

**The role of thoracic ultrasonography in the assessment of extravascular lung
water and breathlessness**

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ABSTRACT

Patients with respiratory failure and breathlessness frequently present clinicians with a unique diagnostic and therapeutic challenge. These patients may be acutely unwell and in need of rapid intervention with limited information available to guide the responsible clinician. The range of different conditions that can present with breathlessness is broad, and differentiating one from another may be extremely difficult in a patient with multiple overlapping co-morbidities. Even when the cause of a patient's breathlessness appears obvious, as can be the case with malignant pleural disease, identifying the best treatment option for that individual may not always be a straightforward process.

The use of bedside, or point-of-care ultrasound has become increasingly common over the past decade; moving away from a traditional home in the radiology department and entering the hands of clinicians who are responsible for diagnosing and treating patients on a day-to-day basis. The most widely accepted role for thoracic ultrasound is as an adjunct to pleural procedures, but as clinicians have become more familiar with its use the ways in which thoracic ultrasound is utilized have begun to diversify. As a result, there is growing interest in how thoracic ultrasonography might be used as a diagnostic tool in patients who are breathless, and in turn have a positive impact on their treatment and key clinical outcomes.

The purpose of this thesis is to evaluate some of the differing roles that thoracic ultrasonography might have in the clinical assessment and management of the patient with breathlessness and respiratory failure, and to focus on areas that are outside what is currently regarded as conventional practice. This thesis will begin to answer, through a series of clinical studies, specific questions that have the potential to change the way clinicians use bedside thoracic ultrasound examination to diagnose and treat their patients.

Malignant pleural effusion is an increasingly common problem, traditionally managed by chest tube drainage and intrapleural administration of a chemical

sclerosant such as talc with the aim of achieving pleurodesis and preventing fluid recurrence. This treatment strategy is however unsuccessful in up to 30% of patients. The first study presented in this thesis examined the ability of thoracic ultrasound to predict long-term pleurodesis success in the immediate aftermath of talc slurry administration via an intercostal chest tube to treat recurrent symptomatic malignant pleural effusion, recognizing the ability of thoracic ultrasound to identify the presence of pleural adhesions in other clinical scenarios through the loss of the normal “lung sliding” artefact. 18 participants were recruited to a prospective observational cohort feasibility study, undergoing a standardised nine-point thoracic ultrasound examination immediately before, and 24 hours after talc slurry administration in order to derive a pleural adherence score for the affected hemithorax at each of these timepoints. The ultrasound scans were reported by the primary bedside operator and two independent assessors blinded to the participant’s clinical status. Study participants who went on to suffer pleurodesis failure had a lower pleural adherence score at 24 hours post-talc instillation than those who were successful. This novel association between a thoracic ultrasound-derived pleural adherence score and long-term pleurodesis success and failure should now be evaluated in further research to assess its utility in supporting decision making in the treatment of patients with malignant pleural effusion.

The second study looked at whether thoracic ultrasound examination prior to any intervention for a symptomatic pleural effusion could predict the presence of unexpandable lung and the subsequent relief of breathlessness; two clinical outcomes that are of great relevance to both patients and clinicians in determining longer-term management strategies, such as a decision to proceed with an attempt at chemical pleurodesis. 92 participants were recruited to this prospective observational study assessing whether any parameters included in a standardised in-depth thoracic ultrasound examination were associated with the outcomes of interest described above. A reduction in the excursion of atelectatic lung with cardiac pulse transmission, as measured by motion (M-) mode ultrasound, was associated with the presence of unexpandable lung; as were the presence of

anechoic pleural fluid and pleural fluid septations in a subsequent exploratory regression model. Future studies should explore these candidate parameters in greater depth with a view to validating an ultrasound-based model that can predict the presence of unexpandable lung prior to any pleural intervention, with potential implications for personalized care of patients with symptomatic pleural effusion.

The presence of extravascular lung water, for example in the form of pulmonary oedema secondary to congestive cardiac failure, is among the most common causes of breathlessness that may result in a patient presenting for medical treatment. The third study presented in this thesis assessed the ability of thoracic ultrasound to detect the presence of, and identify real-time changes in extravascular lung water in patients with end-stage renal failure undergoing haemodialysis. Computed tomography was utilized to provide a gold-standard radiologic reference test to correlate with the findings on thoracic ultrasound in this patient population. 30 participants were recruited to this prospective observational study, undergoing a standardised 20-point thoracic ultrasound examination to derive a total lung ultrasound B-line score before, during and after haemodialysis. The ultrasound scans were reported by the primary bedside operator and two independent assessors blinded to the participant's clinical status. The results suggest an association between a reduction in total B-line score and an increasing volume of fluid removed during haemodialysis, with potentially greater sensitivity to this physiological change in total body fluid status and extravascular lung water than computed tomography. Further research is needed to further evaluate the potential capability of thoracic ultrasound in both this controlled setting and other relevant clinical scenarios as a point-of-care diagnostic tool, with a view to how this might influence the management of acutely breathless patients and/or those with excess lung water.

PRIOR PUBLICATIONS

The studies presented in this thesis have been previously published in either abstract and/or manuscript form, in chronological order, as follows:

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Corcoran JP, Hallifax RJ, Yousuf A, Mercer RM, Asciak R, Hassan M, Psallidas I, Rahman NM (2017). P233 Thoracic ultrasonography as a predictor of pleurodesis success in malignant pleural effusion. *Thorax*; 72: A210. doi: 10.1136/thoraxjnl-2017-210983.375

Corcoran JP, Hallifax RJ, Mercer RM, Yousuf A, Asciak R, Hassan M, Piotrowska HE, Psallidas I, Rahman NM (2018). Thoracic Ultrasound as an Early Predictor of Pleurodesis Success in Malignant Pleural Effusion. *Chest*; 154(5): 1115-1120. doi: 10.1016/j.chest.2018.08.1031

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1. INTRODUCTION

Ultrasound has been used as a diagnostic tool in medicine for over sixty years (Donald, Macvicar, & Brown, 1958) but the decentralization of services away from radiology departments and into the hands of physicians at the patient's bedside is a more recent development (Edwards, 2010; Moore & Copel, 2011), primarily facilitated by changing technology as machines become smaller and more portable without compromising image quality.

The uptake of thoracic ultrasound by non-radiologists has been predominantly driven by two different agendas. Concerns regarding patient safety relating to pleural procedures reached a clinical nadir with the publication of a UK National Patient Safety Agency alert in 2008 (Lamont et al., 2009), highlighting the need for a change in practice given the extent of avoidable iatrogenic harm caused by blind pleural intervention. The subsequent acceptance that to perform a pleural procedure for suspected fluid without the use of ultrasound immediately beforehand is unsafe and almost indefensible has resulted in a generation of clinicians trained in and using ultrasound on a regular basis (Mayo et al., 2009; Sivakumar, Kamalanathan, Collett, & Ahmed, 2017; Williamson et al., 2017).

An increased familiarity with and access to ultrasound, alongside a recognition of the limitations of both physical examination and chest X-ray, has also encouraged clinicians to explore the possibilities that ultrasound offers as a diagnostic tool (Koenig, Narasimhan, & Mayo, 2011; Sperandeo et al., 2014). This has been most apparent in the critical care environment, where more traditional techniques of examination, investigation and diagnosis are frequently hindered by the characteristics of the patient population; and in the emergency department, where time and information are frequently limited, and a non-invasive tool that provides the clinician with instant feedback to guide urgent care will always be welcomed.

As thoracic ultrasound has become as essential a tool as the stethoscope in the management of patients with respiratory disease, the way clinicians work has

already changed and will inevitably continue to evolve. Developing a robust evidence base to underpin the expanding role that thoracic ultrasound fills in everyday practice is no less important than identifying the new areas where its use might enhance outcomes of interest to clinicians and patients alike.

1.1 Basic principles and evidence underlying the use of diagnostic lung ultrasound

Ultrasound of the lung is similar to that of other organs in that it relies on changes in and differences between the density of tissue through which high-frequency sound waves are propagated in order to generate images. Solid organs and soft tissue possess a close enough similarity in terms of the physical and acoustic properties of the different structures being examined to allow transmission of ultrasound waves to the required depth, whilst being sufficiently different to provide the necessary contrast in the images that are produced. However, the large difference in acoustic impedance between soft tissue (that is, a patient's chest wall) and air (a patient's lung) results in more than 99 percent of ultrasound energy being ordinarily reflected at this particular interface. This basic principle of ultrasound physics (Ziskin, 1993) represented for some time both an acoustic and cognitive barrier to meaningful sonographic examination of the lung for many practitioners.

Nonetheless, the concept that ultrasound might be able to differentiate between healthy and diseased lung tissue has been around for over forty years (Sagar et al., 1978) and has gained increasing credibility over the past two decades (Lichtenstein et al., 1997; Jambrik et al., 2004; Lichtenstein & Mezière, 2008). In contrast to other organs and soft tissue structures where the presence of ultrasound artefacts tends to detract from assessment of the desired images, diagnostic lung ultrasound is instead frequently and heavily reliant on the identification and interpretation of various sonographic artefacts (Soldati et al., 2019) that may be present or absent in health and disease. This need to rely on artefacts means the lung ultrasound operator must try to work with a raw unrefined image; the inbuilt noise reduction and smoothing software that many modern machines utilise routinely to enhance image acquisition can be to the very detriment of lung ultrasound interpretation

(Lichtenstein, 2007).

By extension of the basic principles outlined above these sonographic artefacts will usually arise at the interface between chest wall and lung, where parietal and visceral pleura make contact. In normal health the aerated lung immediately beneath the visceral pleura will reflect most ultrasound waves back to the transducer, which in turn will reflect some of these waves back into the chest again. This reverberation of ultrasound waves back and forth between transducer and the visceral-parietal pleural interface, also known as the pleural line, creates the artefact known as A-lines; these are seen on lung ultrasound images as horizontal lines below the pleural line that are spaced out at roughly the same distance as exists between the transducer and the pleural line. Any change in the characteristics of the lung tissue immediately beneath the visceral pleura, most frequently as a consequence of an increase in fluid content caused by a pathological state, will result in a change in sonographic appearance with artefact formation dependent on the extent to which the balance of air to fluid in the lung tissue has been disrupted. The presence of A-lines is not specific to aerated lung though since it is an artefact generated by the change in acoustic impedance between soft tissue and air; as such, a pneumothorax (that is, free air within the pleural space) will create the same effect.

