discussed topic within the critical care community and the data obtained should help to clarify the importance or otherwise of this issue. Linking the database should generate a good volume of quality data.
(b) The study design	Good.
(c) The research methods - the appropriateness and achievability of the chosen methods and outcome measures in meeting the objectives of the study	Good. Linking of databases in this way should ensure economy of effort.

(d) Sampling – the appropriateness of the sampling methods and the inclusion/exclusion criteria	The inclusion and exclusion criteria are sensible. This should be a representative sample of heterogenous ICU patients.
(e) Screening tools and questionnaires (where applicable) are these appropriate and have questionnaires been appropriately validated?	NA
(f) Appropriateness of data analysis methods and planned statistical tests	Statistical methods clearly stated
(g) Risks and benefits to participants	No risk to participants. No direct benefit but potential to influence outcome of future ICU patients.
(h) Importance to patients/service users	This study should add to the limited data on the association between reversible LV dysfunction and outcome in ICU patients and so inform on the future importance of either ignoring this as a phenomenon or supporting further research into mechanisms and interventions linked to patient centred outcome.
(i) Value for money	V. good
(j) Reputational risk to the University / NHSTrust	None.

Reviewer details:	
Name	**Andrew Walden**
Signature	
Date	**04/07/2013**
Position	**Consultant in Intensive Care medicine, Royal Berkshire hospital, Reading, RG1 5AN. 07769977417**

Peer review ELF 3

UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

University of Oxford CTRG/ Oxford University Hospitals NHS Trust R&D Independent Peer Review Form

1. Full Project Title: (The project protocol should be attached to this form)		
Evaluation of the time course of acute reversible myocardial dysfunction in the general adult intensive care population		
2. Short Title:		
Reversible myocardial dysfunction in the critically ill		
3. Investigators	**Name**	**Department**
(a) Chief Investigator (For NHSTrust / University sponsored studies)	Dr Victoria Trubody	NDCN
(b) Principal Investigator (For External Sponsors)		
4. Application Details		
Funding Body		
Sponsor (if External)		

5. INDEPENDENT PEER REVIEW: Please comment on the following areas:	
Area Reviewed	**Comments**
a) The originality of the research	ALVD is a well described phenomenom however the serial echocardiographic scanning and use of MRI should lead to a greater understanding of the natural history of the condition and to determine whether this is of any clinical significance or a normal variant of acute response to disease. Measuring catecholamine levels may help to determine to what extent this problem is part of the acute illness and what extent an iatrogenic consequence of exogenous pressor use.
b) The study design	Good study design with appropriate inclusion and exclusion criteria, clear description of intervention and schedule of assessments and consent issues.
c) The research methods - appropriateness and achievability of the chosen methods and outcome measures in meeting the objectives of the study	Achievable given the amount of time allocated to the chief investigator and the track record of the second applicant.

d) Sampling – the appropriateness of the sampling methods and the inclusion/exclusion criteria	Appropriate in an attempt to exclude those with pre-existing cardiac disease. A clearer description of what criteria would be used to define ALVD would add to the understanding.
e) Screening tools and questionnaires (where applicable) are these appropriate and have questionnaires been appropriately validated?	Not appropriate
f) Appropriateness of data analysis methods and planned statistical tests	
g) Risks and benefits to participants	Minimal. Echo is a non-invasive test. There is a small risk associated with the contrast media for the cardiac MRI but the investigators are aware of this and have made an attempt to limit the potential harm.
h) Importance to patients/service users	If there is a clear association between exogenous catecholamine use and worsening cardiac function especially if this is linked to multiple organ dysfunction then there is a potential for patient benefit by the use of differing pressor agents.
i) Value for money	The likely output from this would be of a reasonably high impact and therefore the investment requested would have a good return.
j) Reputational risk to the University / NHSTrust	Minimal given the track record of the second applicant in research delivery.

Reviewer details:	
Name	Andrew Walden
Signature	
Date	18/02/2014
Position	Consultant in Intensive care medicine

Appendix 6: Screening log examples

ELF 1

Subject Enrolment, Identification and Code list

Study	ELF 1			Ineligibility Codes	
Principal Investigator	Dr Duncan Young	Site	JR AICU	1. Aged under 16 years 2. ICU length of stay <72 hours 3. Condition rendering TTE unreliable 4. Admission to the ICU as a result of cardiac arrest 5. Cardiac arrest during admission to the ICU	6. Planned, elective admissions to the ICU 7. Limitations in treatment 8. Limitations in the use of English 9. Prisoner

Date screened	Number	Initials	Admit Dx	Age	Eligible	Subject Code (if eligible) or state reason for ineligibility

Form CL-GCP-008

Subject Enrolment, Identification and Code list

Study	RMD in Critical Illness			Ineligibility Codes	
Principal Investigator	Dr Victoria Trubody	Site	JR AICU	1. Aged under 16 years 2. ICU length of stay <72 hours 3. Condition rendering TTE unreliable 4. Admission to the ICU as a result of cardiac arrest 5. Cardiac arrest during admission to the ICU	6. Planned, elective admissions to the ICU 7. Limitations in treatment 8. Limitations in the use of English 9. Prisoner

Date screened	Number	Initials	Admit Dx	Age	Eligible	Subject Code (if eligible) or state reason for ineligibility

Form CL-GCP-008

Appendix 7: Patient/consultee information leaflets and consent/favourable opinion forms

ELF 1 – Patient information leaflet (prospective enrolment)

NUFFIELD DEPARTMENT OF CLINICAL NEUROSCIENCES (NUFFIELD DIVISION OF ANAESTHETICS) UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

Dr Duncan Young
Consultant and Senior Clinical Lecturer
Adult Intensive Care Unit
John Radcliffe Hospital

01865 220621

The John Radcliffe Hospital
Headley Way
Headington
Oxford
OX3 9DU

Study of heart function in the Intensive Care

Information sheet for patients

REC reference: 12/SC/0099
REC centre: South Central - Oxford C
Version 2 - November 5 2012

We would be very grateful if you would take a little time to read the following information. It asks you to think about whether you would consider taking part in a study which is taking place in this hospital at the moment.

What is the purpose of the study?

During severe illness the heart can develop problems. The purpose of this study is to look at how often this occurs in patients who are in Intensive Care and what effect it has on their illness.

In people where we find a reduced function of the heart in the first week of their Intensive Care Unit stay, we want to continue to follow them for three months. This is to assess the change in heart function over time.

Why am I being asked to consider the study?

You have chosen because you have been admitted to the Intensive Care Unit as an emergency.

If we find any problems with your heart in the first week of your Intensive Care Unit stay we would like to continue to monitor your heart with ultrasound examinations up to 1 week after Intensive Care discharge and 3 months later.

Do I have to take part?

No. It is up to you to decide. We will explain the study and go through this information sheet with you. If you do decide to continue, you will be given this sheet to keep and will be asked to sign a consent form. You are still free to withdraw at any time, without giving a reason. This will not affect the care you receive. If you decide to withdraw from the study at a later stage all study information and measurements collected will be securely deleted.

What will happen to me if I decide to take part?

If you decide to take part we will ask you to sign a consent form.

Whilst in the Intensive Care Unit:
You will receive three ultrasound examinations of the heart during your first week in the Intensive Care Unit. Each ultrasound lasts about 20 minutes. Information from your medical record will also be collected during your stay in the Intensive Care Unit. This information will be kept strictly confidential.

During your stay in the Intensive Care Unit you may be given treatment or medication that may affect your ability to understand what is happening to you. If this happens to you, we will ask a close friend or relative, or a professional consultee (a representative from the hospital who takes responsibility for your interests) to consider whether you would want to continue to take part in this research study. When you are well enough to be asked, we will check with you whether you agree with their decision

After the Intensive Care Unit:
We are interested in the long term effects of heart problems that develop because you have been unwell and the way that the heart heals. If you are in hospital one week after your Intensive Care Unit stay we will perform a further ultrasound examination of the heart. After you leave hospital you will be invited for one more ultrasound examination. This will be at 3 months after your Intensive Care Unit admission. This will take place in the outpatients department of the Oxford University Hospitals NHS Trust and are expected to take about 20 minutes.

What are the side effects of taking part?
There are no known side effects of ultrasound examinations and given the nature of this study, it is highly unlikely that you will suffer harm by taking part. However, the University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor.

What are the disadvantages of taking part?
The follow up visit that is offered to people who have been on the Intensive Care Unit will be slightly longer than usual, by an expected 20 minutes.

What are the possible benefits of taking part?
Information learnt from this study will help us in the future to recognise patients who are at risk of developing heart problems and what effect this has on their illness. This may lead to treatments to prevent or reduce heart problems in patients who stay in the Intensive Care Unit.

Will taking part in the study cost me anything?
If you require hospital transport to attend the outpatients appointment this will be available for the appointment at 3 months. You may be able to claim a refund for travel expenses for this visit if you meet the criteria for the NHS Low Income Scheme. There is no payment for taking part in the study.

Are patient details kept confidential?
The information collected on study patients is kept in a secure area of the hospital behind double locked doors. All computer systems are on secure networks and all information is treated as strictly confidential. The chief investigator and his delegates will have access to the stored information. Responsible members of the University of Oxford or the Oxford University Hospitals NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. Any published reports will not identify patients.

What will happen to my information if I decide at a later date that I no longer want to take part?
If you decide to take part in this study but later change your mind and ask to leave the study, no further information will be collected about you. The information collected up to the point of you leaving will be included in the research unless you specifically request that this is destroyed.

Is there a payment for being in this study?
There is no payment for taking part in the study. Some patients may be able to apply through the NHS for travel expenses for the routine outpatients clinic visit at 3 months. All patients will be able to claim reasonable travel expenses for the additional visit at 12 months.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to Dr Andrew Jacques 01865 220620, or Dr Duncan Young 01865 220621, who will do their best to answer your questions.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Duncan Young on 01865 220621 or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or email heather.house@admin.ox.ac.uk.

Who has reviewed the study
All research in Oxford University Hospitals NHS Trust is assessed by an independent group of people, called a Research Ethics Committee to protect your relative's safety, rights, wellbeing and dignity. This research was reviewed by the South Central – Oxford C committee.

Thank you for taking the time to read this leaflet.

Further information and contact details
Dr Andrew Jacques
John Radcliffe Hospital
Headley Way
Oxford OX3 9DU

ajacques@nhs.net
01865 220620

ELF 1 – Patient information leaflet (retrospective enrolment)

NUFFIELD DEPARTMENT OF CLINICAL NEUROSCIENCES (NUFFIELD DIVISION OF ANAESTHETICS) UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

Dr Duncan Young
Consultant and Senior Clinical Lecturer
Adult Intensive Care Unit
John Radcliffe Hospital

01865 220621

The John Radcliffe Hospital
Headley Way
Headington
Oxford
OX3 9DU

Study of heart function in the Intensive Care

Information sheet for patients

REC reference: 12/SC/0099
REC centre: South Central - Oxford C
Version 2 - November 5 2012

While you were unwell on the Intensive Care Unit a friend/relative or professional nominated consultee (a representative from the hospital who takes responsibility for your interests) agreed to let you take part in this research study. Now that you are recovering from your illness you are being invited to continue in this study. To help you decide if you want to continue, you need to understand why the research is being done and what it will involve. We would be very grateful if you would read the following information which explains the risks and possible benefits of continuing to take part.

What is the purpose of the study?

During severe illness the heart can develop problems. The purpose of this study is to look at how often this occurs in patients who are in Intensive Care and what effect it has on their illness.

In people where we find a reduced function of the heart in the first week of their Intensive Care Unit stay, we want to continue to follow them for three months. This is to assess the change in heart function over time.

Why am I being asked to consider the study?

You were chosen because you were admitted to the Intensive Care Unit as an emergency. You had an ultrasound examination of the heart to check if your heart was working normally. We would like to continue to check your heart by ultrasound examination during the first week of your admission.

If we find any problems with your heart in the first week of your Intensive Care stay we would like to continue to monitor your heart with ultrasound examinations up to 1 week after Intensive Care discharge and 3 months later.

Do I have to take part?

No. It is up to you to decide. We will explain the study and go through this information sheet with you. If you do decide to continue, you will be given this sheet to keep and will be asked

to sign a consent form. You are still free to withdraw at any time, without giving a reason. This will not affect the care you receive. If you decide to withdraw from the study at a later stage all study information and measurements collected will be securely deleted.

What will happen to me if I decide to take part?

If you decide to take part we will ask you to sign a consent form.

Whilst in the Intensive Care Unit:

You will have already had at least one ultrasound examination of the heart. If you decide to continue in the study we will perform a total of three ultrasound examinations of the chest in your first week in Intensive Care. Each ultrasound lasts about 20 minutes. Information from your medical record will also be collected during your stay in Intensive Care. This information will be kept strictly confidential.

After the Intensive Care Unit:

We are interested in the long term effects of heart problems that develop because you have been unwell and the way that the heart heals. Patients who have heart problems during their Intensive Care Unit stay will be invited for one more ultrasound examinations. This will be at 3 months after your Intensive Care Unit admission. These will take place in the outpatients department of the Oxford University Hospitals NHS Trust and are expected to take about 20 minutes.

What are the side effects of taking part?

There are no known side effects of ultrasound examinations and given the nature of this study, it is highly unlikely that you will suffer harm by taking part. However, the University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor.

What are the disadvantages of taking part?

The follow up visit that is offered to people who have been on the Intensive Care Unit will be slightly longer than usual, by an expected 20 minutes.

What are the possible benefits of taking part?

Information learnt from this study will help us in the future to recognise patients who are at risk of developing heart problems and what effect this has on their illness. This may lead to treatments to prevent or reduce heart problems in patients who stay in the Intensive Care Unit.

Will taking part in the study cost me anything?

If you require hospital transport to attend the outpatients appointment this will be available for the appointment at 3 months. You may be able to claim a refund for travel expenses for this visit if you meet the criteria for the NHS Low Income Scheme. There is no payment for taking part in the study.

Are patient details kept confidential?
The information collected on study patients is kept in a secure area of the hospital behind double locked doors. All computer systems are on secure networks and all information is treated as strictly confidential. The chief investigator and his delegates will have access to the stored information. Responsible members of the University of Oxford or the Oxford University Hospitals NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. Any published reports will not identify patients.

What will happen to my information if I decide at a later date that I no longer want to take part?
If you decide to take part in this study but later change your mind and ask to leave the study, no further information will be collected about you. The information collected up to the point of you leaving will be included in the research unless you specifically request that this is destroyed.

Is there a payment for being in this study?
There is no payment for taking part in the study. Some patients may be able to apply through the NHS for travel expenses for the routine outpatients clinic visit at 3 months.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to Dr Andrew Jacques 01865 220620, or Dr Duncan Young 01865 220621, who will do their best to answer your questions.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Duncan Young on 01865 220621 or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or email heather.house@admin.ox.ac.uk.

Who has reviewed the study
All research in Oxford University Hospitals NHS Trust is assessed by an independent group of people, called a Research Ethics Committee to protect your relative's safety, rights, wellbeing and dignity. This research was reviewed by the South Central – Oxford C committee.

Thank you for taking the time to read this leaflet.

Further information and contact details
Dr Andrew Jacques
John Radcliffe Hospital
Headley Way
Oxford OX3 9DU

ajacques@nhs.net
01865 220620

ELF 1 Consultee information sheet

NUFFIELD DEPARTMENT OF CLINICAL NEUROSCIENCES (NUFFIELD DIVISION OF ANAESTHETICS) UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

Dr Duncan Young
Consultant and Senior Clinical Lecturer
Adult Intensive Care Unit
John Radcliffe Hospital

01865 220621

The John Radcliffe Hospital
Headley Way
Headington
Oxford
OX3 9DU

Study of heart function in the Intensive Care

Information sheet for consultees

REC reference: 12/SC/0099
REC centre: South Central – Oxford C
Version 2 – November 5 2012

Your relative, friend, or person you are representing is being treated on an Intensive Care Unit and we know this must be an extremely anxious time for you. We would however be grateful if you would take a little time to read this information. It asks you to think about whether the person you are representing would have any objection to taking part in a study which is taking place in this hospital.

What is the purpose of the study?

During severe illness the heart can develop problems. The purpose of this study is to look at how often this occurs in patients who are in Intensive Care and what effect it has on their illness.

Why am I being asked to consider the study?

Normally we ask patients themselves if they would consider taking part in research studies, but as your relative, friend or person you are representing is very unwell we can't discuss it with him or her. We are, therefore, approaching you, as someone who has their welfare and best interests in mind, to consider whether they would want to take part in this research study. Once your relative, friend or person you are representing is well enough, we will ask them to confirm your decision.

Declining to join the study will not affect the care they receive in any way.

If you (or the patient when he/she can make decisions again), change your mind, they can be withdrawn from the study at any time. If you or they do withdraw, this will not affect their care in any way. All study information and measurements collected will be securely deleted.

What will happen to them if I decide they should take part?

Whilst in the Intensive Care Unit:

If you decide that your friend or relative or person you are representing should take part they will be examined by a study doctor. This will involve an ultrasound examination of the chest looking in particular at the heart. The examination lasts approximately 20 minutes. This

ultrasound examination will be performed up to three times during the first week of their stay in Intensive Care.
Information from the medical records of your friend or relative or person you are representing will be collected during their stay in the Intensive Care Unit. This information will be kept strictly confidential.

During their stay in the Intensive Care Unit your friend or relative or person you are representing may be given treatment or medication that may affect their ability to understand what is happening. If this happens to them, we will come back to you to consider whether they would want to continue to take part in this research study. When they are well enough to be asked, we will check with your friend or relative or person you are representing whether they agree with your decision.

After the Intensive Care Unit:
We are interested in the long term effects of heart problems and the way the heart heals. Patients who were seen to have heart impairment during their Intensive Care stay will have a repeat ultrasound on the ward if they are still in hospital one week after their Intensive Care Unit stay. They will then be invited to attend for a repeat ultrasound examination at 3 months after their Intensive Care Unit admission. These will take place in the outpatients department of the Oxford University Hospitals NHS Trust and would be expected to take about 20 minutes.

What are the side effects of taking part?
There are no known side effects of ultrasound examinations and given the nature of this study, it is highly unlikely that they will suffer harm by taking part. However, the University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor.

What are the disadvantages of taking part?
The follow up visit that is offered to people who have been on the Intensive Care Unit will be slightly longer than usual, by an expected 20 minutes.

What are the possible benefits of taking part?
Information learnt from this study will help us in the future to recognise patients who are at risk of developing heart problems and what effect this has on their illness . This may lead to treatments to prevent or reduce heart problems in patients admitted to Intensive Care.

Will taking part in the study cost them anything?
If hospital transport is required to attend the outpatients appointment this will be available for the appointment at 3 months. It may be possible to claim a refund for travel expenses for this visit if the criteria for the NHS Low Income Scheme are met. There is no payment for taking part in the study.

Are patient details kept confidential?
The information collected on study patients is kept in a secure area of the hospital behind double locked doors. All computer systems are on secure networks and all information is treated as strictly confidential. The chief investigator and his delegates will have access to the stored information. Responsible members of the University of Oxford or the Oxford University Hospitals NHS Trust may be given access to data for monitoring and/or audit of

the study to ensure we are complying with regulations. Any published reports will not identify patients.

What will happen to the patient's information if they decide that they no longer want to take part?

If you agree that your friend or relative or person you are representing should take part in this research study, but at a later date they decide that they do not want to take part and ask to leave the study, no further information will be collected about them. The information collected up to the point of them leaving the study will be included in the research unless they specifically request that this is destroyed.

Is there a payment for being in this study?

There is no payment for taking part in the study. Some patients may be able to apply through the NHS for travel expenses for the routine outpatients clinic visit at 3 months.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to Dr Andrew Jacques 01865 220620, or Dr Duncan Young 01865 220621, who will do their best to answer your questions.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Duncan Young on 01865 220621 or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or email heather.house@admin.ox.ac.uk.

Who has reviewed the study

All research in Oxford University Hospitals NHS Trust is assessed by an independent group of people, called a Research Ethics Committee to protect your friend or relative's safety, rights, wellbeing and dignity.

Thank you for taking the time to read this information leaflet.

Further information and contact details

Dr Andrew Jacques
John Radcliffe Hospital, Headley Way
Oxford OX3 9DU

ajacques@nhs.net
01865 220620

ELF 1 Patient consent form

NUFFIELD DEPARTMENT OF CLINICAL NEUROSCIENCES (NUFFIELD DIVISION OF ANAESTHETICS) UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

Dr Duncan Young
Consultant and Senior Clinical Lecturer
Adult Intensive Care Unit
John Radcliffe Hospital

01865 220621

The John Radcliffe Hospital
Headley Way
Headington
Oxford
OX3 9DU

Study of heart function in the Intensive Care Unit

PATIENT CONSENT FORM

Version 2 – 5 November 2012
REC reference:12/SC/0099
REC Centre:South Central – Oxford C

*Please **INITIAL** each box if in agreement*

1. I confirm that I have read and understand the information leaflet dated *5th November 2012 version 2* for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical are or legal rights being affected ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Oxford, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study and being sent my results. ☐
5. I understand that if I choose to leave the study at any time the information collected up to that point will be included in the research unless I specifically request it to be destroyed ☐
6. I agree that the study office can contact me by post to invite me back for a repeat ultrasound examination of the heart three months after my treatment in the Intensive Care Unit. ☐
7. I agree to take part in this study ☐

If you would like further information before signing this form please contact:
Dr Andrew Jacques or Dr Duncan Young, Intensive Care Unit, John Radcliffe Hospital, 01865 220620

Name (PRINT)	Date	Signature
Name of person taking consent	Date	Signature
Top copy: Study file at site	*1 copy: Patient*	*1 copy: Patients hospital record*

ELF 1 Consultee favourable opinion form

NUFFIELD DEPARTMENT OF CLINICAL NEUROSCIENCES (NUFFIELD DIVISION OF ANAESTHETICS) UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

Dr Duncan Young
Consultant and Senior Clinical Lecturer
Adult Intensive Care Unit
John Radcliffe Hospital

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The John Radcliffe Hospital
Headley Way
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Study of heart function in the Intensive Care Unit

CONSULTEE DECLARATION FORM

Version 2 – 5th November 2012
REC reference:12/SC/0099
REC Centre:South Central – Oxford C

Regarding patient: _____
(please write patients name here)

*Please **INITIAL** each box if in agreement*

1. I confirm that I have read and understand the information leaflet dated *5 November 2012 version 2* for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily. ☐
2. I confirm that I am voluntarily stating that I know of no reason why the above patient would not wish to take part in the study and that once they regain capacity they will be free to withdraw at any time, without giving any reason, and without their medical care or legal rights being affected ☐
3. I understand that relevant sections of the patient's medical notes and data collected during the study may be looked at by individuals from the University of Oxford, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to the patient's records. ☐
4. I agree to the patient's GP being informed of my participation in the study and being sent their results. ☐
5. I understand that if the patient chooses to leave the study at any time the information collected up to that point will be included in the research unless they specifically request it to be destroyed ☐
6. I agree that the patient may take part in this study ☐
7. I agree to discuss this with the patient when they regain capacity to consent for themselves ☐

If you would like further information before signing this form please contact:
Dr Andrew Jacques or Dr Duncan Young, Intensive Care Unit, John Radcliffe Hospital 01865 220620

Consultee assent form continued over the page

My relationship to the patient is: _____

(please write your relationship to the patient here, for example wife/partner/brother etc.) Or 'Nominated Professional Consultee'

Name (PRINT)	Date	Signature
Name of person taking agreement	Date	Signature

Top copy: Study file at site *1 copy: Consultee* *1 copy: Patients hospital notes*

Data Collection Rules

The ELF Studies

Version 1.0

0. Data sources

Data can be collected from a number of different sources. Briefly, these will be discussed in turn.

Carevue (Philips Healthcare), is an integrated electronic system that collects and aggregates patient clinical data. Observations are recorded depending on the clinical need of the patient, but are typically recorded at least hourly. Additionally, pharmacological therapies, urine and drain outputs, ventilation requirements and laboratory investigations are also recorded. Access is available at each bedspace and at a number of computer terminals in AICU. Screenshots of relevant fields and location of specific data, are provided later in the collection rules.

Patient medical records are kept in a folder by the bedside and contain details of the current, and any previous, hospital admission, outpatient correspondence and some investigation reports. This source can be particularly useful in identifying the past medical history. Care must be taken to ensure that all volumes of records are reviewed.

The electronic patient record (EPR) aggregates patient tracking, some investigations and discharge information. This system is currently being rolled out and is therefore still in its infancy. The main utility of EPR is to access discharge data, including in hospital deaths, and to review haematological and biochemical results that are unavailable on Carevue. These data are periodically linked to national death registries.

Also, the superseded system for reviewing laboratory investigations, Casenotes, is still available, if necessary, for researchers to review historical records. This can be accessed from any NHS computer on the right hand side of the intranet main page.

The local ICNARC submission database (4D MEDICUs, Mela Solutions) is the source of AICU admission diagnosis and ICNARC score. These data are entered into the database by a trained member of the AICU team, according to the ICNARC data collection methods. Access to these data are via this member of staff.

1. Admission data

1.1. Gender

Gender is defined as the chromosomal gender at birth. This is recorded on the case report form (CRF) as male or female.

1.2. Date of birth

The date of birth of the patient is to be recorded in the format dd/mm/yyyy. This information should be sourced from the patient wristband. If the patient's identity is unknown at the time of AICU admission, provisionally leave this field blank on the CRF. Once identity has been established, document the date of birth as described above.

1.3. Height, weight and body surface area

The height and weight of the patient is recorded on the demographics page, under "admission information" of Carevue. Either estimated or measured values are acceptable. Record the height of the patient in centimeters, and the weight of the patient in kilograms, up to one decimal place. Missing values are to be recorded as "missing" on the CRF, and the relevant fields left blank.

The Mostellar formula was used in the calculation of body surface area (BSA). BSA (m^2) = √((height (cm) x weight (kg))/3600.

1.4. Transfer from another hospital/AICU

Patients transferred to the recruitment site from a hospital outside the trust or from another AICU must be identified. The origin of the patient (intra or inter-hospital) should be verified by two sources; review of AICU admission clerking and, the nursing admission information (medical history information) on Carevue.