Also seen at the pleural line in normal health is the sonographic phenomenon known as “lung sliding” (Lichtenstein & Menu, 1995), representing the real-time movement of visceral and parietal pleura over one another in synchrony with respiration. Lung sliding is usually most easily visualised towards the lung bases, where the anatomy of the lung and its greater expansion with inspiratory effort result in a proportionally increased range of movement in comparison to the apices (Mayo & Doelken, 2006; Lichtenstein, 2007). Proximity to the diaphragm also increases lung excursion in this anatomical region, and provides an easily visualised sonographic contrast that is manifest in the “curtain sign” where the lung expands during inspiration to obscure sub-diaphragmatic organs from view. The absence of lung sliding is most commonly associated by ultrasound practitioners with the

presence of a pneumothorax (Lichtenstein & Menu, 1995) which prevents direct apposition of visceral and parietal pleura, but it is not a sign unique to this condition. An absence of lung sliding will also be noted where the two pleural surfaces are adherent to one another, either as part of an acute (for example, pneumonia) or prior (for example, following chemical or mechanical pleurodesis) pleural inflammatory insult. An underlying lung parenchymal condition such as acute respiratory distress syndrome or chronic obstructive pulmonary disease (Slater et al., 2006; Mallow & Isakow, 2019); or poor examination technique with a failure of the operator to either orientate the transducer perpendicular to the pleural surfaces and/or turn off any inbuilt noise reduction software, may also confound the interpretation of lung sliding on ultrasound and result in a false positive diagnosis of, for example, pneumothorax being made.

Of the different sonographic artefacts that originate from the pleural line, it is B-lines that are of greatest interest in diagnostic lung ultrasound. This artefact is precisely defined as a discrete vertical hyperechoic line that arises from the pleural line, extends through the depth of the ultrasound image without fading, erases A-lines, and moves synchronously with lung sliding (Lichtenstein et al., 1997; Volpicelli et al., 2012). Whilst B-lines are also seen in normal healthy lung, the presence of more than two B-lines in a sonographic field of view between two adjacent ribs is considered pathological. It is therefore of equal interest that our understanding of how sonographic B-lines are generated at an anatomical level within abnormal lung tissue remains imprecise (Soldati, Copetti & Sher, 2009; Volpicelli et al., 2012), with the most likely explanation being that they represent a reverberation artefact created by the interaction between aerated alveoli and adjacent fluid-filled interlobular septae (Lichtenstein et al., 1997).

The presence of pathological B-lines on lung ultrasound can be further distinguished by describing their distribution as either diffuse or localised with respect to the wider lung fields being examined, and either homogeneous or non-homogeneous with respect to the single sonographic field of view (Volpicelli et al., 2012). This in turn allows the differential diagnosis to be narrowed and sonographic findings

integrated with the clinical information available to identify the most likely underlying pathology. The label “interstitial syndrome” is specifically used to describe a range of conditions that are defined by an excess of B-lines distributed in a diffuse bilateral manner on lung ultrasound; these include pulmonary oedema, interstitial pneumonia, and diffuse parenchymal lung disease. Given the dynamic nature of pulmonary oedema in particular, there has been specific interest in correlating the presence of pathological B-lines with other measures of pulmonary congestion and fluid overload such as pulmonary artery occlusion pressure and transpulmonary thermodilution (Agricola et al., 2005; Lichtenstein et al., 2009; Volpicelli et al., 2014). These studies, restricted to a critical care population given the invasive nature of the other measurements being taken, have shown some limited success for lung ultrasound in comparison to these other gold-standard physiologic tests when excluding the presence of interstitial oedema; there is, however, less evidence as to how lung ultrasound might perform in this setting with changing fluid status over time and in a healthier patient population. The fact that the interstitial syndrome encompasses a diverse range of conditions also highlights the risk that concomitant pathology, such as cardiogenic pulmonary oedema and interstitial lung disease, may act as co-confounders when evaluating the diseased lung using ultrasound.

1.2 The burden of malignant pleural disease

Malignant pleural effusion is an increasingly common problem, with an estimated 50,000 new cases identified in the United Kingdom on an annual basis (Clive et al., 2014; Roberts et al., 2010), and regarded as a marker of advanced malignant disease. Furthermore, with an aging population and more patients with metastatic cancer surviving long-term (Maddams, Utley, & Møller, 2012), the number of patients with malignant pleural effusion seen by physicians is expected to continue rising consistently year-on-year. The majority of patients with malignant pleural effusion develop disabling symptoms including breathlessness and chest pain (Roberts et al., 2010) and require drainage of the excess fluid to relieve these symptoms. However, in most cases the fluid subsequently recurs, and definitive treatment is required. This commonly involves drainage of the fluid and

introduction of a chemical irritant sclerosing agent, usually sterile talc, into the pleural space to generate an inflammatory response, formation of fibrotic pleural adhesions, and ultimately obliteration of the pleural space (Roberts et al., 2010; Shaw & Agarwal, 2013) to prevent the future re-accumulation of fluid.

At present this process of pleurodesis is most frequently conducted using a talc slurry technique, whereby an intercostal chest drain is first inserted in order to drain the offending effusion over a 24- to 48-hour period, before instilling the talc (mixed with normal saline to form a slurry) into the now dry pleural space via the same chest drain. The chest drain is then left in-situ for a further period of time, normally 24 to 72 hours, as it is thought that talc administration may increase pleural fluid production through an inflammatory response and early drain withdrawal may result in immediate fluid recurrence and ultimate failure of the visceral and parietal pleural surfaces to opposed and permanently adhere.

There is little evidence to guide clinicians on the optimal timing of talc slurry instillation following chest drain insertion and drainage of a malignant pleural effusion, although it is widely assumed to be once the fluid output has fallen sufficiently and a chest X-ray suggests the pleural space is “dry” with adequate re-expansion of the underlying lung (Roberts et al., 2010). There is a similar lack of data to indicate when it might be appropriate to remove a chest drain after the talc has been administered intrapleurally; only one randomized trial addressing this issue has been published (Goodman & Davies, 2006), which showed no difference in primary outcome (pleurodesis success at one month) when comparing chest drain removal at 24 hours and 72 hours following talc slurry instillation. However, the study was underpowered, designed as a superiority rather than non-inferiority study, and utilized a radiological measure of pleurodesis success in isolation.

Talc slurry pleurodesis has a reported success rate of 60-70% in various randomized studies (Roberts et al., 2010; Shaw & Agarwal, 2013) and is associated with a modest cost with respect to medical equipment. However, the technique requires the patient to remain in hospital for the duration of the drainage and subsequent

pleurodesis; with recent randomized studies reporting a median inpatient stay of between four and ten days (Davies et al., 2012; Rahman et al., 2015; Thomas et al., 2017). This imposes a significant financial burden on healthcare providers, and a human cost for the individual involved. Patients with malignant pleural effusion have a limited life expectancy, with a median survival quoted at between 3 and 12 months (Clive et al., 2014; Roberts et al., 2010). As a result, minimizing the length of hospital stay associated with any treatment for a symptomatic malignant pleural effusion is a priority for both patients and clinicians.

1.3 Unexpandable lung

Although breathlessness is the most common symptom associated with pleural effusions, patients may have a variable and unpredictable response to medical intervention. Two recent prospective studies of patients undergoing therapeutic drainage for either malignant pleural effusion (Mishra et al., 2015), or effusions of all causes (Psallidas et al., 2017), both reported that around 15% of patients experienced either no improvement or a worsening of breathlessness following their procedure. One possible explanation for this variability in symptomatic response is the prior unidentified presence of unexpandable lung.

Unexpandable lung is reported to be present in around 30% of patients presenting to healthcare services with a significant pleural effusion requiring diagnostic and/or therapeutic intervention (Divietro et al., 2011; Dresler et al., 2005). The term describes a clinical situation in which the lung is restricted by a pathological process that leaves it unable to fully expand to allow apposition of the visceral and parietal pleural surfaces; this in turn creates a potential space for the recurrent accumulation of pleural fluid. It also means that any attempt to form a pleurodesis is likely to be futile; either as a result of insufficient pleural apposition to allow adhesion formation, or the inherent tendency of the affected lung to recoil from the chest wall. Unexpandable lung arises in the setting of either trapped lung or lung entrapment (Huggins et al., 2018); terms that sound similar but describe distinct processes that are generally distinguished by the timing of any insult to the pleura relative to the clinical presentation, and whether there is evidence of an ongoing

inflammatory response. Early recognition of the latter feature, more commonly associated with lung entrapment secondary to active pleural infection or malignancy, may allow longer-term resolution if the underlying process can be treated successfully. In contrast, identifying features in the clinical history that point to a long-standing process in an asymptomatic patient referred with an effusion diagnosed incidentally on radiologic tests done for other reasons, may allow the clinician to avoid excessive and unnecessary investigation of a persistent unexplained effusion that was secondary to chronic trapped lung.

Pragmatically though, the clinical problems that arise at initial presentation as a result of unexpandable lung are broadly similar regardless of the underlying cause, and present clinicians with several challenges. Any effusion associated with unexpandable lung is liable to recur quickly as a result of the potential space caused by the failure of the lung to expand and replace any fluid that has been removed. The symptomatic benefit from draining an effusion secondary to unexpandable lung can be highly variable, particularly if there are features to suggest chronicity of the fluid in the context of a temporally remote pleural insult that is likely to have resulted in trapped lung developing over time, and subsequent adaptation of ipsilateral chest wall and diaphragm mechanics. Indeed, the excessive drainage of pleural fluid in the context of unexpandable lung may worsen a patient's condition as the resultant negative intrapleural pressure can cause distressing symptoms including chest pain, intractable cough, and worsened breathlessness as a result of re-expansion pulmonary oedema.

This results in a situation in which clinicians have no robust prospective means of predicting which patients presenting with a large pleural effusion might have unexpandable lung, and which patients will benefit symptomatically from pleural drainage. Currently available strategies rely on the patient having an initial invasive pleural intervention, usually large-volume thoracentesis, to allow the use of either pleural manometry to demonstrate an abnormal elastance curve (Feller-Kopman, 2013) as fluid is removed, and/or post-drainage imaging (chest X-ray or computed tomography) to identify pneumothorax ex-vacuo; thereby confirming a diagnosis of

unexpandable lung. A non-invasive means of identifying those patients with pleural effusions who have unexpandable lung, and/or would benefit symptomatically from drainage of their fluid, would have a significant impact by allowing clinicians to select at an earlier stage the most appropriate management pathway and inform patients of the likely outcome of any intervention.

1.4 Thoracic ultrasound as an outcome prediction tool in pleural disease

There is a robust evidence base demonstrating the efficacy and utility of thoracic ultrasound in the hands of trained physicians (Hammerschlag et al., 2017; Rahman et al., 2010), predominantly focused on its use as an adjunct to percutaneous transthoracic interventions to both reduce the risk of iatrogenic complications (Duncan, Morgenthaler, Ryu, & Daniels, 2009; Mercaldi & Lanes, 2013) and improve diagnostic yield (Diacon et al., 2004; Hallifax et al., 2014; Laursen et al., 2016). There is also data describing the diagnostic capabilities of thoracic ultrasound in separating out malignant from benign pleural disease prior to these same interventions (Bugalho et al., 2014; Qureshi, Rahman, & Gleeson, 2009). Fewer data exist, however, to inform patients and clinicians as to the longer-term outcomes of procedures being performed primarily for therapeutic purposes; that is, with the relief of symptoms such as breathlessness in mind.