Patients who have been transferred into the recruitment site from another critical care unit within, or external to, the trust need to be carefully reviewed to ensure study eligibility criteria are met. Furthermore, patients transferred from another hospital to the trust need careful review of medical records to establish that the admission to AICU is the first episode of critical care, and to ensure study eligibility.

1.5. Date and time of admission to hospital

The date and time of hospital admission is sourced from the medical notes. This is to be identified through emergency department triage documentation, and is the earliest recorded date and time of hospital care related to the current admission.

In the absence of adequate triage documentation, discrepancies or missing values in recorded data, the date and time should be taken from the hospital admission clerking. For patients transferred from another hospital, the admission date and time to the hospital of origin should be used.

If these data are missing, this field should be recorded as unknown on the CRF.

Date should be recorded in the format dd/mm/yyyy, and time should be recorded in the 24-hour format.

1.6. Date and time of AICU admission

The date and time of AICU admission is identified from the Carevue demographics page, under inpatient details.

In the event of inadequate documentation, the date and time of AICU admission should be taken from the first recorded observation made in AICU, which is found on the Carevue observation flowsheets.

For patients that are transferred to AICU from another critical care unit, the date and time of admission to the original unit should be recorded.

Date should be recorded in the format dd/mm/yyyy, and time should be recorded in the 24-hour format.

1.7. AICU admission diagnosis

The primary AICU admission diagnosis for each patient is extracted from local submissions to the ICNARC database (4D MEDICUs, Mela Solutions). This database records diagnoses according to the hierarchical structure of the ICNARC coding method (Young et al. 2001), which identifies the type of admission (surgical or non-surgical), the organ system, the site, the pathophysiological process and condition that resulted in admission to AICU. Data are coded by the local ICNARC data manager.

For the study, these data are obtained by supplying the database manager with the hospital record number, initials of the patient and dates of AICU admission.

The admission diagnosis should be recorded in the CRF in the ICNARC coding method format.

1.8. Readmission to AICU

Readmission to AICU is defined as a return to the AICU within the same episode of care. This information can be found under inpatient details on the patient demographics page (admission information) on Carevue, and should be verified by cross-referencing the AICU medical admission notes.

Discrepancies are to be resolved by review of the patient medical records for the current episode of care to identify admissions to critical care units.

This information should be checked at AICU admission and at hospital discharge to identify if the patient had subsequent AICU admissions.

2. Past medical history

2.1. Previous cardiovascular disease

Pre-existing cardiovascular disease is determined by review of medical records. Additionally, where possible, participants (or their consultee) are to be questioned about pre-existing cardiac disease.

Pre-existing cardiovascular diseases can be elicited from medical records. As documentation can be incomplete or unreliable, a minimum level of evidence is required before pre-existing cardiovascular disease is deemed present. This evidence is detailed in table 1.

Table 1: Minimum level of evidence of pre-existing cardiovascular disease

Pathology/Intervention	Evidence in medical records	Minimum documentation in CRF
Acute myocardial infarction	Documentation of diagnosis of S-T segment myocardial infarction or non S-T segment myocardial infarction	Year of acute myocardial infarction
Cardiac arrest	Documented cardiopulmonary resuscitation	Year of cardiac arrest
Valvular abnormalities (including severity)	Documented murmur or valve replacement, or previous valvular pathology on echocardiogram	Pathology, affected valve, severity, any treatment (and year)
Hypertension	Chronic elevation of blood pressure that has resulted in initiation of anti-hypertensive medication	Pre-existing hypertension
Coronary angiography	Documentation of previous angiography procedure	Year and angiography report details
Heart Failure (and class)	Hospital admission for heart failure or diagnosis by expert opinion, or specific therapy to support diagnosis.	New York Heart Association classification
Coronary Artery Bypass Graft (CABG)	Documentation of CAGB	Year of procedure
Arrhythmia	Documented history of pre-existing arrhythmia, preferably confirmed by prior ECG	Arrhythmia type
Cardiomyopathy	Documented history and confirmation of cardiomyopathy by genetic testing, expert opinion or echocardiography	Type and year of diagnosis

3. AICU scoring systems

3.1. APACHE II score

This is composite score comprised of acute physiology, age and chronic health sub-scores.

The physiology score is calculated by assigning a score between 0 – 4 to the most deranged variables recorded in the first 24 hours of AICU admission; The score for these 12 variables are summed and added to the neurological score (15 minus the worst GCS score), to obtain the acute physiology score. Additional points are awarded based on age and chronic co-morbidities. These are combined with the physiology score to give a total APACHE II score.

All variables are required in the calculation of the score. Blood samples within the four hours immediately prior to AICU admission may be used if no samples in the first 24 hours are available. The lowest recorded Glasgow Coma Score (GCS) during non-sedation or paralysis is used in the calculation of the physiology score. If the patient does not have a sedation-free period in the first 24 hours of AICU, the GCS recorded immediately prior to sedation can be used.

A copy of the APACHE II scoring sheet is contained within the CRF, directly circle the score assigned to the degree of physiological derangement on to the form. The appropriate score assigned to age must be circled, as must the presence of chronic disease. The definitions of chronic diseases are listed below (Knaus et al. 1985), and may be identified from the medical records:

- Biopsy proven cirrhosis and documented portal hypertension
- Previous upper gastrointestinal bleeding attributed to portal hypertension
- Previous hepatic failure
- Previous hepatic encephalopathy
- New York Heart Association class IV heart failure
- Chronic restrictive, obstructive, or vascular lung disease resulting in severe exercise restriction
- Documented hypoxemia or hypercapnia
- Secondary polycythemia
- Severe pulmonary hypertension (>40 mmHg)
- Ventilator dependence
- Chronic hemodialysis
- Immunosuppression from chemotherapy, radiation therapy, long-term or recent high-dose steroids, or immunodeficiency.

Missing values must be recorded as missing and may not be derived.

3.2. ICNARC score

Individual patient physiology scores are extracted from local ICNARC submission database. These data are collected according to ICNARC definitions by local, trained staff.

For the study, these data are obtained by supplying the database manager with the hospital record number, initials of the patient and dates of AICU admission.

4. AICU interventions

4.1. Vasoactive days

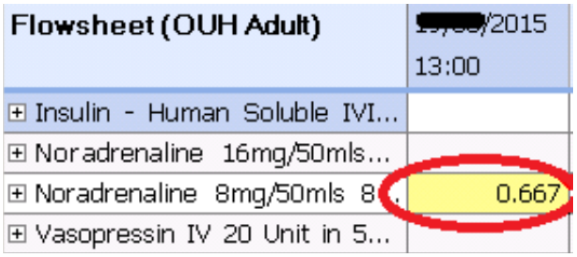
A vasoactive day is defined as the continuous infusion of either a vasopressor or inotrope for a minimum of one hour in a 24-hour period. Data are recorded for seven days from AICU admission. A capture period of seven days was chosen as it encompasses the national median and inter-quartile range of AICU length of stay (Intensive Care National Audit & Research Centre 2013) (median 2.2 (IQR 1.0 – 5.1)); this, therefore, should capture the majority of admissions, but not skew the data by recording rare cases of protracted vasoactive therapy . Participants who die whilst receiving vasoactive therapy are recorded as receiving therapy for the remainder of the data collection period. If a participant is discharged before the end of the data collection period, only record the number of vasoactive days during AICU admission.

Vasopressors and inotropes are defined as infusion of one or more of the following drugs:

- Dobutamine
- Noradrenaline
- Adrenaline
- Dopamine
- Dopexamine
- Milrinone
- Vasopressin

Note: this list is **NOT** comprehensive, but reflects commonly administered drugs at the recruitment site. If in doubt, refer to the Up-to-date website for further information.

The drug infusion therapy information is found on Carevue under flowcharts.



Record the number of days of vasoactive therapy as a whole number. Missing values must be recorded as missing.

4.2. Duration of mechanical ventilation

Mechanical ventilation was defined as where some (or all) of the energy required to increase lung volume during inspiration is supplied by a mechanical device. Continuous positive airway pressure (CPAP) alone is not considered mechanical ventilation.

Total duration of mechanical ventilation is given in total number of hours. Time of commencement and cessation is recorded to the nearest hour. Trial periods of spontaneous breathing or non-invasive ventilation are included in the calculation. Cessation of ventilation is defined when the patient has successfully transitioned to spontaneous breathing or non-invasive ventilation with no further periods of mechanical ventilation for at least 48 hours.

If the patient is successfully liberated from mechanical ventilation for >48 hours, but then requires recommencement, the collection of data is restarted and a summed duration for the AICU admission is recorded.

If the patient is transferred from the AICU to another centre (e.g. for repatriation) whilst receiving mechanical ventilation, then the cessation time is left blank.

Information of ventilation mode, start and cessation times can be located under respiratory observations the Carevue flowsheet.

Duration of mechanical ventilation is determined by the following procedure in Excel:

1. Transform dates from dd/mm/yyyy format to "number" format
2. Transform times from 00:00 format to "number" format
3. In a new column, add the ventilation start date and time numbers together
4. In another new column, add the ventilation cease date and time numbers together
5. Subtract the ventilation start time number from the ventilation cease date number
6. Multiply resultant number by 24 to get the duration of mechanical ventilation in hours.

4.3. Weaning failure

Weaning failure is defined as either re-intubation and/or resumption of ventilator support following successful extubation, or death, within 48 hours following extubation. Failure of spontaneous breathing trial was not included in this definition. This information can be elucidated by review of respiratory observations flowsheet on Carevue.

4.4. Other interventions occurring in AICU

More uncommon interventions must also be recorded. These interventions can be elicited from review of the AICU discharge summary on Carevue.

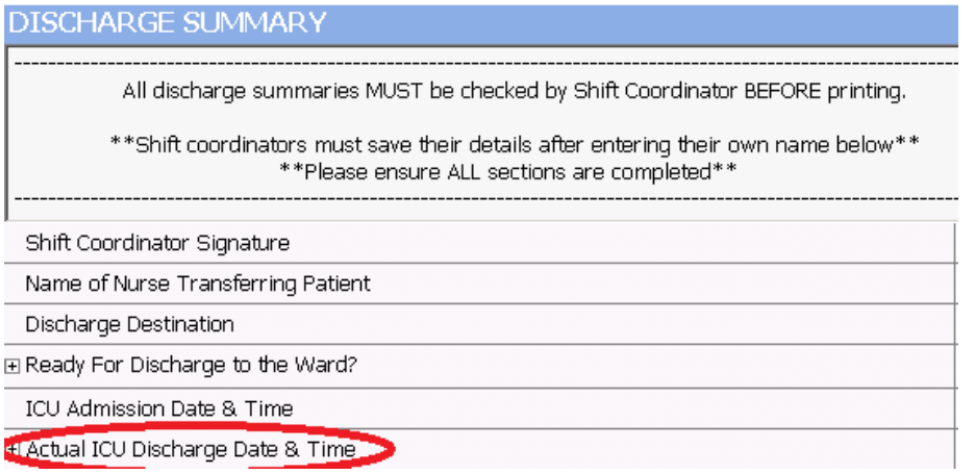
Intervention	Document
Extra-corporeal membrane oxygenation	Duration of therapy

Intra-aortic balloon pump	Duration of therapy
Implant of cardiac defibrillator or pacemaker	Device type
Angiography	Investigation findings
Temporary cardiac pacing	Duration of therapy

5. Discharge and outcome data

5.1. Date and time of discharge from AICU

The date and time of discharge from AICU must be recorded in the format dd/mm/yyyy and in 24-hour time. This data can be located in the AICU discharge summary on Carevue, under "actual departure from AICU".



If these data are missing, the time and date of the last recorded observation is used.

If the participant dies whilst in AICU, the date and time of death is taken as the date and time of discharge.

5.2. Date of hospital discharge

The date of hospital discharge should be obtained from the hospital electronic medical record (EPR) and recorded in the dd/mm/yyyy format. Hospital discharge is defined as the cessation of acute hospital care. Transfer to community hospitals, hospices and rehabilitation facilities are deemed cessation of acute hospital care. If a participant dies in hospital, the date of death is used the date of hospital discharge.

In the event of missing data, a request for the paper medical records should be made, and the last recorded observation/entry before discharge should be used to determine the hospital discharge date.

5.3. Mortality

The death of patients within AICU should be recorded on the CRF. The date and time of death is also used as date and time of AICU discharge (discussed

above). The date and time of death will be recorded on the AICU discharge summary.

The death of patients within hospital should also be recorded, with the date of death indicating date of hospital discharge. The in-hospital date of death will be available on the hospital electronic patient record.

The 90-day mortality immediately following AICU discharge is also to be determined. These data can be accessed using the electronic patient record. These records are linked to national Health Episode Statistics.

6. Variables collected at the time of echocardiography

6.1. Haemodynamic and ventilation variables

A number of haemodynamic and ventilation variables are to be collected at the time of echocardiography. All data can be sourced from the bedside from standard monitoring equipment at the time of echocardiography. This is also stored on Carevue on the patient flowsheets.