The physiology underpinning the development of breathlessness with pleural effusions, and its subsequent relief following drainage of fluid is poorly understood. Published data imply that any improvement in gas exchange is unlikely to be of relevance; most patients with pleural effusions are not hypoxaemic at presentation, and indeed some may transiently drop their oxygen saturations in the immediate aftermath of a large-volume thoracentesis (Brandstetter & Cohen, 1979; Karetzky, Kothari, Fourre, & Khan, 1978; Perpina et al., 1983). Changes in ventilatory capacity and lung volumes are similarly insufficient to explain the improvement in symptoms reported by patients following pleural drainage (Brown, Zamel, & Aberman, 1978; Light, Stansbury, & Brown, 1986).

Instead, the most widely accepted theory is that an effusion, and the accompanying

increase in intrapleural pressure and thoracic volume, causes disruption to the normally efficient mechanics of the chest wall muscles and diaphragm. The resulting neural feedback is responsible for the sensation of breathlessness, subsequently relieved by drainage of the fluid and restoration of normal function to the thoracic cage structures. As a result, there has been interest in whether sonographic assessment of diaphragm function, and in particular the identification of either inversion and/or paradoxical motion, can predict a likely improvement in breathlessness following large-volume thoracentesis. Studies in this area have thus far been heterogeneous with respect to design, measurement of outcome, and interventions undertaken; and recruited small numbers of patients with mixed results as a consequence (Estenne, Yernault, & De Troyer, 1983; Garske et al., 2018; J.S. Wang & Tseng, 1995; L.M. Wang, Cherng, & Wang, 2007).

The presence of unexpandable lung may also impact on a patient's likely response to pleural intervention. A recent proof of concept study (Salamonsen et al., 2014) has looked at whether an advanced ultrasonographic assessment of patients with pleural effusion could identify the presence of unexpandable lung before any invasive procedure is performed. This focused on the hypothesis that unexpandable lung would have restricted movement within an effusion, and therefore be less likely to transmit the cardiac impulse. Motion (M-) mode ultrasound and speckle tracking imaging analysis were used to measure tissue displacement and deformation in the lung tissue underlying an effusion at functional residual capacity; with pleural manometry performed during subsequent thoracentesis to allow the calculation of pleural elastance according to previously established methodology (Feller-Kopman, 2013). The diagnosis of unexpandable lung was made thereafter by two clinicians using post-drainage radiology and any available clinical information. The results suggested that both speckle tracking and M-mode ultrasound outperformed pleural manometry in the diagnosis of unexpandable lung; however, these findings are yet to be replicated in a separate study, require an ultrasound skill set and software analysis that are likely to be outside most clinicians' everyday practice, and did not collect data on patient-reported outcomes following pleural intervention.

There are limited data relating to outcome prediction following the intrapleural administration of talc for malignant pleural effusion, even though pleurodesis by this method fails in around 30% of patients. Previous work has identified only pleural pH as a possible biomarker for prediction of long-term pleurodesis success with modest results (Heffner, Nietert, & Barbieri, 2000), whilst a recent large multi-cohort analysis failed to identify any pleural fluid biomarkers of interest (Psallidas et al., 2018). In the absence of a prospective test that predicts success prior to intrapleural administration of talc, the next best thing would be a test that identifies likely success or failure as early as possible following treatment.

Studies in animal and human subjects suggest that thoracic ultrasound can detect the presence of pleural adhesions, thought to be a central step in the development of long-term pleurodesis, via the loss of the normal “lung sliding” sign. Work in an experimental rabbit model of chemically-induced pleurodesis demonstrated a strong correlation between a thoracic ultrasound scoring system assessing lung sliding and the development of a successful pleurodesis as determined by the post-mortem identification of pleural fibrosis (Zhu et al., 2005). Human studies using thoracic ultrasound to detect the presence of pleural adhesions either prior to thoracic surgical intervention (Cassanelli et al., 2012; Sasaki et al., 2005) or following surgical pleurodesis in the context of recurrent pneumothorax (Leo et al., 2005) have shown this technique to be feasible and of potential clinical utility. It is important to recognize, however, that both animal (Zhu et al., 2005) and human (Leo et al., 2005) studies used thoracic ultrasound to evaluate lung sliding at a delayed interval – that is, two and four weeks – post-intervention. This makes it impossible to ascertain the precise timing of any change in sonographic appearances and, by extension, the ability to use thoracic ultrasound to influence a treatment pathway for patients undergoing an attempt at pleurodesis for any clinical indication. For thoracic ultrasound to have a meaningful impact on patient care and clinical decision making, particularly with respect to any potential reduction in length of hospital stay, it would need to be capable of identifying a signal relevant to long-term outcome as early as possible following any therapeutic intervention. There are no data either to support the use of thoracic ultrasound as

a predictive tool or clinical decision-making adjunct in the context of talc pleurodesis for malignant pleural effusion specifically.

1.5 Thoracic ultrasound in the assessment of extravascular lung water

Patients with breathlessness and/or respiratory failure represent a significant and increasing proportion of admissions to emergency departments and acute medical units (Ray et al., 2006; Stefan et al., 2013), and commonly require rapid treatment with limited information available to guide the attending clinician. The range of diseases that can present with acute breathlessness is broad and difficult to differentiate clinically in a time-pressured environment and the context of a patient group who often have multiple medical co-morbidities potentially responsible for their symptoms. This can lead to non-specific treatment directed at all possibilities in the presence of diagnostic uncertainty, with the associated risks of treatment complications and poor outcomes in a patient population with limited physiological reserve (Ray et al., 2006).

Thoracic ultrasound represents a potentially paradigm changing opportunity in the assessment of patients with acute breathlessness, with particular interest in its ability to differentiate cardiogenic pulmonary oedema from other conditions that can present with similar symptoms (Al Deeb et al., 2014; Maw et al., 2019). The utility of thoracic ultrasound in this setting relies on the concept of extravascular lung water; using the presence, number and pattern of B-lines on lung ultrasound as a surrogate marker for pulmonary oedema (Jambrik et al., 2004; Lichtenstein et al., 1997). This utilizes the principle that whilst ultrasound waves are normally reflected by aerated lung, creating the horizontal reverberation artefacts known as A-lines, in the setting of pulmonary oedema the congested interstitium results in the creation of vertical B-lines extending from the pleural interface that increase in number and density as the condition worsens. This is not a phenomenon specific to pulmonary oedema though, with an excess of B-lines on thoracic ultrasound also seen in other pathological processes including interstitial lung disease and acute respiratory distress syndrome (Lichtenstein et al., 1997); as a result, the findings on ultrasound examination must be integrated with other clinical information before

coming to a final diagnosis.

Despite the publication of consensus guidelines on the use of point-of-care lung ultrasound (Volpicelli et al., 2012) and the potential for important diagnostic and therapeutic gains, there remains a shortage of evidence and physiological data to better define the role of thoracic ultrasound in either evaluating extravascular lung water, or as part of a wider diagnostic approach to the breathless patient. A landmark paper (Lichtenstein & Mezière, 2008) frequently cited in the literature around point-of-care lung ultrasound described an algorithm of assessment in patients with respiratory failure in the critical care setting, defining patterns of ultrasonographic appearance for various diagnoses and reporting a sensitivity of 97% and specificity of 95% for cardiogenic pulmonary oedema. However, the primary outcome comparing diagnostic accuracy of the scan to final discharge diagnosis from the intensive care unit was open to bias with the assessors responsible for making these two different diagnoses being neither blinded nor independent; whilst patients with difficult or uncertain diagnoses, those in whom ultrasound may have the greatest potential benefit and making up approximately 14% (40/301) of those patients originally recruited to the study, were excluded from the final analysis. As such, it is difficult to know how the outcomes measured could be extrapolated to a wider clinical setting.

Recognizing the challenges involved in the detailed evaluation of an unselected population of patients with acute breathlessness, a study of thoracic ultrasound was undertaken in patients with end-stage renal failure undergoing haemodialysis with the intention of demonstrating the correlation between changing fluid status and the presence of extravascular lung water, indicated by the number of B-lines visualized at different timepoints of the dialysis session (Noble et al., 2009). This physiological study had encouraging results but limitations including a failure to blind individuals reporting the ultrasound scans to clinical information, and a lack of an alternative gold-standard radiologic or physiological test for reference; a recurrent problem when trying to assess the strength of the evidence base for thoracic ultrasound in this area of clinical practice (Hew et al., 2015). Similar work

from a separate group (Mallamaci et al., 2010) improved on the previous study's methodology by utilizing multiple scorers, but again lacked a reference radiologic test and only included a limited evaluation of reproducibility of ultrasound scoring between different observers. A better understanding of how B-lines on lung ultrasound relate to fluid status and correlate with other measures already used to monitor any response to treatment, such as body weight in patients on renal replacement therapy or being diuresed for heart failure, could in the longer term facilitate further studies addressing whether ultrasound-guided management of fluid balance improves morbidity and mortality in these populations.

2. METHODS

2.1 Thoracic ultrasound as an early predictor of pleurodesis success in malignant pleural effusion

As specified in the introduction, there are data from both animal and human studies suggesting that thoracic ultrasound can detect the presence of pleural adhesions via the loss of the normal “lung sliding” sign. However, there are no data to support the use of thoracic ultrasound as a clinical decision-making adjunct in the context of chemical pleurodesis for malignant pleural effusion. A feasibility study was therefore planned to determine whether an ultrasound evaluation similar to that performed in animal studies (Zhu et al., 2005) could be replicated in and prove acceptable to human subjects; that a similar large-scale study would be deliverable in this patient population; and to test the hypothesis that this thoracic ultrasound evaluation could be utilized to detect the early formation of pleural adhesions and therefore potentially predict the successful development of a long-term pleurodesis following talc slurry instillation for the management of malignant pleural effusion.

2.1.1 Objectives and Outcome Measures

The primary objective of the study was to assess the ability of a pre-defined thoracic ultrasound scoring system to predict short- (one month) and longer-term (three month) success of pleurodesis following talc slurry instillation for the management of malignant pleural effusion.

The primary outcome measure was the mean pleural adherence score as determined by a pre-defined thoracic ultrasound assessment in patients with and without clinico-radiological confirmation of pleurodesis success at one- and three-month follow-up. Pleurodesis failure was defined as the symptomatic recurrence of pleural fluid in the ipsilateral hemithorax requiring further intervention at any point up to three months following talc slurry instillation, in association with radiological evidence (on chest X-ray, computed tomography, and/or thoracic ultrasound) of pleural fluid recurrence. Consistency of the diagnosis of pleurodesis failure was

ensured through independent assessment of each individual participant's study data by two respiratory physicians, neither of whom were directly involved in the participant's clinical care or original study data collection. In the event of any disagreement occurring between these two independent assessors, a third respiratory physician was available to provide a deciding vote.

Secondary objectives of the study were: (a) to assess patient satisfaction with thoracic ultrasound assessment; and (b) to assess the potential of thoracic ultrasound assessment to facilitate earlier discharge from hospital following talc slurry instillation.