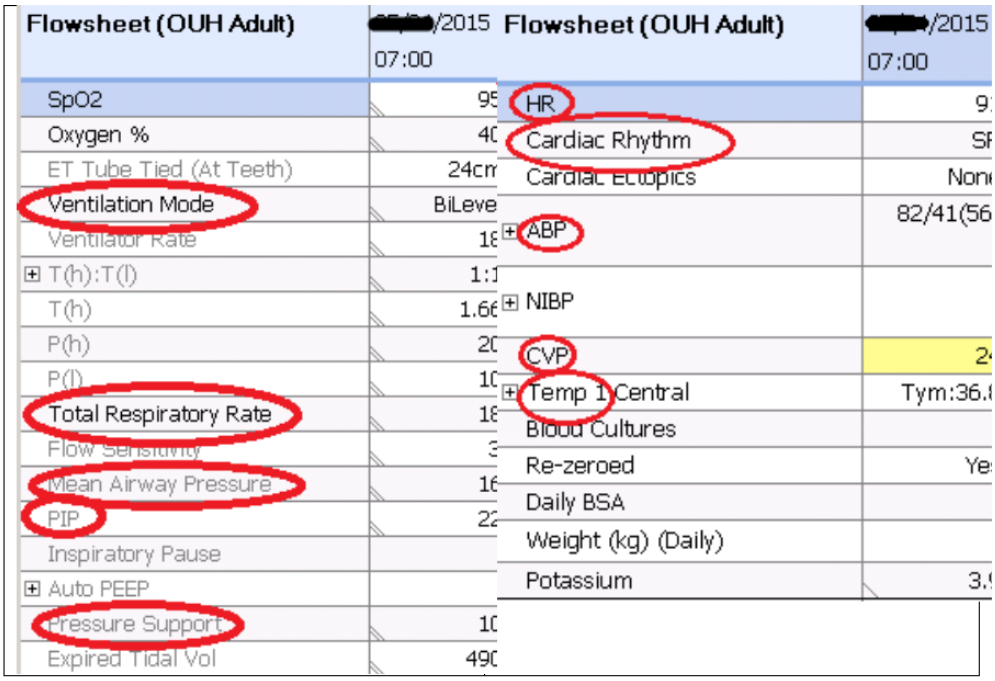
If data are not immediately recorded at the time of echocardiography, Carevue should be reviewed and the variable measurement recorded if it falls within the one hour preceding echocardiography. Similarly, if the was echocardiogram was clinically indicated, the medical records should be reviewed to identify if haemodynamic or other relevant variables were documented at the time of imaging.

Table 1: Variables and associated units

Variable	Unit
Heart rate	Beats per minute (BPM)
Heart rhythm	N/A
Systolic blood pressure	Millimetres of mercury (mmHg)
Diastolic blood pressure	Millimetres of mercury (mmHg)
Central venous pressure	Centimetres of water (cmH_2O)
Mode of ventilation	N/A
Mean airway pressure	Centimetres of water (cmH_2O)
Peak inspiratory pressure	Centimetres of water (cmH_2O)
Pressure support	Centimetres of water (cmH_2O)
Positive end expiratory pressure	Centimetres of water (cmH_2O)

Table 2 Location of variables recorded on the CRF on Carevue flowsheets

Respiratory observations	Vital sign observations



Flowsheet (OUH Adult)	[redacted]/2015 07:00
SpO2	9
Oxygen %	4
ET Tube Tied (At Teeth)	24cm
Ventilation Mode	BiLeve
Ventilator Rate	1
T(h):T(l)	1:1
T(h)	1.6
P(h)	2
P(l)	1
Total Respiratory Rate	1
Flow Sensitivity	3
Mean Airway Pressure	1
PIP	2
Inspiratory Pause	
Auto PEEP	
Pressure Support	1
Expired Tidal Vol	49

Flowsheet (OUH Adult)	[redacted]/2015 07:00
HR	9
Cardiac Rhythm	SI
Cardiac Ectopics	Non
ABP	82/41(56
NIBP	
CVP	2
Temp 1 Central	Tym:36.
Blood Cultures	
Re-zeroed	Ye
Daily BSA	
Weight (kg) (Daily)	
Potassium	3.

6.2. Inotrope and vasopressor requirements at the time of echo

Record the use of any inotrope and/or vasopressor at the time of echocardiography. Infusion rates, mcg/kg/min or units/min, should also be documented.

If these data are not recorded at the time of echocardiography, consult the drug infusion intake section on Carevue. Only record the use of vasopressor or inotropic drugs if it is documented that the drug was infusing at the time of echocardiography.

Flowsheet (OUH Adult)	[redacted]/2015 13:00
Insulin - Human Soluble IVI...	
Noradrenaline 16mg/50mls...	
Noradrenaline 8mg/50mls 8...	0.667
Vasopressin IV 20 Unit in 5...	

6.3. SOFA score

SOFA scores are calculated at the time of echocardiography during AICU admission. The most deranged physiological variables in the preceding 24-hour period are used in the calculation.

Haemodynamic and laboratory variables, in addition to examination findings are used to calculate the SOFA score. If not recorded directly at the time of echocardiography, these data can be found on Carevue.

Laboratory variables can be found under the laboratory variables flowsheet. Haemodynamic variables, the GCS, and arterial blood gas results, can be found on the patient observation flowsheet.

In the absence of a sedation-free neurological assessment, the pre-sedation Glasgow Coma Scale (GCS) is used. If a variable is missing, a mean of the preceding and subsequent variable can be taken, if two consecutive values are missing, the score is recorded as normal (a score of zero)(Ferreira et al. 2001).

SOFA scores are to be directly transcribed onto the table in the CRF. An example of this table is given in figure 1.

Figure 1: Example of SOFA scoring

Organ System	0	1	2	3	4
Respiratory PaO_2/FiO_2 ratio	>53	<53	<40	<26.6 + ventilated	<13 + ventilated
Renal creatinine (µmol/L)	<110	110-170	171-299	300-440	>440
Hepatic bilirubin (µmol/L)	<20	20-32	33-101	102-204	>204
Cardiovascular Mean arterial pressure (MAP) or vasopressor requirements (mcg/kg/min)	No hypotension	MAP <70 mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine ≥5 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
Haematological platelets (x 10^3/L)	>150	<150	<100	<50	<20
Neurological GCS	15	13-14	10-12	6-9	<6

6.4. SIRS, organ dysfunction and severe sepsis

During AICU admission, systemic inflammatory response syndrome (SIRS), organ dysfunction and severe sepsis data are collected at the time of echocardiography.

The definition from the ICNARC Case Mix Programme of SIRS, organ dysfunction and severe sepsis is used (Padkin et al. 2003). Severe sepsis was confirmed with the presence of SIRS, infection and organ dysfunction.

These criteria were assessed at each echocardiogram, and are given in table 3

Table 3: SIRS, organ dysfunction and infection definitions

SIRS, Infection and Severe Sepsis			
SIRS **Three of the four criteria listed below are required within the first 24-hours of ICU admission for the diagnosis of SIRS**		SIRS	Severe Sepsis
Temperature	Core temperature >38°C or < 36°C		
Heart Rate	> 90 beats per minute		
Respiratory	>20 breaths min or $PaCO_2$ <32 mmHg in a non-ventilated patient or mechanical ventilation in the first 24-hours in an patient not previously receiving home ventilation		
White Cell Count	> $12x10^9$ or < $4 x10^9$		
Infection **Diagnosis of infection as primary or secondary reason for AICU admission or laboratory confirmed/strongly suspected infection in first 24-hours in AICU.**		Infection	
Organ Dysfunction **Satisfaction of organ dysfunction criteria required at least one of these to be present during the first 24-hours in AICU.**		Organ Dysfunction	
Cardiovascular	SBP <90 mmHg or mean arterial pressure <70 mmHg or the use of vasoactive drugs for ≥1 hour in the first 24-hours		
Renal	Mean hourly urine output <0.5 mL/kg body weight in the first 24-hours in AICU or for the duration of stay if <24-hours in AICU. If on chronic renal replacement therapy, admission needed to meet another organ dysfunction criteria.		
Respiratory	PaO_2/FiO_2 ratio <250 mmHg. If the lung is the sole organ meeting an organ dysfunction criterion and primary/secondary reason for AICU admission indicated lung infection, PaO_2/FiO_2 ratio must be <200 mmHg.		
Haematological	Platelet count < $80x10^9$		
Metabolic	Base deficit <5.0 mmol/L		

The rules for collection of each of these variables and their source are given in table 4. Missing values are to be left blank.

Table 4: Rules for data collection for SIRS, sepsis and organ dysfunction

Variable	Sources	Rules
Temperature	Carevue	The most recent tympanic temperature observation is taken. Values up to 4 hours prior to echocardiogram are accepted.
Cardiovascular: Heart rate Systolic blood pressure Mean arterial pressure Vasoactive use	Carevue/ ECG at the time of echocardiography	Heart rate taken as close to the time of echocardiography as possible, maximum of one hour preceding examination. Blood pressure (from which mean arterial pressure is derived) taken as close to the time of echocardiography as possible, maximum of one hour preceding examination. Vasoactive requirements at the time of echocardiography are recorded.
Respiratory: $PaCO_2$ PaO_2/FiO_2 ratio Respiratory rate Ventilation status	Carevue	$PaCO_2$ and PaO_2/FiO_2 are obtained from the most recent arterial blood gas (gases up to four hours before echocardiogram are accepted). Respiratory rate is taken as close to the time of echocardiography as possible, maximum of one hour preceding examination. Ventilation status is determined at the time of echocardiography. Ventilation mode is available on Carevue.
White cell count Platelets	Carevue/Casenotes/EPR	Most recent blood results, results up to 24 hours before echocardiography are accepted
Infection	Medical records – admission clerking and ward round	Working or confirmed diagnosis.
Renal	Carevue	A mean of the hourly urine output in the 24-hours immediately prior to echocardiogram was calculated.

		Participants that are not catheterised are deemed to have adequate urine output and thus do not meet the criteria for organ dysfunction.
Metabolic	Carevue	Most recent arterial blood gas. Values up to 4 hours prior to echocardiogram are accepted.

7. Echocardiographic data

Note: the following section details the collection procedure of echocardiographic data. It does not provide guidelines for conducting the echocardiogram.

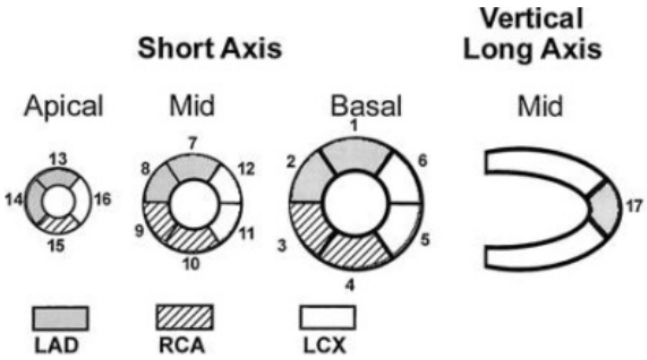
7.1. Identification of regional wall motion abnormalities

The presence of regional wall motion abnormalities (RWMA) can result in spurious measurements of cardiac dimensions, which, in turn, can result in incongruent or implausible measures of systolic function. Consequently, RWMA must be identified prior to measurement.

Firstly, review the participant's past cardiac history for any conditions associated with RWMA (e.g. previous acute myocardial infarction); if found, these participants are flagged for external review. Document this on the cover of the CRF. If no pre-existing condition associated with RWMA is found in the participant's history, then proceed with image review.

These studies use the 17-segment approach that has been widely adopted to describe areas of the myocardium. All segments of the LV must be reviewed in all available imaging windows. Observe the myocardial thickening and movement of each segment. Look for tethering to the adjacent segments. In healthy myocardium, each segment will symmetrically thicken and move towards the centre of the ventricle.

Be mindful that normally the lateral walls have more longitudinal movement compared with the septum. Additionally, in a correctly obtained view, the apex will not thicken to the same extent as adjacent myocardium. Any area of dyssynchronous contraction, or absence of normal myocardial thickening, must be recorded on the diagram below. Additionally, if the distribution of the RWMA corresponds to a typical coronary artery territory, this must be documented on the appropriate section of the CRF.



Participants with RWMA must be flagged for external review.

The above process must be followed for each and every echocardiogram.

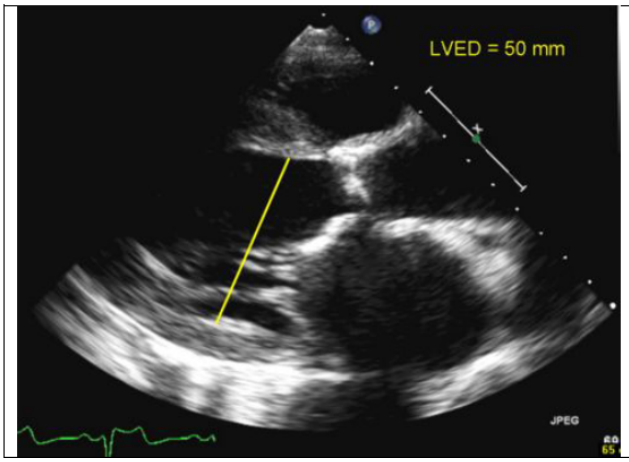
7.2 Ejection fraction

Once the absence of RWMA has been established, ejection fraction can be measured.

Firstly, check the quality of images in the parasternal long axis window; review the endocardial border delineation throughout the cardiac cycle (it should be easy to determine the blood-endocardium interface) and ensure the image is not foreshortened (that the image is slicing through the true apex). If the image quality is sub-optimal, flag the image for expert review, otherwise continue.

NB: measurements should not be taken from the cardiac cycle immediately following an ectopic beat. All participants should have three measurements of ejection fraction recorded. Participants in atrial fibrillation should have five.

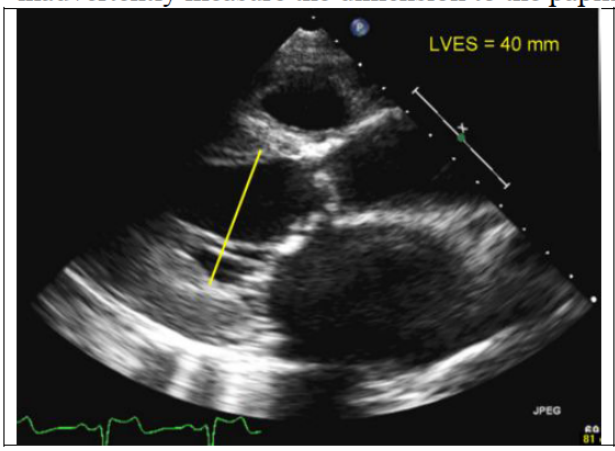
Next, identify the maximal LV internal dimension in diastole. This is usually the first frame after the closure of the mitral valve. Then identify the tips of the mitral valve leaflets. Using the caliper, measure the thickness of the inter-ventricular septum and the LV internal dimension in diastole – the caliper should pass through the tips of the mitral valve leaflets and end at the blood-endocardial interface on the lateral wall of the LV, and be perpendicular to the long axis of the LV.

	Correct placement of the caliper measuring the LV internal dimension in diastole

https://web.stanford.edu/group/ccm_echocardio/cgi-bin/mediawiki/index.php/Left_ventricle_size

Ensure the true internal dimensions are measured, taking care to avoid sub-endocardial bulges that be present in older participants. Also measure the posterior wall thickness – which is taken as the diameter from blood-endocardial interface to the beginning of the pericardium.

Next, identify the minimal internal diameter in systole from the same cardiac cycle. This is usually the frame immediately preceding the opening of the mitral valve. The measurement should be taken from the same location on the endocardium as the measurement in diastole, and pass through the tips of the mitral valve leaflets. Take care to identify the true endocardium and not inadvertently measure the dimension to the papillary muscles.



Correct placement of the caliper measuring the LV internal dimension in systole

Following the measurement of LVIDs, the software will automatically calculate the ejection fraction using the Teichholz formula.

Appendix 9: Examples of case report forms

ELF 1

The ELF Study: Evaluation of the incidence of acute, reversible, left ventricular dysfunction

PATIENT DATA BOOKLET
(CRF)
VERSION 2.0

THIS BOOKLET SHOULD BE COMPLETED IN BLACK INK AND BLOCK CAPITALS

PATIENT STUDY ID:

J	**R**		

PATIENT DEMOGRAPHICS

Name SURNAME GIVEN NAME

Sex Date of birth

Likely contact details after discharge:

Address line 1
Address line 2
Postal town
County
Postcode
Telephone 1
Telephone 2

Hospital number

CONSENT/ OPINION

Date consent obtained

Date opinion obtained

Name of person providing opinion:……..…….…….……..…

Relationship to patient:…….…….…….…….……..……..

ADMISSION DATA

Date and time of admission to hospital

Date and time of admission to AICU

Was the patient transferred from another hospital? YES / NO

Was the patient transferred from another AICU? YES / NO

Is this an AICU readmission? YES / NO

Past Cardiac History

		Details, including source
Acute myocardial infarction	Yes / No	Year
Heart failure	Yes / No	
Valve disease	Yes / No	
Infective endocarditis	Yes / No	
Valve replacement	Yes / No	
Cardiac arrest	Yes / No	Year
Hypertension	Yes / No	
Arrhythmia	Yes / No	
Cardiomyopathy	Yes / No	
Coronary artery bypass graft	Yes / No	Year

Height ☐☐☐ cm Weight ☐☐☐ kg

AICU ADMISSION

AICU Admission Diagnosis (ICNARC Coding Method)

Type	
System	
Site	
Process	
Condition	

[redacted] Apache II Score Worksheet version 1.0 01 Dec 2011	Patient Randomization number |___|___| – |___|___|___|	1st 24 hours in ICU (Q5.7/5.7.1) Randomisation (Q7.4)

APACHE II SCORE WORKSHEET FOR USE WITH APACHE II TOOL IN eCRF (see CRF instructions Section 5.7)

Circle the appropriate range that includes the worst value (the value that gives the highest score 0-4) and record GCS below

Score		4	3	2	1	0	1	2	3	4
Central Temperature (°C) *		≥ 41	39 - 40.9		38.5 - 38.9	36 - 38.4	34 - 35.9	32 - 33.9	30 - 31.9	≤ 29.9
Mean Arterial Pressure (mmHg)* *		≥ 160	130 – 159	110 - 129		70 - 109		50-69		≤ 49
Heart Rate / minute		≥ 180	140 – 179	110 - 139		70 - 109		55-69	40 - 54	≤ 39
Respiratory Rate / minute ***		≥ 50	35 – 49		25 - 34	12 - 24	10 - 11	6 - 9		≤ 5
Glasgow Coma Score (3-15)										
Oxygen	if FiO_2 ≥ 0.5 use $AaDO_2$†	≥ 500	350 – 499	200 - 349		≤ 200				
	if FiO_2 < 0.5 use PaO_2					> 70mmHg (9.33 kPa)	61 – 70mmHg (8.07-9.33kPa)		55 - 60 mmHg (7.33-8.06kPa)	<55 mmHg (7.33kPa)
Arterial pH		≥ 7.7	7.6 - 7.69		7.5 - 7.59	7.33 - 7.49		7.25 - 7.32	7.15 - 7.24	<7.15
White blood cells (10 ^ 9/L)		≥ 40		20 - 39.9	15 - 19.9	3 - 14.9		1 - 2.9		< 1
Hematocrit (%)		≥ 60.0		50.0-59.9	46.0-49.9	30.0-45.9		20.0-29.9		< 20.0
Sodium (mmol/L)		≥180	160 – 179	155 - 159	150 - 154	130 - 149		120 - 129	111 - 119	≤110
Potassium (mmol/L)		≥ 7	6 - 6.9		5.5 - 5.9	3.5 - 5.4	3 - 3.4	2.5 - 2.9		<2.5
Creatinine(umol/ L)		≥309	177 – 308	132 - 177		53 - 131		<53		
Acute renal failure††		Y		N						
Serum HCO_3 (mmol/L) (Use only if no pH or H^+ on ABG's)		≥52	41 - 51.9		32 - 40.9	22 - 31.9		18 - 21.9	15 - 17.9	<15

Circle the appropriate category for patient below										
Age of Patient	≤44		45-54		55-64		65-74		≥75	
Chronic Health status†††	**Non-chronic**		**Chronic non-operative or emergency post-operative**				**Chronic elective post-operative**			

***Central Temperature** (rectal, tympanic etc) - Add 0.3°C if oral or 0.6°C if axillary

****MAP** = {[(2 x DBP) + SBP] / 3}

*****Respiratory rate** Ventilated or non-ventilated.

†**$AaDO_2$** = {(713 x FiO_2) – (pCO_2 (mmHg) x 1.23) – PaO_2 (mmHg)}. **OR** {(713 x FiO_2) – (pCO_2 (kPa) x 9.225) – (PaO_2 (kPa) x 7.5)}

††**Acute renal failure** is defined as serum creatinine > 221 µmol/L in a patient with prior normal kidney function..
a patient with chronic renal failure develops an acute form of renal failure when their creatinine level doubles from baseline within 24 hours (acute on chronic):

†††**Chronic Health Status:** **IF** history of severe organ system insufficiency or iimmunocompromise (see definition) **THEN** classify as **EITHER** noperative or emergency post-op **OR** elective post-operative patients **on eCRF**

INTERVENTIONS

During this episode of care did the participant require:

Extra-corporeal membrane oxygenation	Yes / No	
Intra-aortic balloon pump	Yes / No	
Temporary pacing	Yes / No	
Cardiac implant	Yes / No	
Angiography	Yes / No	
Vasoactive support	Yes / No	Vasoactive days:
Mechanical ventilation	Yes / No	Date/ time ventilation start:
Failed extubation	Yes / No	Date/ time ventilation cease:

DISCHARGE DATA

Date and time of discharge from AICU:

Dead Alive

Date of discharge from acute hospital:

Dead Alive

SCORING

APACHE II*

ICNARC

*Scoring sheet on page 4

DAY 1 AICU

DATE and TIME | | | | | | | | | | | | |

Haemodynamic and ventilation data

Heart rate	
Heart rhythm	
Blood pressure	
Mean arterial pressure	
Central venous pressure	
Mode of ventilation	
Mean airway pressure	
Peak inspiratory pressure	
Pressure support	
Positive end expiratory pressure	

Vasopressor or Inotropic support required at time of echo? YES / NO

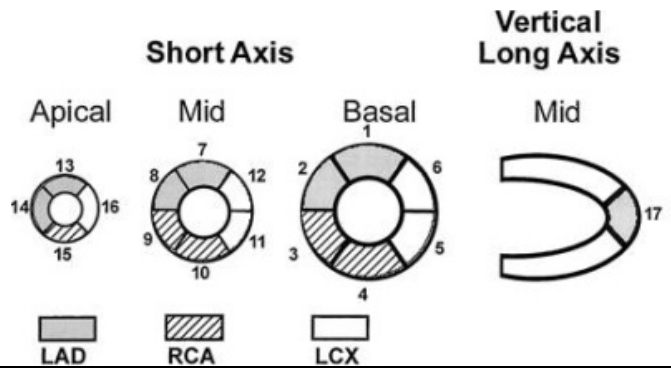
Drug (circle all that apply)	Rate of infusion at time of TTE (mcg/kg/min)
Dobutamine	
Noradrenaline	
Milrinone	
Dopamine	
Metaraminol	
Adrenaline	
Dopexamine	
Vasopressin	units/kg/hr

SIRS/ Severe Sepsis

	Yes	No	
Temperature <36º or > 38º C			SIRS
Heart rate > 90 bpm			
White cell count <4 x 10^9 or >12 x 10^9 or >10% immature bands			
Respiratory rate > 20 breaths/min or $PaCO_2$ < 32mmHg (4.3 kPa)			
Diagnosis of infection as primary or secondary reason for AICU admission or laboratory confirmed /strongly suspected infection in first 24-hours in AICU.			Infect
Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or the use of vasoactive drugs for >1 hour in the first 24-hours			Organ Dysfunct
Mean hourly urine output <0.5 mL/kg body weight in the first 24-			

hours in AICU or for the duration of stay if < 24-hours in AICU.			
PaO_2/FiO_2 ratio < 250 mmHg (<33.3 kPa). If the lung is the sole organ meeting an organ dysfunction criterion and primary/secondary reason for AICU admission indicated lung infection, PaO_2 / FiO_2 must be < 200 mmHg (<26.7 kPa).			
Platelet count < 80 x 10^9			
Base deficit < 5.0 mmol/L			
Severe Sepsis: All three (SIRS, infection, organ dysfunction)	YES / NO		

Echo Measures

Variable	Measurements		
Measurements LVIDd: LVIDs: IVSd: LVPWd:			
Ejection Fraction (%)			
Evidence of RWMA	YES / NO If Yes, single coronary artery territory: YES / NO 		

DAY 3-5 AICU ADMISSION

Date and time of echo | | | | | | | | | | | | |

Haemodynamic and ventilation data

Heart rate	
Heart rhythm	
Blood pressure	
Mean arterial pressure	
Central venous pressure	
Mode of ventilation	
Mean airway pressure	
Peak inspiratory pressure	
Pressure support	
Positive end expiratory pressure	

Vasopressor or Inotropic support required at time of echo? YES / NO

Drug (circle all that apply)	Rate of infusion at time of TTE (mcg/kg/min)
Dobutamine	
Noradrenaline	
Milrinone	
Dopamine	
Metaraminol	
Adrenaline	
Dopexamine	
Vasopressin	units/kg/hr