The secondary outcome measures were: (a) measurement of patient satisfaction using visual analogue and Likert-type scales; and (b) comparison of a hypothetical discharge date based on thoracic ultrasound findings with the actual discharge date (or date when the patient was defined as being medically suitable for discharge, pending social care arrangements, if sooner) based on standard clinical care.

2.1.2 Study Design

The study was designed as a prospective observational cohort feasibility study, recruiting at a single site. Participants were screened from referrals made to the Oxford Centre for Respiratory Medicine and Pleural Disease Unit by the clinicians responsible for this service (including the study's Chief Investigator and Study Coordinator by necessity as part of usual clinical practice), and from patients directly admitted to the respiratory medicine ward(s) within Oxford University Hospitals NHS Foundation Trust. As this was a feasibility study, a power calculation to determine the number of patients needed to recruit to detect a significant difference between the two populations (that is, those who had a successful and those who had a failed pleurodesis) was not undertaken.

Patients were invited to take part in the study on the day it was determined that it was clinically appropriate to carry out talc slurry instillation, having already undergone drainage of a malignant pleural effusion via intercostal chest drain (12

French per usual local practice). The decision to proceed with talc slurry instillation and whether or not suction should be applied thereafter was made by the patient's responsible inpatient medical team, independent of the study team and based on standard clinical guidelines followed by clinicians working within Oxford University Hospitals NHS Foundation Trust and that had been written in line with pre-existing national recommendations (Roberts et al., 2010). Patients were provided with written information relating to the study and an appropriate period of reflection before being asked to consent to study participation. Informed written consent was obtained in line with GCP standards, following which a unique participant study identification number was issued by the study management team. This identification number was then used to complete all study-related documentation, including any other material related to the study such as radiological images.

Study participants were reviewed as an inpatient for study purposes for up to three days following talc slurry instillation, or until the day of their discharge from hospital (whichever was sooner). Follow-up for study purposes was carried out at pre-defined timepoints to fit with the study's primary objective, either at hospital visits which were planned as part of usual clinical care or via telephone if the former was not going to be achievable in a timely fashion.

2.1.3 Study Management and Oversight

The study was sponsored by the University of Oxford, and managed through the University of Oxford Respiratory Trials Unit. A study management group comprising the Chief Investigator, Study Coordinator, and Senior Clinical Trials Manager was responsible for all aspects of the study including recruitment, protocol compliance, and ensuring appropriate measures were in place to safeguard study participants and the overall quality of the study. As a low-risk observational feasibility study, neither an independent steering committee nor a data monitoring committee were deemed unnecessary.

The study was registered on a freely accessible registry of clinical trials and studies (www.clinicaltrials.gov – registration number NCT02625675). The study protocol

and subsequent amendments were approved by the UK National Research Ethics Service (reference 15/LO/0382).

2.1.4 Study Participants

Adults (≥ 18 years old) undergoing drainage of a malignant pleural effusion and subsequent talc slurry instillation via an intercostal chest drain as part of their routine planned clinical care were considered for study participation.

The diagnosis of a malignant pleural effusion was made clinico-radiologically, defined as a collection of excess pleural fluid seen in the context of (a) histologically proven malignancy within the pleural space; (b) macroscopic features of malignant pleural disease on previous thoracoscopy; (c) malignancy at a site distal from the thorax as proven either histo-cytologically or radiologically; and/or (d) pleural malignancy diagnosed on computed tomography with a concurrent consistent clinical history.

Inclusion criteria were:

1. Fully informed consent for study participation.
2. Diagnosis with a malignant pleural effusion requiring intercostal chest drain insertion and deemed suitable, on the basis of post-drainage radiology and clinical assessment, for subsequent talc slurry instillation for symptom relief and/or other therapeutic purposes as part of routine clinical care.

Exclusion criteria were:

1. Age less than 18 years.
2. The inability to provide informed consent.
3. A known hypersensitivity or allergy to medical talc, or other contraindication to the administration of intrapleural talc, as determined by the responsible clinician.
4. Evidence of significant unexpandable lung that would prevent a successful pleurodesis from developing following talc slurry instillation, as determined by the responsible clinician.

5. An expected survival of less than one month due to underlying co-morbidities.

2.1.5 Study Procedures

An enrolment case report form was completed for all study participants, collecting a standardised data set to include demographics, past medical history, current medications, and the underlying clinical diagnosis for the malignant pleural effusion. Talc slurry instillation via intercostal chest drain was carried out by the study participants' responsible medical inpatient team, according to standard clinical guidelines used within Oxford University Hospitals NHS Foundation Trust. Details of talc slurry instillation including the use of pre-medication or analgesia, dose of talc, and side-effects or complications of the procedure were also recorded as part of the enrolment case report form.

All study participants underwent a bedside brightness (B-) mode thoracic ultrasound assessment immediately prior to (day 0) and 24 hours after (day 1) talc slurry instillation. An early timepoint for thoracic ultrasound assessment following talc slurry instillation in comparison to previously published studies (Zhu et al., 2005; Leo et al., 2005) was deemed necessary in order to ascertain whether an early signal of long-term pleurodesis success might be identifiable, and to allow in turn a meaningful assessment of whether the use of thoracic ultrasound to guide chest drain management might have a meaningful impact on a patient's length of hospital stay. Thoracic ultrasound assessments were carried out by a member of the study team and documented on an ultrasound case report form, independent of the participant's responsible medical inpatient team who remained blind to any findings. Thoracic ultrasound assessment was a standardised examination scoring lung sliding in nine zones (upper, middle, and lower zones in the anterior, lateral, and posterior chest wall) across the affected hemithorax. A standard abdominal curvilinear transducer (3-6 MHz) was used for image acquisition. Lung sliding was scored by the primary ultrasound operator in real-time at the patient's bedside as present (=0), questionable (=1), or absent (=2) in each zone per previously published data (Zhu et al., 2005), generating a total pleural adherence score for the

hemithorax being assessed. Ultrasound clips (6-10 seconds in duration, to include at least two full respiratory cycles) were recorded concurrently to facilitate remote scoring by two independent assessors not involved in the original bedside ultrasound scoring and blinded to the study participants' clinical status. The presence of any residual pleural fluid was also documented as part of the thoracic ultrasound assessment, including details of the size (based on the number of rib spaces where pleural fluid was visible, and the maximum depth of the effusion measured in cm) and characteristics (including echogenicity and presence of septations) of this residual fluid. The time taken to perform each thoracic ultrasound examination was recorded to permit a basic assessment of practical deliverability in real-life clinical practice. All ultrasound scorers (primary and blinded) held Royal College of Radiologists level 1 accreditation in thoracic ultrasound (The Royal College of Radiologists, 2017) as a minimum standard.

All study participants were asked to complete a questionnaire relating to their experience and satisfaction with thoracic ultrasound assessment prior to their discharge from hospital. This included a visual analogue scale score of pain caused by thoracic ultrasound examination (0-100 mm, with no pain at 0 mm and worst possible pain at 100 mm), and an assessment of understanding and willingness to have thoracic ultrasound assessment again in future for these purposes measured using a Likert-type scale.

The decision to remove the intercostal chest drain following talc slurry instillation was made by the study participants' responsible medical inpatient team, independent of the study team and according to British Thoracic Society recommendations (Roberts et al., 2010) adapted for local practice.

Study follow-up took place at 1 and 3 months post-pleurodesis, or until death if sooner. Study participants were assessed for evidence of pleurodesis failure, using the objective criteria specified elsewhere in the study methodology (section 2.1.1).

2.1.6 Safety Reporting

No significant safety concerns were anticipated in relation to any study-specific procedures or measurements. The key study intervention (that is, thoracic ultrasound examination) was not expected to present any additional risk to study participants or result in any complications as a non-invasive test. As such no specific safety outcome monitoring was felt to be required. Nonetheless, the pleural procedures (intercostal chest drain insertion, and talc slurry instillation) to be carried out as part of the study participants' normal clinical care could be associated with potential complications that would be discussed as part of the standard informed consent process. As such, adverse events or complications related to these procedures carried out as part of normal clinical care were recorded on study adverse event forms; these were not, however, subject to normal reporting timelines and were reviewed at the end of the study by the study management group.

2.1.7 Data Management

Study data were stored on an electronic data capture system based around a fully licensed enterprise version of OpenClinica, with support services provided by OpenClinica LLC. The study database was bespoke and hosted on a secure server provided by the University of Oxford. Data were stored in line with ICH-GCP standards and data protection principles. Data monitoring and validation processes were carried out internally to ensure appropriate integrity and quality of the data according to University of Oxford Respiratory Trials Unit standard operating procedures both during and at the end of the study.

2.1.8 Statistical Analysis

A statistical analysis plan was written and agreed before any data were assessed or analyzed. In brief, the baseline characteristics of study participants would be described including basic demographics and clinical features including the underlying primary malignancy and LENT score (Clive et al., 2014).

The study's primary analysis explored whether a difference in the mean total pleural adherence score, as determined by a standardised nine-point thoracic ultrasound examination, could be identified either immediately prior to and/or at 24 hours post-talc slurry instillation between those patients who went on to have a successful pleurodesis and those whose pleurodesis failed according to the study definition. A total pleural adherence score as determined on thoracic ultrasound would be calculated for day 0 (pre-talc slurry instillation) and day 1 (24 hours post-talc slurry instillation) for each participant, with scores available from the original primary scorer, and two independent blinded scorers. The mean total pleural adherence score as ascertained from the ultrasound data for those patients with successful versus failed pleurodesis would be analysed first for the individual scorers (that is, the primary operator and the two blinded assessors), and then as a combined dataset. An area under the receiver operating characteristic (ROC) curve for would also be reported for the combined ultrasound dataset at day 0 and day 1 with the aim of determining a potential cut-off adherence score to facilitate subsequent chest drain removal. An arbitrary specificity of 90% for long-term pleurodesis success was chosen in order to ensure confidence in any future study that might use this cut-off value to guide the decision to remove a chest drain earlier than might have been the case in ordinary clinical circumstances. The consistency of ultrasound scoring between the three assessors would be compared for both the total pleural adherence score and at individual anatomical points.

It was recognized that the nature of the patient population being studied meant that some study participants might not survive to the pre-specified follow-up points; that is, 1- and 3-months following recruitment and talc slurry instillation. For any study patient who failed to survive to the earlier 1-month follow-up point, their baseline ultrasound data and subsequent clinical outcome would be described but otherwise not included in the final detailed primary analysis.

For the secondary analyses, the cut-off total adherence score identified from the ROC curve would be used to determine how many patients could have had their chest drain removed early (that is, 24 hours following talc slurry instillation) to

facilitate discharge and the potential saving in hospital bed days in comparison to standard care. Data pertaining to patient satisfaction with ultrasound examination would be reported in a descriptive manner.

IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, New York) was used for statistical analyses. *t*-tests were used for parametric data, and Fisher's exact test for categorical variables. A *p*-value of <0.05 was considered significant. Interrater reliability was calculated using the intraclass correlation coefficient for continuous variables, and using free-marginal kappa for categorical data. Descriptive statistics were used to summarize patient characteristics.