SOFA Score

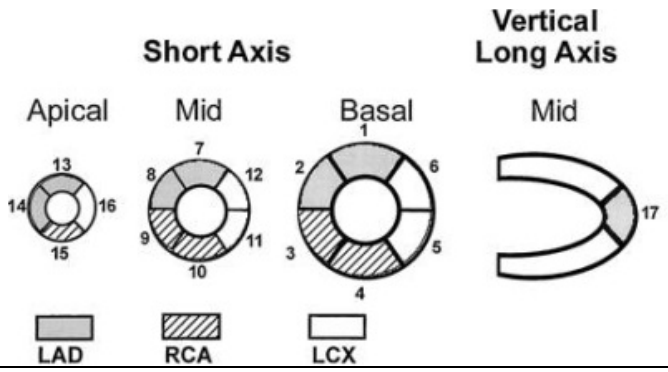
Organ System	0	1	2	3	4
Respiratory PaO_2/FiO_2 ratio	>53	<53	<40	<26.6 + vent	<13 + vent
Renal creatinine (µmol/L)	<110	110-170	171-299	300-440	>440
Hepatic bilirubin (µmol/L)	<20	20-32	33-101	102-204	>204
Cardiovascular Mean arterial pressure (MAP) or vasopressor requirements	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine ≥5 or Adrenaline ≤0.1 or Noradrenaline ≤0.1	Dopamine >15 or Adrenaline >0.1 or Noradrenaline >0.1
Haematological platelets (x 10^3/L)	>150	<150	<100	<50	<20

Neurological GCS	15	13-14	10-12	6-9	<6

SIRS/ Severe Sepsis

	Yes	No	
Temperature <36º or > 38º C			SIRS
Heart rate > 90 bpm			
White cell count <4 x 10^9 or >12 x 10^9 or >10% immature bands			
Respiratory rate > 20 breaths/min or $PaCO_2$ < 32mmHg (4.3 kPa)			
Diagnosis of infection as primary or secondary reason for AICU admission or laboratory confirmed /strongly suspected infection in first 24-hours in AICU.			Infect
Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or the use of vasoactive drugs for >1 hour in the first 24-hours			Organ Dysfunction
Mean hourly urine output <0.5 mL/kg body weight in the first 24-hours in AICU or for the duration of stay if < 24-hours in AICU.			
PaO_2/FiO_2 ratio < 250 mmHg (<33.3 kPa). If the lung is the sole organ meeting an organ dysfunction criterion and primary/secondary reason for AICU admission indicated lung infection, PaO_2 / FiO_2 must be < 200 mmHg (<26.7 kPa).			
Platelet count < 80 x 10^9			
Base deficit < 5.0 mmol/L			
Severe Sepsis: All three (SIRS, infection, organ dysfunction)	YES / NO		

Echo Measures

Variable	Measurements		
Measurements LVIDd: LVIDs: IVSd: LVPWd:			
Ejection Fraction (%)			
Evidence of RWMA	YES / NO If Yes, single coronary artery territory: YES / NO  		

AICU DISCHARGE EXPECTED WITHIN 24 HOURS

Date and time of echo | | | | | | | | | | | | |

Haemodynamic and ventilation data

Heart rate	
Heart rhythm	
Blood pressure	
Mean arterial pressure	
Central venous pressure	
Mode of ventilation	
Mean airway pressure	
Peak inspiratory pressure	
Pressure support	
Positive end expiratory pressure	

Vasopressor or Inotropic support required at time of echo? YES / NO

Drug (circle all that apply)	Rate of infusion at time of TTE (mcg/kg/min)
Dobutamine	
Noradrenaline	
Milrinone	
Dopamine	
Metaraminol	
Adrenaline	
Dopexamine	
Vasopressin	units/kg/hr

SOFA Score

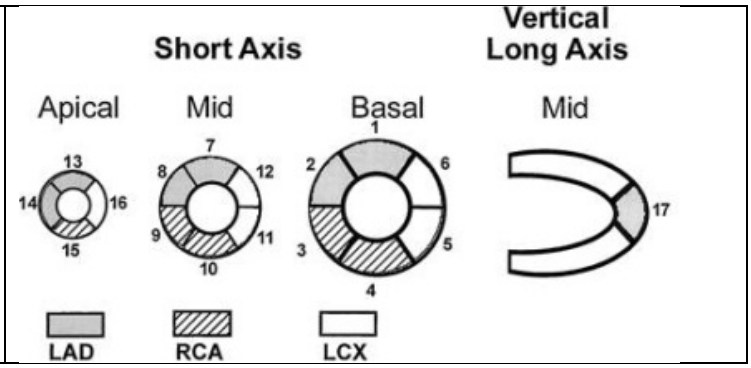
Organ System	0	1	2	3	4
Respiratory PaO_2/FiO_2 ratio	>53	<53	<40	<26.6 + vent	<13 + vent
Renal creatinine (µmol/L)	<110	110-170	171-299	300-440	>440
Hepatic bilirubin (µmol/L)	<20	20-32	33-101	102-204	>204
Cardiovascular Mean arterial pressure (MAP) or vasopressor requirements	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine ≥5 or Adrenaline ≤0.1 or Noradrenaline ≤0.1	Dopamine >15 or Adrenaline >0.1 or Noradrenaline >0.1
Haematological platelets (x 10^3/L)	>150	<150	<100	<50	<20
Neurological GCS	15	13-14	10-12	6-9	<6

SIRS/ Severe Sepsis

	Yes	No	
Temperature <36º or > 38º C			SIRS
Heart rate > 90 bpm			
White cell count <4 x 10^9 or >12 x 10^9 or >10% immature bands			
Respiratory rate > 20 breaths/min or $PaCO_2$ < 32mmHg (4.3 kPa)			
Diagnosis of infection as primary or secondary reason for AICU admission or laboratory confirmed /strongly suspected infection in first 24-hours in AICU.			Infect
Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or the use of vasoactive drugs for >1 hour in the first 24-hours			Organ Dysfunction
Mean hourly urine output <0.5 mL/kg body weight in the first 24-hours in AICU or for the duration of stay if < 24-hours in AICU.			
PaO_2/FiO_2 ratio < 250 mmHg (<33.3 kPa). If the lung is the sole organ meeting an organ dysfunction criterion and primary/secondary reason for AICU admission indicated lung infection, PaO_2 / FiO_2 must be < 200 mmHg (<26.7 kPa).			
Platelet count < 80 x 10^9			
Base deficit < 5.0 mmol/L			
Severe Sepsis: All three (SIRS, infection, organ dysfunction)	YES / NO		

Echo Measures

Variable	Measurements		
Measurements LVIDd: LVIDs: IVSd: LVPWd:			
Ejection Fraction (%)			
Evidence of RWMA	YES / NO If Yes, single coronary artery territory: YES / NO		


Short Axis
Vertical Long Axis
Apical
Mid
Basal
Mid
13
14
16
15
7
8
12
9
11
10
1
2
6
3
5
4
17
LAD
RCA
LCX

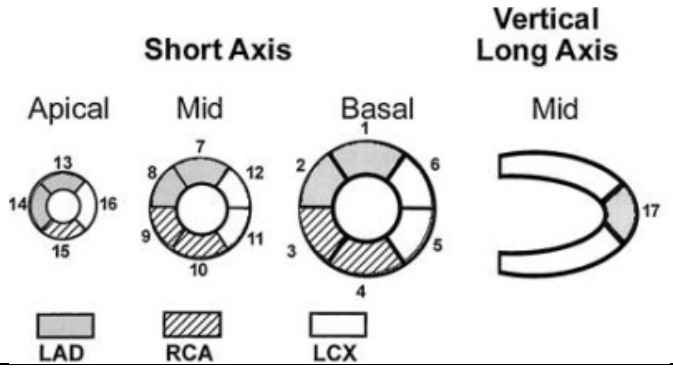
3 MONTHS FOLLOWING AICU DISCHARGE

Date and time of echo | | | | | | | | | | | | |

Haemodynamic and ventilation data

Heart rate	
Heart rhythm	
Blood pressure	
Mean arterial pressure	

Echo Measures

Variable	Measurements		
Measurements LVIDd: LVIDs: IVSd: LVPWd:			
Ejection Fraction (%)			
Evidence of RWMA	YES / NO If Yes, single coronary artery territory: YES / NO 		

CASE REPORT FORM ELF 2

Version 1.0 8th March 2014

MRN:	Study Number:
Initials:	Entered: Y / N

ADMISSION AND DISCHARGE DATA

Date and time of admission to hospital

Date and time of admission to AICU

Date and time of discharge from AICU:

Dead Alive

Date of discharge from acute hospital:

Dead

Was the patient transferred from another hospital? YES / NO

Was the patient transferred from another AICU? YES / NO

Was there an AICU readmission? YES / NO

Admission height cm weight kg

AICU ADMISSION DIAGNOSIS

AICU Admission Diagnosis (ICNARC Coding Method)

Type	
System	
Site	

Process	
Condition	

PAST CARDIAC HISTORY

		Details, including source
Acute myocardial infarction	Yes / No	Year
Heart failure	Yes / No	
Valve disease	Yes / No	
Infective endocarditis	Yes / No	
Valve replacement	Yes / No	
Cardiac arrest	Yes / No	Year
Hypertension	Yes / No	
Arrhythmia	Yes / No	
Cardiomyopathy	Yes / No	
Coronary artery bypass graft	Yes / No	Year

AICU INTERVENTIONS

During the episode of care did the participant require:

Extra-corporeal membrane oxygenation	Yes / No	
Intra-aortic balloon pump	Yes / No	
Temporary pacing	Yes / No	
Cardiac implant	Yes / No	
Angiography	Yes / No	
Vasoactive support	Yes / No	Vasoactive days:
Mechanical ventilation	Yes / No	Date/ time ventilation start:
Failed extubation	Yes / No	Date/ time ventilation cease:

SCORING

APACHE II ☐☐ ICNARC ☐☐☐

[redacted] Apache II Score Worksheet version 1.0 01 Dec 2011	Patient Randomization number |___|___| – |___|___|___|	1st 24 hours in ICU (Q5.7/5.7.1) Randomisation (Q7.4)

APACHE II SCORE WORKSHEET FOR USE WITH APACHE II TOOL IN eCRF (see CRF instructions Section 5.7)

Circle the appropriate range that includes the worst value (the value that gives the highest score 0-4) and record GCS below

Score		4	3	2	1	0	1	2	3	4
Central Temperature (°C) *		≥ 41	39 - 40.9		38.5 - 38.9	36 - 38.4	34 - 35.9	32 - 33.9	30 - 31.9	≤ 29.9
Mean Arterial Pressure (mmHg)* *		≥ 160	130 – 159	110 - 129		70 - 109		50-69		≤ 49
Heart Rate / minute		≥ 180	140 – 179	110 - 139		70 - 109		55-69	40 - 54	≤ 39
Respiratory Rate / minute ***		≥ 50	35 – 49		25 - 34	12 - 24	10 - 11	6 - 9		≤ 5
Glasgow Coma Score (3-15)										
Oxygen	if $FiO_2 \geq 0.5$ use $AaDO_2$†	≥ 500	350 – 499	200 - 349		≤ 200				
	if $FiO_2 < 0.5$ use PaO_2					> 70mmHg (9.33 kPa)	61 – 70mmHg (8.07-9.33kPa)		55 - 60 mmHg (7.33-8.06kPa)	<55 mmHg (7.33kPa)
Arterial pH		≥ 7.7	7.6 - 7.69		7.5 - 7.59	7.33 - 7.49		7.25 - 7.32	7.15 - 7.24	<7.15
White blood cells (10 ^ 9/L)		≥ 40		20 - 39.9	15 - 19.9	3 - 14.9		1 - 2.9		< 1
Hematocrit (%)		≥ 60.0		50.0-59.9	46.0-49.9	30.0-45.9		20.0-29.9		< 20.0
Sodium (mmol/L)		≥180	160 – 179	155 - 159	150 - 154	130 - 149		120 - 129	111 - 119	≤110
Potassium (mmol/L)		≥ 7	6 - 6.9		5.5 - 5.9	3.5 - 5.4	3 - 3.4	2.5 - 2.9		<2.5
Creatinine(umol/ L)		≥309	177 – 308	132 - 177		53 - 131		<53		
Acute renal failure††		Y		N						
Serum HCO_3 (mmol/L) (Use only if no pH or H^+ on ABG's)		≥52	41 - 51.9		32 - 40.9	22 - 31.9		18 - 21.9	15 - 17.9	<15

Circle the appropriate category for patient below

Age of Patient	≤44		45-54		55-64		65-74	≥75
Chronic Health status†††	Non-chronic		Chronic non-operative or emergency post-operative				Chronic elective post-operative	

***Central Temperature** (rectal, tympanic etc) - Add 0.3°C if oral or 0.6°C if axillary

****MAP** = {[(2 x DBP) + SBP] / 3}

*****Respiratory rate** Ventilated or non-ventilated.

†**$AaDO_2$** = {(713 x FiO_2) – (pCO_2 (mmHg) x 1.23) – PaO_2 (mmHg)}. **OR** {(713 x FiO_2) – (pCO_2 (kPa) x 9.225) – (PaO_2 (kPa) x 7.5)}

††**Acute renal failure** is defined as serum creatinine > 221 µmol/L in a patient with prior normal kidney function..
a patient with chronic renal failure develops an acute form of renal failure when their creatinine level doubles from baseline within 24 hours (acute on chronic):

†††**Chronic Health Status:** **IF** history of severe organ system insufficiency or iimmunocompromise (see definition) **THEN** classify as **EITHER** noperative or emergency post-op **OR** elective post-operative patients **on eCRF**

Echo Details

Echo date/ time	During / Post AICU stay
Indication recorded	Y / N Details:
Formally reported	Y / N
Study type	TTE / TOE

Haemodynamic variables

Heart Rate	
Heart Rhythm	
Blood Pressure (SBP/DBP)	
Mean Arterial Pressure	
Central Venous Pressure	

Ventilation variables

Mechanically ventilated	Y / N
Mode of ventilation	
Mean airway pressure	
Peak inspiratory pressure	
Pressure support	
Positive end expiratory pressure	

Vasoactives required Y / N

Drug	Rate of infusion at time of TTE (mcg/kg/min)
Dobutamine	
Noradrenaline	
Milrinone	
Dopamine	
Metaraminol	
Adrenaline	
Dopexamine	
Vasopressin	units/kg/hr

SOFA Score

Organ System	0	1	2	3	4
Respiratory PaO_2/FiO_2 ratio	>53	<53	<40	<26.6 + vent	<13 + vent
Renal creatinine (µmol/L)	<110	110-170	171-299	300-440	>440
Hepatic bilirubin (µmol/L)	<20	20-32	33-101	102-204	>204
Cardiovascular Mean arterial pressure (MAP) or vasopressor requirements	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine ≥5 or Adrenaline ≤0.1 or Noradrenaline ≤0.1	Dopamine >15 or Adrenaline >0.1 or Noradrenaline >0.1
Haematological platelets (x 10^3/L)	>150	<150	<100	<50	<20
Neurological GCS	15	13-14	10-12	6-9	<6

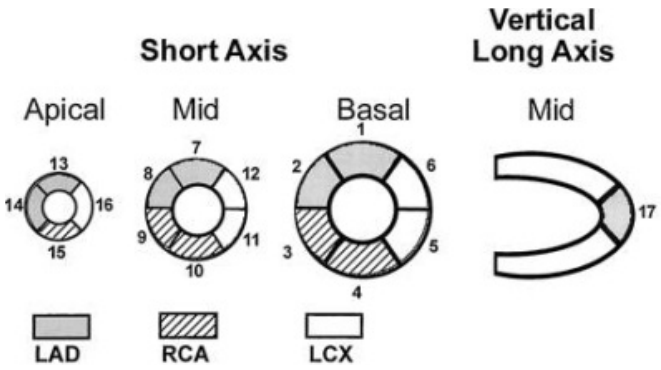
SIRS/ Severe Sepsis

	Yes	No	
Temperature <36º or > 38º C			SIRS
Heart rate > 90 bpm			
White cell count <4 x 10^9 or >12 x 10^9 or >10% immature bands			
Respiratory rate > 20 breaths/min or $PaCO_2$ < 32mmHg (4.3 kPa)			
Diagnosis of infection as primary or secondary reason for AICU admission or laboratory confirmed /strongly suspected infection in first 24-hours in AICU.			Infect
Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or the use of vasoactive drugs for >1 hour in the first 24-hours			Organ Dysfunction
Mean hourly urine output <0.5 mL/kg body weight in the first 24-hours in AICU or for the duration of stay if < 24-hours in AICU.			
PaO_2/FiO_2 ratio < 250 mmHg (<33.3 kPa). If the lung is the sole organ meeting an organ dysfunction criterion and primary/secondary reason for AICU admission indicated lung infection, PaO_2 / FiO_2 must be < 200 mmHg (<26.7 kPa).			
Platelet count < 80 x 10^9			
Base deficit < 5.0 mmol/L			
Severe Sepsis: All three (SIRS, infection, organ dysfunction)	YES / NO		

Echo measures

Variable	Measurement
Dimensions (cm)	LVIDd: LVIDs: IVSd: LVPWd:
Ejection Fraction (%)	

RWMA present Yes/ No
If Yes, single coronary artery Yes/ No



ELF 3 Case report form

PATIENT DEMOGRAPHICS

Name SURNAME GIVEN NAME

Sex Date of birth

Likely contact details after discharge:

Address line 1
Address line 2
Postal town
County
Postcode
Telephone 1
Telephone 2

Hospital number

CONSENT/ OPINION

Date consent obtained

Date opinion obtained

Name of person providing opinion:……..…….…….……

Relationship to patient:…….…….…….…….……..

ADMISSION DATA

Date and time of admission to hospital

Date and time of admission to AICU

Was the patient transferred from another hospital? YES / NO

Was the patient transferred from another AICU? YES / NO

Is this an AICU readmission? YES / NO

Past Cardiac History

		Details, including source
Acute myocardial infarction	Yes / No	Year
Heart failure	Yes / No	
Valve disease	Yes / No	
Infective endocarditis	Yes / No	
Valve replacement	Yes / No	
Cardiac arrest	Yes / No	Year
Hypertension	Yes / No	
Arrhythmia	Yes / No	
Cardiomyopathy	Yes / No	
Coronary artery bypass graft	Yes / No	Year

Height cm Weight kg

AICU ADMISSION

AICU Admission Diagnosis (ICNARC Coding Method)

Type	
System	
Site	
Process	
Condition	

[redacted] Apache II Score Worksheet version 1.0 01 Dec 2011	Patient Randomization number |___|___| – |___|___|___|	1st 24 hours in ICU (Q5.7/5.7.1) Randomisation (Q7.4)

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Central Temperature (°C) *		≥ 41	39 - 40.9		38.5 - 38.9	36 - 38.4	34 - 35.9	32 - 33.9	30 - 31.9	≤ 29.9
Mean Arterial Pressure (mmHg)**		≥ 160	130 – 159	110 - 129		70 - 109		50-69		≤ 49
Heart Rate / minute		≥ 180	140 – 179	110 - 139		70 - 109		55-69	40 - 54	≤ 39
Respiratory Rate / minute ***		≥ 50	35 – 49		25 - 34	12 - 24	10 - 11	6 - 9		≤ 5
Glasgow Coma Score (3-15)										
Oxygen	if $FiO_2 \geq 0.5$ use $AaDO_2$†	≥ 500	350 – 499	200 - 349		≤ 200				
	if $FiO_2 < 0.5$ use PaO_2					> 70mmHg (9.33 kPa)	61 – 70mmHg (8.07-9.33kPa)		55 - 60 mmHg (7.33-8.06kPa)	<55 mmHg (7.33kPa)
Arterial pH		≥ 7.7	7.6 - 7.69		7.5 - 7.59	7.33 - 7.49		7.25 - 7.32	7.15 - 7.24	<7.15
White blood cells (10 ^ 9/L)		≥ 40		20 - 39.9	15 - 19.9	3 - 14.9		1 - 2.9		< 1
Hematocrit (%)		≥ 60.0		50.0-59.9	46.0-49.9	30.0-45.9		20.0-29.9		< 20.0
Sodium (mmol/L)		≥180	160 – 179	155 - 159	150 - 154	130 - 149		120 - 129	111 - 119	≤110
Potassium (mmol/L)		≥ 7	6 - 6.9		5.5 - 5.9	3.5 - 5.4	3 - 3.4	2.5 - 2.9		<2.5
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Acute renal failure††		Y		N						
Serum HCO_3 (mmol/L) (Use only if no pH or H^+ on ABG's)		≥52	41 - 51.9		32 - 40.9	22 - 31.9		18 - 21.9	15 - 17.9	<15

Circle the appropriate category for patient below

Age of Patient	≤44		45-54		55-64		65-74		≥75	
Chronic Health status†††	Non-chronic		Chronic non-operative or emergency post-operative				Chronic elective post-operative			

***Central Temperature** (rectal, tympanic etc) - Add 0.3°C if oral or 0.6°C if axillary

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†††**Chronic Health Status:** **IF** history of severe organ system insufficiency or iimmunocompromise (see definition) **THEN** classify as **EITHER** noperative or emergency post-op **OR** elective post-operative patients **on eCRF**

INTERVENTIONS

During this episode of care did the participant require:

Extra-corporeal membrane oxygenation	Yes / No	
Intra-aortic balloon pump	Yes / No	
Temporary pacing	Yes / No	
Cardiac implant	Yes / No	
Angiography	Yes / No	
Vasoactive support	Yes / No	Vasoactive days:
Mechanical ventilation	Yes / No	Date/ time ventilation start:
Failed extubation	Yes / No	Date/ time ventilation cease:

DISCHARGE DATA

Date and time of discharge from AICU: ☐☐ ☐☐ ☐☐☐☐ ☐☐☐☐

Dead ☐ Alive ☐

Date of discharge from acute hospital: ☐☐ ☐☐ ☐☐☐☐

Dead ☐ ☐

SCORING

APACHE II ☐☐ ICNARC ☐☐☐

Haemodynamics

Heart Rate	
Heart Rhythm	
Blood Pressure (SBP/DBP)	
Mean Arterial Pressure	
Central Venous Pressure	

Ventilation

Mode of ventilation	
Mean airway pressure	
Peak inspiratory pressure	
Pressure support	
Positive end expiratory pressure	

Vasoactive Therapy

Required: Yes / No

Drug (Tick all that apply)	Rate of infusion at time of TTE (mcg/kg/min)
Dobutamine	
Noradrenaline	
Milrinone	
Dopamine	
Metaraminol	
Adrenaline	
Dopexamine	
Vasopressin	units/kg/hr

SOFA Scoring

Organ System	0	1	2	3	4
Respiratory PaO_2/FiO_2 ratio	>53	<53	<40	<26.6 + vent	<13 + vent
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Haematological platelets (x 10^3/L)	>150	<150	<100	<50	<20
Neurological GCS	15	13-14	10-12	6-9	<6

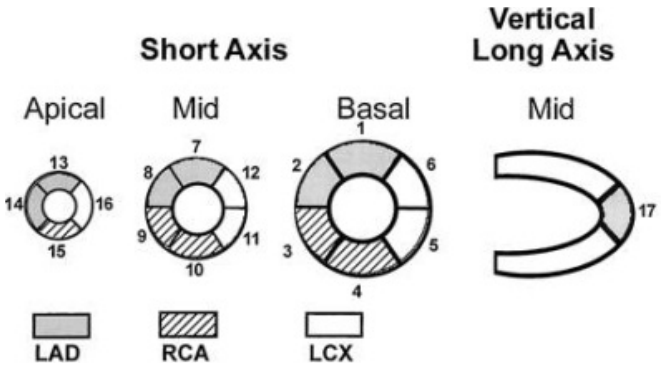
SIRS/ Severe Sepsis

	Yes	No	
Temperature <36º or > 38º C			SIRS
Heart rate > 90 bpm			
White cell count <4 x 10^9 or >12 x 10^9 or >10% immature bands			
Respiratory rate > 20 breaths/min or $PaCO_2$ < 32mmHg (4.3 kPa)			
Diagnosis of infection as primary or secondary reason for AICU admission or laboratory confirmed /strongly suspected infection in first 24-hours in AICU.			Infect
Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or the use of vasoactive drugs for >1 hour in the first 24-hours			Organ Dysfunction
Mean hourly urine output <0.5 mL/kg body weight in the first 24-hours in AICU or for the duration of stay if < 24-hours in AICU.			
PaO_2/FiO_2 ratio < 250 mmHg (<33.3 kPa). If the lung is the sole organ meeting an organ dysfunction criterion and primary/secondary reason for AICU admission indicated lung infection, PaO_2 / FiO_2 must be < 200 mmHg (<26.7 kPa).			
Platelet count < 80 x 10^9			
Base deficit < 5.0 mmol/L			
Severe Sepsis: All three (SIRS, infection, organ dysfunction)	YES / NO		

Echo Variables

RWMA present YES / NO

Single coronary artery territory YES / NO



Variable	Measurement
Dimensions (cm)	LVIDd: LVIDs: IVSd: LVPWd:
Ejection Fraction (%)	
Fractional Shortening (%)	

Appendix 10: Justification for candidate explanatory variables

Included candidate variables

Selected input variables

Variable	Justification for inclusion
Gender	Some prior studies have observed myocardial depression occurring more commonly in females in sub-populations of patients experiencing critical illness. Thus, gender was included as a candidate variable to explore the significance of gender on the development of myocardial depression in the general AICU population.
Age	Some studies have observed myocardial depression occurring more commonly in older patients, whilst others have reported it occurring in younger age groups. Consequently, the affect of age on risk of developing myocardial depression is unclear. Therefore, age was included as a candidate variable.
Heart rate	Heart rate as been identified as a useful predictor of outcomes in sub-populations of critically ill patients with myocardial depression[4,6].
Sinus rhythm	Arrhythmias have been observed in patients with myocardial depression. The relationship and effect of heart rhythm on the risk of myocardial depression is unknown.