2. METHODS

2.2 Thoracic ultrasound as a predictor of unexpandable lung and symptomatic improvement prior to pleural intervention

As specified in the introduction there are a significant minority of patients with pleural effusions and breathlessness who have unexpandable lung, or will not benefit symptomatically from having their fluid drained. This can result in patients requiring multiple pleural procedures prior to definitive treatment for their effusion, or having a procedure without any hope of improvement in their breathlessness. A feasibility study was therefore planned to evaluate whether an in-depth thoracic ultrasound examination prior to pleural intervention was deliverable in the context of a real-life and busy clinical service; and could identify any sonographic features associated with pleural effusions that would predict either the presence of unexpandable lung, or the patient's symptomatic response to drainage, via an analysis of data collected prospectively in routine clinical practice. This same data might in turn allow hypothesis generation for testing in future research studies.

2.2.1 Study Population

Study data were collected prospectively from adult patients (≥ 18 years old) being assessed with thoracic ultrasound as part of their routine clinical care immediately prior to a diagnostic and/or therapeutic pleural intervention, under the care of the Pleural Disease Unit at the Oxford Centre for Respiratory Medicine, over a 15-month period (February 2016 to May 2017). The inclusion of patients was non-consecutive and based on a convenience sampling approach, being dependent on when there was a suitable ultrasound practitioner available to carry out the in-depth examination and the confines of the clinical service. Patients were considered suitable for inclusion in the study when there was a unilocular pleural effusion and an expectation that ≥ 500 mL of pleural fluid would be drained during the subsequent intervention; and they could provide fully informed written consent for the pleural procedure being performed. As this was a feasibility study, a power

calculation to determine the number of patients needed to detect a significant difference on sonographic examination between the two patient populations of interest (that is, those with expandable versus those with unexpandable lung) was not undertaken.

The activity to be undertaken was discussed with the local institutional governance body (Oxford Joint Research Office, covering both the University of Oxford and Oxford University Hospitals NHS Foundation Trust) prior to any data collection commencing and approved as part of service development and evaluation, and therefore not subject to the requirement for further research ethics review or governance. This was justified on the grounds that thoracic ultrasound examination was already performed routinely as standard of care in all patients undergoing pleural intervention within the clinical service. Many of the ultrasound parameters being recorded and analysed for this study were already documented as part of the standardised ultrasound reporting template used by the clinical service; and the additional ultrasound parameters being collected (that is, the use of motion (M-) mode to evaluate the atelectatic lung underlying any pleural fluid) were established from prior published data (Salamonsen et al., 2014) with one goal of this study being to see if examination for these specific sonographic features was deliverable in a real-life clinical setting.

2.2.2 Thoracic ultrasound protocol

A standardised in-depth thoracic ultrasound examination (**figure 1**) was performed immediately prior to pleural intervention by a respiratory physician holding Royal College of Radiologists level 1 accreditation in thoracic ultrasound (The Royal College of Radiologists, 2017) as a minimum standard. Ultrasound images were acquired with a standard abdominal curvilinear transducer (3-6 MHz) and ultrasound machine used for routine interventional pleural work within the department (HiVision Avius, Hitachi Medical Systems Europe), and saved on a local hard drive per usual practice and quality assurance requirements.

Ultrasound data recorded included both static and dynamic features characterizing the effusion and surrounding thoracic anatomy as described previously (Qureshi, Rahman, & Gleeson, 2009), alongside M-mode evaluation of the underlying atelectatic lung within an effusion using a technique similar to that described in previous work (Salamonsen et al., 2014). In brief, the M-mode evaluation was performed with the ultrasound probe placed on the patient's posterolateral chest wall at the level of the diaphragm and oriented to lie within a single rib space. The probe was then moved superiorly from one rib space to the next until atelectatic lung could be clearly visualized within the pleural fluid. The probe angle was oriented to ensure the M-mode cursor was kept perpendicular (or close to as possible) to the area of atelectatic lung tissue being assessed. M-mode measurements of atelectatic lung excursion with cardiac pulse transmission were then taken during both end-tidal inspiratory (at approximately total lung capacity less inspiratory reserve volume) and expiratory (at approximately functional residual capacity) breath hold manoeuvres.

Septations were defined as hyperechoic lines within the pleural collection, with these fibrin strands forming a weblike or branching pattern as described in prior literature (Yang et al., 1992). The presence of septations within the pleural collection was specifically assessed per previous published data (Psallidas et al., 2017) at the point of maximal septation identifiable on ultrasound examination of the relevant hemithorax; and scored as either absent (no septations), mild (1-2 septations), moderate (3-4 septations) or severe (≥ 5 septations in a single ultrasound field of view).

All thoracic ultrasound data and measurements were acquired and documented in real-time by the primary operator. The subsequent pleural intervention was then performed and documented in the patient's clinical record per usual standards of care; this data included demographics, volume of pleural fluid drained, and any procedural complications.

Figure 1 Copy of the case report form used by clinicians to document their findings on standardised in-depth thoracic ultrasound examination




Detailed thoracic ultrasound assessment

Please complete this assessment for all patients who are expected to undergo large volume pleural drainage (>500mL fluid).

Patient MRN: _____

Procedure Date: _____

Procedure Type: _____

Ultrasonographer(s): _____

PLEURA & FLUID:

Side of procedure: ☐ Right ☐ Left

Size of effusion: ☐ Small ☐ Moderate ☐ Large

Maximum depth: _____ cm ☐ Anterior ☐ Lateral ☐ Posterior

Septations: ☐ None ☐ Mild ☐ Moderate ☐ Severe

☐ Heterogeneous ☐ Homogeneous

Echogenicity: ☐ Anechoic ☐ Echogenic

Parietal thickening: ☐ No ☐ Yes _____ mm thickness

☐ Anterior ☐ Lateral ☐ Posterior

Nodularity: ☐ No ☐ Parietal ☐ Diaphragmatic

Diaphragm motion: ☐ Normal ☐ Paradoxical

LUNG:

Lung consolidation: ☐ No ☐ Yes

☐ Anterior ☐ Lateral ☐ Posterior

Soft tissue mass: ☐ No ☐ Yes _____ cm diameter

Visceral thickening: ☐ No ☐ Yes _____ mm thickness

Version 1.0 10th September 2015




Targeted assessment of ipsilateral lower lobe of lung

Identify the diaphragm posteriorly (posterior axillary line or more posterior) and move progressively superior through the rib spaces until atelectatic lung is clearly identified.

Can atelectatic lung be identified? ☐ Yes ☐ No

If YES, please continue and complete the following details

Is the atelectatic lung moving freely? ☐ Yes ☐ No

Is there evidence of lung aeration during respiration? ☐ Yes ☐ No

Is there good evidence of lung expansion with inspiration? ☐ Yes ☐ No

Please zoom in on the "upper" surface of the atelectatic lung closest to the chest wall and assess the following

INSPIRATORY BREATH HOLD (aim for 5-10 seconds)

Can you clearly identify transmission of cardiac pulsation through the atelectatic lung? ☐ Yes ☐ No

Using M-mode assessment, what is the greatest excursion of the visceral pleural edge? _____ mm

EXPIRATORY BREATH HOLD (aim for 5-10 seconds)

Can you clearly identify transmission of cardiac pulsation through the atelectatic lung? ☐ Yes ☐ No

Using M-mode assessment, what is the greatest excursion of the visceral pleural edge? _____ mm

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2.2.3 Clinical outcome data

Clinical, radiological, and diagnostic data were recorded in the clinical records of individual patients as part of routine clinical care pre- and post-procedure, and at subsequent in- or out-patient follow-up within the Oxford Centre for Respiratory Medicine or other specialist hospital-based services.

The diagnosis of unexpandable lung was made by consensus between two independent respiratory physicians reviewing the clinical records of individual patients, with a third respiratory physician available to arbitrate in the event of any disagreement. Radiological evidence of unexpandable lung was defined using computed tomography and/or chest X-ray to demonstrate the presence of a pneumothorax or hydropneumothorax of a size considered to be clinically relevant by the independent assessing physician(s) following pleural drainage, alongside other features that could be associated with unexpandable lung such as visible visceral pleural thickening or mediastinal shift toward the ipsilateral hemithorax. The physicians carrying out this radiological assessment were also involved in the collection of ultrasound data, but did not have access to either the clinical ultrasound reports in patients' medical notes or the ultrasound case report forms at the time of reviewing any radiology; the thoracic imaging studies were also anonymised to further minimize the risk of bias.

All thoracic imaging studies taken up to four months after the index pleural intervention were reviewed to make the diagnosis of unexpandable lung. This approach was felt to be advantageous for several reasons. It avoided relying on imaging collected at a single point in time, which could otherwise misdiagnose lung which was slow to expand rather than truly unexpandable. It prevented the iatrogenic introduction of air into the pleural space during the index pleural intervention, more common during procedures such as indwelling pleural catheter insertion or medical thoracoscopy, from confounding the diagnosis of unexpandable lung. Finally, it allowed the outcome of future procedures, which might have resulted in complete drainage of the pleural effusion, and associated imaging to be taken into consideration.

Clinical evidence of unexpandable lung was defined by a failure to passively drain a pleural effusion under gravity alone; that is, without the application of external negative pressure suction. This was taken to represent equalization of intrapleural and atmospheric pressures. Again, clinical records were reviewed for a period of up to four months after the index pleural intervention. This allowed the failure of passive drainage to be confirmed on any future procedures as a genuine finding, as opposed to a technical issue with, for example, equipment used at the time of the study pleural intervention.

In both circumstances, the residual pleural collection (air and/or fluid) needed to be of sufficient volume that it would be expected to cause persistent symptoms such as pain or breathlessness, and/or prevent apposition of visceral and parietal pleura to an extent that would preclude an attempt at pleurodesis were this indicated.

All patients were invited to voluntarily complete a standardised paper-based questionnaire (**figure 2**) used as part of routine clinical practice and described in previous work published by the Pleural Disease Unit in Oxford (Psallidas et al., 2017). Data included visual analogue scale and Likert-type scores relating to the patients' experience and symptoms pre- and post-procedure. Patients attending for a day-case procedure returned their questionnaire on the same day; patients who were either being or were already admitted to hospital were asked to complete and return their questionnaire the following day.

2.2.4 Statistical analysis

An outline statistical analysis plan was written and agreed prior to any data being assessed or analysed. IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, New York) would be used for statistical analyses, with a p-value of <0.05 considered significant. Baseline characteristics of the study population including basic demographics and clinical information, including the aetiology for the pleural effusion and procedure undertaken, would be defined using descriptive statistics as appropriate.