Systolic blood pressure	Systolic blood pressure was included as a candidate variable. It has been demonstrated to be a useful predictor across a range of outcomes, including troponin-I release following SAH[6].
Cardiovascular organ dysfunction	Cardiovascular organ dysfunction is a composite variable taken from the definitions of organ dysfunction described by Padkin[145]. This binary variable is comprised of systolic blood pressure (<90 mmHg), mean arterial pressure (<70 mmHg) or the use of vasoactive drugs >1 hour in the first 24 hours of AICU. Traditionally, composite variables are considered unfavourable in predictive models, as the individual effects of the components on the development of the outcome cannot be elucidated. Nevertheless, this was included as a candidate variable as inclusion of too many predictor variables increases the risk of overfitting the model. This variable encompasses multiple indicators of cardiovascular disturbance, thus this could potentially be used instead of multiple individual variables, thereby reducing the risk of overfitting the model.
Vasopressor administration	This was included as catecholamine exposure has been a proposed as a mechanism for the development of myocardial depression. This was included as a binary variable.
Respiratory organ dysfunction	This is a composite score taken from the definitions of organ dysfunction described by

	Padkin. Respiratory rate, $PaCO_2$ and the need for mechanical ventilation criteria are included. This was included as a candidate explanatory variable as respiratory dysfunction occurring during the early stages of critical illness may be useful discriminator between patients who do and do not develop myocardial depression.
Mean airway pressure	The mean airway pressure in spontaneously ventilating patients approximates zero. Therefore, this variable can be used recorded in both spontaneously breathing and artificially ventilated participants. Thus, this variable has few missing data in comparison with other ventilation variables. This was included as a candidate explanatory variable as this may provide a useful discriminator of risk using a routinely collected ventilation observation.
Severe sepsis	Severe sepsis was included as a candidate variable as myocardial depression has been frequently described in sub-populations of critically ill patients with sepsis.
Regional wall motion abnormalities	Regional wall motion abnormalities have been observed in patients with myocardial depression but the frequency and significance of this finding is unclear.
Surgical admission	Park[60] and colleagues flagged this as an area of future research in patients experiencing critical illness. The physiological stress of surgery could potentially induce myocardial depression.

Excluded candidate variables

Demographic Variables

Variable	Justification for exclusion as input variable
ICNARC and APACHE II scores	The ICNARC score predicts risk of death before hospital discharge and the APACHE II score describes severity of illness. These are composite scores, comprised of many explanatory variables. These scores will be highly correlated to many other explanatory variables, making elucidation of their effect on the development of myocardial depression difficult. These variables are unlikely to yield any explanatory power, therefore these were excluded as candidate variables.
History of valvular disease	History of valvular disease was excluded as a candidate explanatory variable as too few participants had the outcome (n = 5, 4.5%). This is considered a rare event and is therefore not appropriate as a predictor variable.
History of CABG	History of CABG was excluded as a candidate explanatory as too few participants of the total population had the outcome (n = 6, 5%). This is a borderline rare event (frequency <5%). The prevalence of patients with previous CABG is low, additionally, no participant demonstrating myocardial depression had a CABG; therefore it is unlikely that prior CABG is a useful predictor variable, and was thus excluded as a candidate explanatory variable.

History of heart failure	History of heart failure was excluded as an explanatory variable as the prevalence of amongst all participants was too low (n = 8, 7%) to be a useful predictor. As only one patient with myocardial depression had a history of heart failure, it is highly unlikely this variable would be a useful, generalisable, predictor.
History of cardiac arrest	History of cardiac arrest was excluded as an explanatory variable. The number of participants with a previously documented cardiac arrest is 16 (14.3%), however this was recorded in only four participants demonstrating myocardial depression. Consequently, history of cardiac arrest was excluded as an explanatory variable as the prevalence is low, and only a quarter of these participants developed myocardial depression, and it is therefore unlikely to be useful predictor.
History of arrhythmia	History of arrhythmia was excluded as a candidate explanatory variable. The study definition used to identify history of arrhythmia requires evidence of pre-existing arrhythmia prior to AICU admission and does therefore not include participants who developed an arrhythmia during the current admission. Consequently, the binary variable "sinus rhythm", which documents the rhythm at the time of baseline echocardiography was considered preferable, as it captures new arrhythmias. This was included as a candidate explanatory variable, and is discussed further in the above section "included candidate variables".

History of acute myocardial infarction (AMI)	16% of the development population had a history of AMI (n = 18). These data were collected to identify participants at risk of demonstrating RWMA on echocardiography. This was not included as a candidate variable because it was felt that the time between AMI and AICU admission was important and there were too few events to meaningfully create these data into ordinal variables.
History of hypertension	History of hypertension was excluded as a candidate predictor as cardiac risk factors (including hypertension) had not been useful in other studies[3–6]. Systolic blood pressure (continuous variable) is included as a candidate explanatory variable. This was considered preferable as there are few missing data and is not dependent on the recall/medical engagement of the participant.
History of cardiomyopathy	Too few participants had a history of cardiomyopathy (n = 3). This was therefore excluded as a predictor variable.
AICU admission diagnosis	The inclusion criteria to the studies were kept broad. Consequently, a heterogeneous group of participants, with a wide range of admission diagnoses, were enrolled in the studies. AICU admission diagnosis was excluded as a candidate predictor variable, as the reasons for AICU admission were heterogeneous amongst participants. Additionally, reversible myocardial depression

	has been observed in patients with severe sepsis. Not infrequently, participants were admitted to AICU for treatment of sepsis. Severe sepsis was included as a candidate predictor variable, discussed above under "included candidate variables".
Height and weight	Height, weight and their expression as body surface area (BSA) were discounted as candidate explanatory variables. These data were collected in the event that additional echocardiography measures that are indexed to BSA were adopted in later studies. BSA has been trialled as an explanatory variable to predict the development of RWMA, the pattern of RWMA, and troponin-I release, in patients with non-traumatic subarachnoid haemorrhage. BSA was not found to be a useful predictor on univariate analysis[3,4,6]. In the interests of rationalising candidate variables to avoid overfitting, BSA (and height and weight) was excluded as candidate explanatory variables.

AICU therapies

Variable	Justification for exclusion as input variable
Mode of ventilation	The mode of ventilation (spontaneous vs. mechanical) was excluded as a candidate predictor variable. The type of mechanical ventilation is heavily influenced by clinician preference, and is

	therefore not a useful, repeatable, discriminator between participants.
Duration of mechanical ventilation	This variable is unknown within the first 24 hours of AICU admission.
Peak inspiratory pressure Positive end expiratory pressure Pressure support	Peak inspiratory pressure, positive end expiratory pressure and pressure support were excluded as candidate variables as they are only measureable in patients receiving mechanical ventilation at the time of echocardiography during the first 24 hours (n = 67, 59.8%). As missing values cannot be reasonably imputed, this would result in an unacceptably high amount of missing data (39.2%), therefore these variables were excluded as candidate predictor variables.
Failed extubation	This variable is unknown within the first 24 hours of AICU admission.
Vasopressor days	This variable is unknown within the first 24 hours of AICU admission.
Required ECMO	This variable is unknown within the first 24 hours of AICU admission.
Required an IABP	This variable is unknown within the first 24 hours of AICU admission.
Required pacing	This variable is unknown within the first 24 hours of AICU admission.
Required cardiac implantable	This variable is unknown within the first 24

device	hours of AICU admission.

Haemodynamic variables

Variable	Justification for exclusion as input variable
Diastolic blood pressure	Diastolic blood pressure was not included as a candidate predictor variable as systolic blood pressure has been identified to be a superior predictor variable in a range of cardiovascular diseases. Furthermore, diastolic blood pressure was trialled as a predictor variable in identifying cardiac outcomes in patients with subarachnoid haemorrhage, and it was not found to be useful. Again, systolic blood pressure was found to be a useful predictor in this setting[6].
Mean arterial pressure	This variable is an expression of systolic and diastolic blood pressure. This is mathematically linked, and therefore not an ideal predictor variable. This was therefore excluded.
Central venous pressure	This variable was only recorded in 67% of participants during the first 24 hours of AICU admission. This was excluded due to the incompleteness of the data.

Clinical descriptors

Variable	Justification for exclusion as input variable

SIRS criteria	Temperature <36º or >38º C	These three variables, temperature, white cell count and respiratory dysfunction, were excluded as individual candidate explanatory variables. These binary variables form part of the SIRS criteria, which mandate that at least three of the four criteria are met for SIRS to be present. In turn, the SIRS criteria, along with infection and organ dysfunction, must be met for severe sepsis to be present. Therefore, derangement of temperature, white cell count and respiratory function will be captured within severe sepsis if they are present in conjunction with infection and organ dysfunction.
	White cell count $<4x10^9$ or $>12x10^9$	
	Respiratory rate >20 breaths/minute or $PaCO_2$ <32mmHg in a non-ventilated patient or the need for mechanical ventilation	
	Heart rate > 90 beats/minute	Captured as a continuous variable.
Infection known or suspected		Infection was excluded as a candidate explanatory variable. The presence of infection forms an integral part of the severe sepsis criteria, and is therefore captured within this variable. Thus, in the interests of rationalising candidate explanatory variables, infection as a individual variable was excluded.
Organ dysfunction	Mean hourly urine output <0.5 mL/kg in the first 24-hours in a patient not receiving chronic renal replacement therapy	These three binary variables were not included as candidate predictors. Inclusion of too many predictor variables increases the risk of overfitting the model, it was felt these variables were likely to be useful predictors and thus were excluded,
	Platelet count $<80 \times 10^9$	
	Base deficit <5.0 mmol/L	

Appendix 11: Comparison of models

Model all 12 candidate variables

	Estimate	Standard error	p value
Intercept	-1.47	2.67	
Rate	-0.03	0.02	0.0696
Sinus rhythm	-1.17	0.70	0.0921
SBP	0.04	2.52	0.0116
Mean airway pressure	-0.04	0.05	0.3794
Vasopressors	0.60	0.68	0.3791
Respiratory organ dysfunction	0.45	0.62	0.4732
Cardiovascular organ dysfunction	0.56	0.68	0.4074
Severe sepsis	0.81	0.64	0.2051
RWMA	0.30	0.63	0.6375
Male	-0.15	0.69	0.8309
Age	-0.02	0.02	0.1298
Surgical admission	0.35	0.73	0.6357

Model AIC: 117.6

Model with only SBP and severe sepsis as predictor variables

	Estimate	Standard error	p value
Intercept	-4.12	1.46	
SBP	0.03	0.01	0.03425
Severe sepsis	0.73	0.53	0.16878

Model AIC 108.41

Appendix 12: Comparison of the 12 candidate explanatory variables across the ELF studies

Note: continuous variables were reviewed by histogram to determine if they were normally distributed. Continuous variables that were normally distributed are presented as mean and standard deviation. Continuous variables that were not normally distributed are presented as median and interquartile range.

Variable	ELF 1 (n = 49)	ELF 2 (n = 42)	ELF 3 (n = 21)	Development population (n = 112)
Male gender (n,%)	34 (69.4%)	26 (61.9%)	15 (71.4%)	75 (67.0%)
Age (median, IQR)	66 (IQR 47 – 75)	57 (IQR 38-70)	70 (IQR 58 – 79)	64 (IQR 45 – 76)
Heart rate (mean, std. dev)	98 (SD 24)	94 (SD 26)	88 (SD 13)	95 (SD 23)
Absence of sinus rhythm (n, %)	25 (51.0%)	27 (64.3%)	7 (33.3%)	59 (52.7%)
Systolic blood pressure (mean, std. dev)	116 (SD 20)	105 (SD 21)	118 (SD 15)	112 (SD 20)
Absence of cardiovascular organ dysfunction	31 (63.3%)	12 (28.6%)	9 (42.9%)	52 (46.4%)

(n, %)				
Absence of respiratory organ dysfunction (n, %)	23 (46.9%)	19 (45.2%)	9 (42.9%)	50 (44.6%)
Absence of severe sepsis (n,%)	38 (77.6%)	26 (61.9%)	18 (85.7%)	81 (72.3%)
Mean airway pressure (median, IQR)	8 (IQR 0 – 13)	9 (IQR 0 – 13)	8 (IQR 0 – 11)	8 (IQR 0 – 12)
Absence of vasopressor administration	24 (49.0%)	19 (45.2%)	10 (47.6%)	53 (47.3%)
Absence of surgical admission (n, %)	41 (83.7%)	38 (90.5%)	15 (71.4%)	94 (83.9%)
Absence of regional wall motion abnormalities (n,%)	45 (91.8%)	19 (45.2%)	18 (85.7%)	82 (73.2%)

Appendix 13: Variable elimination

Pair 1

	Effect on correlation	Decision
Factor less mean airway pressure	0.33	Drop mean airway pressure from the factor
Factor less cardiovascular organ dysfunction	0.32	

Pair 2

	Effect on correlation	Decision
Factor less respiratory organ dysfunction	0.34	Drop respiratory organ dysfunction from the factor
Factor less severe sepsis	0.33	

Pair 3

	Effect on correlation	Decision
Factor less age	0.33	Drop male gender from the factor
Factor less male gender	0.36	

Pair 4

	Effect on correlation	Decision
Factor less heart rate	0.31	Drop regional wall motion abnormalities from the factor
Factor less regional wall motion abnormalities	0.36	

Pair 5

	Effect on correlation	Decision
Factor less vasopressors	0.35	Drop vasopressors from the factor
Factor less cardiovascular organ dysfunction	0.34	

Final elimination

	Effect on correlation	Decision
Factor less age and surgical admission	0.28	Remove age and surgical admission from the factor

Appendix 14: Probability thresholds for development of myocardial depression

Probability	False positives	False negatives
0.2	68.0% (51/75)	16.2% (6/37)
0.25	59.6% (31/52)	15.0% (9/60)
0.35	53.8% (14/26)	20.9% (18/86)
0.45	27.3% (3/11)	21.7% (22/101)
0.50	30.0% (3/10)	22.5% (23/102)
0.55	33.3% (2/6)	24.5% (26/106)