The presence of unexpandable lung, as determined using the radiological and clinical characteristics outlined above, was the primary clinical outcome of interest in this study. Individual ultrasound variables would therefore be evaluated for their association with unexpandable lung using *t*-tests to examine differences between groups for those parameters with parametric data, whilst either a chi-squared test with Yates' correction or Fisher's exact test would be used to analyze categorical data depending on the sample size and/or distribution of that data. Individual ultrasound parameters shown to have a significant association with the presence of unexpandable lung, and also felt to have a biologically plausible explanation for this association, would then be considered for inclusion in an exploratory multivariable logistic regression analysis.

An area under the receiver operating characteristic (ROC) curve would also be reported for the M-mode evaluation of cardiac pulse transmission through the atelectatic lung in order to describe this test's diagnostic accuracy; this would also allow a cut-off value to be chosen that would maximize sensitivity and specificity. In contrast to previous work in this area (Salamonsen et al., 2014) though, the sensitivity of M-mode to detect unexpandable lung would be prioritized over specificity for this diagnosis. This decision was based on the increasing use of indwelling pleural catheters in clinical practice, and research describing accelerated treatment protocols with these devices intended to encourage earlier auto-pleurodesis in those patients who have expandable lung (Wahidi et al., 2017; Muruganandan et al., 2018; Bhatnagar et al., 2018).

Collinearity between the individual ultrasound parameters would be assessed where appropriate using either correlation coefficients for continuous data and/or the chi-squared test or Fisher's exact test for categorical data in order to produce a correlation matrix. The number of individual ultrasound parameters to be included in any regression analysis would be limited to ensure the outcome event per variable (EPV) was no lower than 5 and ideally 10 or above (Vittinghoff &

McCulloch, 2007; Ogundimu, Altman, & Collins, 2016), with the aim of limiting bias and overfitting to the development dataset. Testing for multicollinearity between two or more individual variables included in the regression analysis would be performed by calculating the tolerance coefficient, with a threshold for significant collinearity set at a tolerance <0.4 . The Box-Tidwell test would be used to assess any interaction effect for continuous independent variables. This regression analysis would hopefully permit the development of an ultrasound prediction model for unexpandable lung that could then be tested and validated in future research studies.

The association between any change in patient-reported outcome measures, specifically procedure-related pain and breathlessness pre- and post-intervention, and the presence of unexpandable lung would be analysed using either the chi-squared test or Fisher's exact test (depending on sample size) for categorical data, and *t*-tests for continuous data.

Figure 2 Copy of the questionnaire given to all patients undergoing a pleural intervention at the Pleural Disease Unit in Oxford as part of routine clinical practice








PATIENT QUESTIONNAIRE

Thank you for completing the questions below about your symptoms and experience before and after your procedure today.

Patient MRN: _____

Procedure Date: _____

Procedure Type: _____

1) Experience of the procedure

How painful was the procedure?

Not painful at all _____ Worst possible pain

Would you have the procedure again if needed?

Definitely yes _____ Definitely no

2) Your symptoms

How breathless have you felt on average in the last 24 hours before the procedure?

Not breathless at all _____ Worst possible breathlessness

What do you consider to be a change in your breathing that would be worth having this procedure again?

No change in breathlessness _____ Complete resolution of breathlessness

Version 1.0 10th September 2015

On average, how breathless do you feel now after the procedure?

Not breathless at all _____ Worst possible breathlessness

How much change have you noticed in your breathing after the procedure?
Please tick 1 box.

Large or moderately worse	☐
Small but significantly worse	☐
Slightly worse but not significant	☐
No change	☐
Slightly better but not worthwhile	☐
Slightly better but worthwhile	☐
Large or moderately better	☐

Thank you for completing this questionnaire. Please return this to one of the doctors or nurses looking after you.

Version 1.0 10th September 2015

2. METHODS

2.3 Thoracic ultrasound in the assessment of extravascular lung water in patients with end-stage renal failure undergoing haemodialysis

As specified in the introduction there is growing interest in the use of thoracic, and more specifically lung ultrasound as a diagnostic tool. This includes its use to both identify the presence of and monitor changes in extravascular lung water. There remains, however, a lack of robust data to demonstrate the utility of thoracic ultrasound in this area of clinical practice. There is no work comparing ultrasound with computed tomography for these purposes, the latter radiologic test being presently regarded as the gold standard for lung parenchymal assessment (Padley et al., 1991; Storto et al., 1995; Gluecker et al., 1999; Scillia et al., 2004). There are limited data utilizing multiple and/or blinded ultrasound scorers, raising concerns about the existing evidence base with respect to bias and reproducibility of findings.

A study was therefore planned to test the hypothesis that the changes on lung ultrasound would correlate with a reduction in extravascular lung water, utilizing a stable outpatient population under close physiological observation. The study would build on the existing evidence base by facilitating direct comparison with an existing gold standard radiologic test for lung parenchymal assessment (computed tomography); and use multiple assessors blinded to study participants' clinical status to evaluate consistency of ultrasound reporting between different operators.

2.3.1 Objectives and Outcome Measures

The study's primary objective was to assess the relationship between the presence of extravascular lung water, as measured by the number of B-lines seen on thoracic ultrasound examination, and changes in fluid status during haemodialysis.

The primary outcome measure was the correlation between change in the total lung ultrasound B-line score (taken to represent the presence and extent of extravascular lung water) and the contemporaneous associated changes in fluid

status during haemodialysis. Fluid status during haemodialysis was assessed using established physiological markers monitored routinely as standard of care in patients undergoing haemodialysis including body weight pre- and post-dialysis (in kg); the volume of fluid (in mL) removed during dialysis as measured by the haemodialysis machine; and haematocrit pre- and post-dialysis.

Secondary objectives of the study were (a) to assess the association between changes in extravascular lung water and patient-reported breathlessness during haemodialysis; (b) to assess the reliability and consistency of lung ultrasound scoring between different clinicians; (c) to assess the performance of lung ultrasound against computed tomography in identifying the presence of extravascular lung water and any changes in the same following haemodialysis; and (d) to assess patient satisfaction with thoracic ultrasound examination for these purposes.

The secondary outcome measures were (a) the total lung ultrasound B-line score (taken to represent the presence and extent of extravascular lung water) and changes in breathlessness measured using a visual analogue and Likert-type scales; (b) comparison of total lung ultrasound B-line scores and the categorical diagnosis of whether an interstitial syndrome, as defined by the international consensus statement on point-of-care lung ultrasound (Volpicelli et al., 2012), was present or not on individual ultrasound scans; (c) comparison of lung ultrasound and computed tomography findings pre- and post- dialysis for individual patients; and (d) measurement of patient satisfaction using a Likert-type scale.

2.3.2 Study Design

This was a prospective cohort study recruiting at a single site (Oxford University Hospitals NHS Foundation Trust). As this was a non-interventional study with no comparative study arms, a formal statistical sample size calculation was not performed. A pragmatic, non-mandatory recruitment target of 50 participants was chosen based on the size of the outpatient population attending the haemodialysis unit, and the 15-month study recruitment window (November 2014 to January

2016). Participants were screened from normal clinical care at the outpatient haemodialysis unit by the clinicians responsible for this service, and provided with written information relating to the study. If, after an appropriate period of reflection, they indicated a willingness to participate then written informed consent was obtained in line with GCP standards, after which a unique participant study identification number was issued by the study management team. This identification number was then used to complete all study-related documentation, and linked to a set of unique ultrasound identification numbers in a database accessible only to the study management team.

All study-specific procedures (computed tomography, ultrasound scans, blood tests, spirometry, and questionnaire completion) were carried out during a single hospital visit, coordinated with one of the participant's usual regular haemodialysis sessions in order to minimize disruption to either the patient or the outpatient haemodialysis unit. This visit lasted between four and six hours depending on the individual participant's clinical needs.

2.3.3 Study Management and Oversight

The study was sponsored by the University of Oxford, and managed through the University of Oxford Respiratory Trials Unit. A study management group including the Chief Investigator, Key Investigator, Study Coordinator, and Senior Clinical Trials Manager was responsible for all aspects of the study including recruitment, protocol compliance, and ensuring appropriate measures were in place to safeguard study participants and the overall quality of the study. Given the low-risk nature of the study design, the formation of either an independent steering committee or data monitoring committee was deemed unnecessary.

The study was registered on a freely accessible registry of clinical trials and studies (www.clinicaltrials.gov – registration number NCT01949402). The study protocol and subsequent amendments were approved by the UK National Research Ethics Service (reference 13/SC/0319).

2.3.4 Study Funding

Esaote UK provided the ultrasound equipment and associated consumables used in the study free of charge. The Teresa Rosenbaum Golden Charitable Trust (Rosetrees Trust, UK) provided a monetary grant to support study costs including administration and consumables. The funders did not have any input into study design or procedures, data analysis or interpretation, or the production of any subsequent written publications relating to the study.

2.3.5 Study Participants

Adults (≥ 18 years old) with an established diagnosis of end-stage renal failure requiring long-term regular haemodialysis and capable of providing informed written consent were considered for study participation.

Patients were not eligible to enter the study if any of the following exclusion criteria applied:

1. Being aged less than 18 years.
2. Being unable to provide informed consent.
3. Being either pregnant or breastfeeding.

2.3.6 Study Procedures

An enrolment case report form was completed for all study participants, collecting a standardised data set to include demographics, aetiology of and year of diagnosis with end-stage renal failure, other past medical history, smoking history, and current medications. Baseline clinical observations including heart rate, blood pressure, respiratory rate, peripheral pulse oximetry, height, and weight were recorded both pre- and post-dialysis. A full blood count (including haematocrit) was also checked and recorded pre- and post-dialysis.

Haemodialysis was performed using a B. Braun Dialog Plus dialyzer (B. Braun Medical, Melsungen, Germany), with a dry weight target set in advance by the participant's responsible renal physician. A haemodialysis case report form was completed midway through and immediately following haemodialysis; documenting

routine clinical observations and the volume of fluid (in mL) removed as measured by the dialyzer at that point in time.

Thoracic ultrasound examination was performed by a single primary operator according to a standardised protocol before (contemporaneous to completion of the enrolment case report form), midway through, and immediately following haemodialysis (contemporaneous to completion of the relevant haemodialysis case report forms described above); the findings on ultrasound examination were recorded on a separate ultrasound case report form. Ultrasound images were acquired using an Esaote MyLab25 Gold machine (Esaote UK, Cambridge, UK) and a standard abdominal curvilinear transducer (3-6 MHz). Patients were positioned sitting up at an angle between 45 and 90 degrees according to comfort. Ultrasound images (stills) and clips (6-10 seconds in duration, to include at least two full respiratory cycles) were recorded at 10 points over each hemithorax (approximating to the 2nd, 4th, and 6th intercostal spaces in the mid-clavicular line; the 2nd, 4th, and 6th intercostal spaces in the mid-axillary line; and the 2nd, 5th, 7th, and 9th intercostal spaces posteriorly) as illustrated in **figure 3**. The presence of any pleural effusion was also documented with quantification of size (number of rib spaces spanned by the effusion, and maximal depth in cm) as appropriate.

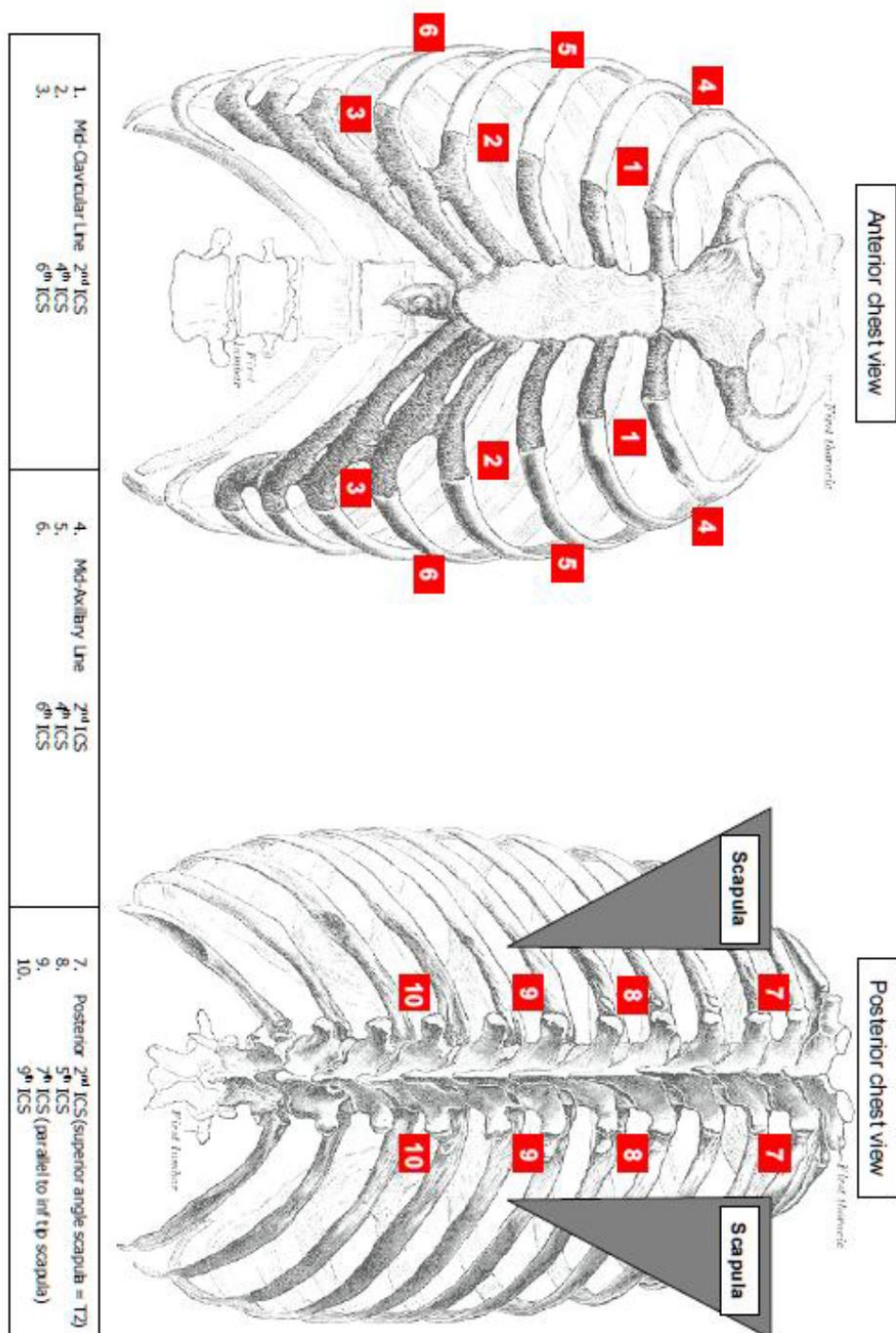
All ultrasound images and clips were labelled with a unique ultrasound identification number, also recorded on the relevant ultrasound case report form. The unique participant study identification number was not attached to any ultrasound images or clips in order to facilitate both blinding and anonymized distribution of ultrasound data to independent scorers at a later stage.

The primary ultrasound operator reported all ultrasound examinations in real-time, documenting the number of B-lines seen at each individual anatomical location on the ultrasound case report form before these were added together to generate a total lung ultrasound B-line score; and whether each examination demonstrated an interstitial syndrome or not. B-lines were defined as echogenic, dynamic wedge-shaped artefacts with a narrow base originating at the pleural line and extending to

the distal edge of the ultrasound image, consistent with prior literature relating to this area of practice (Lichtenstein et al., 1997; Volpicelli et al., 2012). The ultrasound clips were collated at a later stage using professional video editing software (Cyberlink PowerDirector for Windows version 10; Cyberlink Corp., New Taipei City, Taiwan) into a single high-definition video for each examination, labelled using the unique ultrasound identification number. These high-definition videos were distributed to and reported by two clinicians using the same scoring criteria as the primary operator; these clinicians were blinded to the participant's clinical condition and when the ultrasound scan was taken during the haemodialysis session.

Study participants had non-contrast computed tomography of their chest before and after haemodialysis. This was performed with the participant lying supine using a 16-slice scanner (GE Lightspeed; GE Healthcare, Buckinghamshire, UK) with a slice thickness of 0.625 mm. Images were acquired during an inspiratory breath hold of up to 15 seconds to minimize motion artefact. A low-dose protocol was used, with the aim of limiting ionizing radiation exposure to a maximum dose of 1.7 mSv. CT scans were reported by a consultant radiologist with a sub-specialty interest in thoracic imaging. The reporting radiologist was not blinded to the participant's clinical condition or timing of the scan, and was specifically instructed to look for changes that would be suggestive of a change in fluid status.

Figure 3 Anatomical diagram provided for guidance purposes as part of the standardised thoracic ultrasound examination protocol



At the end of their haemodialysis session and once all study radiologic tests (ultrasound and computed tomography) were completed, all study participants were asked to complete a questionnaire (**figure 4**) relating to their symptoms pre- and post-dialysis, and their experience of and satisfaction with thoracic ultrasound examination during the study. This included a visual analogue scale (0-100 mm, with no breathlessness at 0 mm and worst possible breathlessness at 100 mm) and Likert-type scores of breathlessness pre- and post-dialysis; a visual analogue scale score of pain caused by thoracic ultrasound examination (0-100 mm, with no pain at 0 mm and worst possible pain at 100 mm); and an assessment of understanding and willingness to have further thoracic ultrasound assessments in future for these purposes measured using a Likert-type scale.

2.3.7 Safety Reporting

No safety concerns were anticipated as part of this study, with study-specific interventions considered to be non-invasive and therefore not likely to result in any complications or additional risks for participants. As such, no specific safety outcome monitoring was felt to be required.

Adverse events deemed by the Chief Investigator to be directly related to study-specific interventions (that is, radiologic investigations including thoracic ultrasound and computed tomography) were recorded on standard Adverse Event forms used by the University of Oxford Respiratory Trials Unit, but were not subject to any specified reporting timelines or regulations and would instead be reviewed by the study management group at the end of the study.

Figure 4

Copy of the questionnaire given to participants at the end of their haemodialysis session and following their third and final thoracic ultrasound examination for the study



**Oxford University Hospitals
NHS Trust**



**UNIVERSITY OF
OXFORD**

Thoracic Ultrasonography in the Assessment of Extravascular Lung Water & Respiratory Failure

REC REFERENCE: 13/000319

CLINICAL TRIALS GOV IDENTIFIER: NCT0194402

“A NEW WAY OF LOOKING AT YOUR LUNGS”

PARTICIPANT VAS & ULTRASOUND SURVEY FORM

(HAEMODIALYSIS STUDY ARM)

Participant Information

Thoracic Ultrasonography in the Assessment of Extravascular Lung Water & Respiratory Failure

Participant VAS & Ultrasound Survey - Haemodialysis Study Arm v1.2 (25/04/2013)

Participant Study Number:

Participant's DOB
(mm/yyyy only)

1. How breathless have you felt on average in the 24 hours before your dialysis today?

Not breathless at all Worst possible breathlessness

2. How breathless did you feel on average after your dialysis today?

Not breathless at all Worst possible breathlessness

3. Which statement best describes any change you have noticed in your breathing after your dialysis today? Please tick one box only.

☐ My breathing feels significantly worse

☐ My breathing feels moderately worse

☐ My breathing feels slightly worse

☐ I have not noticed any change in my breathing

☐ My breathing feels slightly better

☐ My breathing feels moderately better

☐ My breathing feels significantly better

4. How painful did you find the ultrasound scan(s) that you had today?

Not painful at all Worst possible pain

5. How time consuming did you find the ultrasound scan(s) that you had today? Please tick one box only.

☐ Very time consuming

☐ Slightly time consuming

☐ Not time consuming at all

6. Did the doctor performing the ultrasound scan(s) today give you a clear explanation of what they were looking for?

☐ YES

☐ NO

7. Did you understand what the ultrasound scan(s) being done today were looking for? Please tick one box only.

☐ I understood everything about what the ultrasound scan(s) were looking for.

☐ I understood most things about what the ultrasound scan(s) were looking for.

☐ I understood a little bit about what the ultrasound scan(s) were looking for.

☐ I did not understand anything about what the ultrasound scan(s) were looking for.

8. Did you want to be given more information about what the ultrasound scan(s) being done today were looking for?

☐ YES

☐ NO

9. Would you be willing to have the same ultrasound scan(s) that you had today in the future?

☐ YES

☐ NO

10. Do you have any other comments about your experience today?

2 COPIES - 1 (ORIGINAL) to be sent to ORTU and 1 (COPY) to be filed in patient's notes

Participant VAS & Ultrasound Survey - Haemodialysis Study Arm v1.2 (25/04/2013)

2 COPIES - 1 (ORIGINAL) to be sent to ORTU and 1 (COPY) to be filed in patient's notes

Participant VAS & Ultrasound Survey - Haemodialysis Study Arm v1.2 (25/04/2013)

2.3.8 Data Management

Study data were stored on an electronic data capture system based around a fully licensed enterprise version of OpenClinica, with support services provided by OpenClinica LLC. The study database was bespoke and hosted on a secure server provided by the University of Oxford. Data were stored in line with ICH-GCP standards and data protection principles. Data monitoring and validation processes were carried out internally to ensure appropriate integrity and quality of the data according to University of Oxford Respiratory Trials Unit standard operating procedures both during and at the end of the study.

The raw ultrasound imaging data and processed high-definition videos were stored on a secure server provided by the University of Oxford. The high-definition ultrasound videos were distributed to remote blinded scorers either via a large file exchange service (OxFile, <https://oxfile.ox.ac.uk>) provided by the University of Oxford, or by using a bespoke weblink to a private video channel managed by the study coordinator on an online viewing platform (YouTube, <https://www.youtube.com>). Videos were labelled with a unique ultrasound identification number and did not include any patient identifiable information or the unique participant study identification number.

2.3.9 Statistical Analysis

A statistical analysis plan was written and agreed before any data were assessed or analyzed. IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, New York) was used for statistical analyses. A p-value of <0.05 was considered significant. The baseline characteristics of study participants would be described including basic demographic data and clinical information, including the underlying aetiology for their end-stage renal failure and any significant pre-existing cardio-respiratory disease. Descriptive statistics would be used as appropriate.

The study's primary analysis explored the correlation between any change in the total lung ultrasound B-line score (as a marker of extravascular lung water) and the volume of fluid removed during haemodialysis. The proposed "gold standard" for

the volume of fluid removed during haemodialysis would be that displayed and recorded in mL by the dialyzer machine itself. However, study participants' weight and haematocrit pre- and post-dialysis would also be documented for study purposes, as these measures were also used regularly in clinical practice to help clinicians decide how much fluid should be removed prior to dialysis commencing. A total lung ultrasound B-line score would be calculated immediately before, midway through, and immediately after dialysis for each study participant; scores would be available for analysis from the original primary (bedside) operator, and two independent blinded scorers. The change in total lung ultrasound B-line score would be compared to the volume of fluid removed during dialysis for individual participants, using the Pearson correlation coefficient to measure the linear correlation between these variables across the study population as a whole.

For the secondary analyses, patient-reported change in breathlessness from pre- to post-dialysis would be assessed using a visual analogue scale to distinguish those with a significant symptomatic improvement from those without. The mean change in total lung ultrasound B-line score would then be compared across the two populations. The performance of lung ultrasound against computed tomography for identifying the presence of and any dialysis-related changes in extravascular lung water would be illustrated using two-by-two tables and reporting the individual tests' sensitivity and specificity thereafter. An assessment of interrater reliability for ultrasound scoring would be made across the three raters (original operator and two independent blinded scorers), analysing the diagnosis of whether an interstitial syndrome was present or not using kappa statistics for categorical data; and analysing the total lung ultrasound B-line scores using the intraclass correlation coefficient to estimate the degree of association, alongside Bland-Altman analysis to demonstrate the individual differences between measures (Bland & Altman, 1986).

3. RESULTS

3.1 Thoracic ultrasound as an early predictor of pleurodesis success in malignant pleural effusion

3.1.1 Subjects

A total of 18 participants were recruited to the study; baseline characteristics are provided in **table 1**.

Three participants (16.7%) died before reaching one-month follow-up; all three died as hospital inpatients during the same admission where they underwent chest tube drainage and talc slurry instillation for their malignant pleural effusion. Death occurred at day 15, day 19, and day 20 respectively following study recruitment; all three patients had had their chest drains removed at least a week prior to death. None of the patients required further pleural intervention but, in the absence of either any radiological studies showing evidence of pleural fluid recurrence following chest drain removal and/or a reliable evaluation of symptom burden (notably deteriorating dyspnoea) given the patients' frailty and rapidly deteriorating condition during the remainder of their hospital stay, it was not felt appropriate to include their baseline ultrasound data from day 0 and day 1 in the primary analysis since pleurodesis success or failure could not be reasonably determined.

A further six participants (nine in total, 50.0%) died before reaching the three-month follow-up timepoint; their data were included in subsequent analyses.

Table 1: Baseline characteristics of the study population (total $n = 18$ participants); data are presented as either n (%age) or mean (SD)

Sex	- Male - Female	4 (22.2%) 14 (77.8%)
Age, years		67.6 (9.7)
Primary cancer	- Lung - Gynaecological - Breast - Renal - Colorectal - Pleural mesothelioma	5 (27.8%) 5 (27.8%) 4 (22.2%) 2 (11.1%) 1 (5.6%) 1 (5.6%)
Active oncological treatment	- Yes - No	7 (38.9%) 11 (61.1%)
Side of effusion	- Right - Left	8 (44.4%) 10 (55.6%)
LENT score [Clive et al., 2014]	- Low, 0-1 - Moderate, 2-4 - High, 5-7	2 (11.1%) 14 (77.8%) 2 (11.1%)
Volume of pleural fluid drained, mL		2703 (1062)

3.1.2 Primary analysis

15/18 (83.3%) participants reached the one-month follow-up timepoint and were therefore included in the primary analysis. 4/15 (26.7%) participants had suffered pleurodesis failure, as defined in the study methodology, by this point in time. The total pleural adherence scores as determined using thoracic ultrasound on days 0 (immediately prior to talc slurry instillation) and 1 (24 hours following talc slurry instillation) are shown in **table 2** for the individual original and blinded scorers.

There was a consistently significant difference between the mean total pleural adherence score at day 1 for study participants who went on to have a successful as opposed to failed pleurodesis, seen with all three individual scorers' data as well as with the combined dataset. The area under receiver operating characteristic (ROC) curves for the total pleural adherence scores on day 0 and day 1 (**figure 5**) were 0.798 (95% CI 0.671 to 0.925) and 0.900 (95% CI 0.812 to 0.988) respectively.

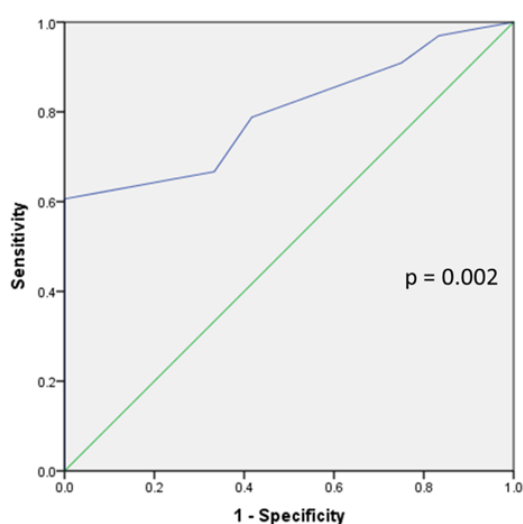
The interrater reliability for the total pleural adherence score determined using thoracic ultrasound was good to excellent, with an intraclass coefficient of 0.762 (95% CI 0.605 to 0.872, $p = <0.001$). This was reaffirmed when looking at the data in greater detail and considering whether raters considered lung sliding to be present, questionable, or absent at individual anatomical points; with a free-marginal kappa of 0.603 (95% CI 0.546 to 0.658, $p = <0.001$).

None of the 11 study participants with a successful pleurodesis as defined according to the pre-specified clinical and radiological criteria at one-month follow-up went on to suffer delayed failure of pleurodesis, either prior to death (4/11, 36.4%) or at the three-month follow-up timepoint that marked the end of the study (7/11, 63.6%).

Table 2: Total pleural adherence scores (minimum 0, maximum 18) on days 0 and 1 for study participants ($n = 15$) with either successful or failed pleurodesis at 1-month follow-up; data are presented as mean (SD).

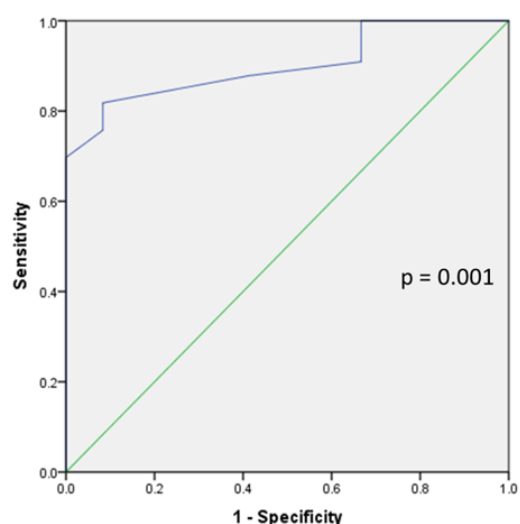
	Pleurodesis success $n = 11$	Pleurodesis failure $n = 4$	p-value (unpaired t -test)
DAY 0			
- Original scorer	10.73 (3.80)	6.50 (1.29)	0.052
- Blind scorer 1	8.91 (4.87)	5.00 (2.16)	0.152
- Blind scorer 2	10.18 (4.26)	5.00 (3.46)	0.049
- COMBINED SCORES	9.94 (4.26)	5.50 (2.35)	0.001
DAY 1			
- Original scorer	13.36 (3.11)	6.75 (2.63)	0.002
- Blind scorer 1	11.91 (3.88)	7.00 (3.74)	0.048
- Blind scorer 2	13.27 (3.95)	6.00 (2.58)	0.005
- COMBINED SCORES	12.85 (3.62)	6.58 (2.78)	<0.001

Figure 5 Receiver operating characteristic (ROC) curves and coordinates for total pleural adherence score on days 0 and 1 using a combined dataset (original and blind scorers) - the proposed score (highlighted) for detecting pleurodesis success using thoracic ultrasound was chosen using a threshold of $\geq 90\%$ specificity



Day 0: ROC area 0.798 (95% CI 0.671 to 0.925)

Day 0 ROC curve coordinates		
Successful pleurodesis if pleural adherence score $\geq$	Sensitivity	1 - Specificity
0	1.000	1.000
1	1.000	1.000
2	1.000	1.000
3	0.970	0.833
4	0.909	0.750
5	0.879	0.667
6	0.818	0.500
7	0.788	0.417
8	0.667	0.333
9	0.606	0.000
10	0.545	0.000
11	0.515	0.000
12	0.394	0.000



Day 1: ROC area 0.900 (95% CI 0.812 to 0.988)

Day 1 ROC curve coordinates		
Successful pleurodesis if pleural adherence score $\geq$	Sensitivity	1 - Specificity
0	1.000	1.000
1	1.000	1.000
2	1.000	1.000
3	1.000	0.917
4	1.000	0.750
5	1.000	0.750
6	1.000	0.667
7	0.909	0.667
8	0.879	0.417
9	0.848	0.250
10	0.818	0.083
11	0.758	0.083
12	0.697	0.000

3.1.3 Secondary analyses

15/18 (83.3%) participants completed the questionnaire relating to their experience and satisfaction with thoracic ultrasound examination. The mean visual analogue scale pain score associated with thoracic ultrasound examination was 8.9 mm (SD 12.9mm, 95% CI 1.8 to 16.1 mm). On a three-point Likert-type scale (not, slightly, and very time consuming), 10/15 (66.7%) participants did not find thoracic ultrasound examination time consuming at all, whilst the remaining 5 (33.3%) participants reported it to be slightly time consuming. All 15 participants were willing to have the same thoracic ultrasound examination(s) again if indicated as part of their clinical care in the future.

The mean time from chest tube insertion to talc slurry instillation was 4.3 days (± 1.53 ; $n = 18$ participants). 5/18 (27.8%) participants suffered a lengthy delay to discharge from hospital in the context of medical and social issues not related to their pleural disease. In light of this, a post-hoc decision was taken to analyse the time from talc slurry instillation to chest drain removal (actual vs. hypothetical based on thoracic ultrasound findings) rather than discharge from hospital. A day 1 total pleural adherence score of ≥ 10 (sensitivity 82%, specificity 91% for pleurodesis success) was used as the cut-off for hypothetical chest drain removal at this time point, based on the ROC curve analysis (**figure 1**) for thoracic ultrasound data described above.

The mean time from talc slurry instillation to chest tube removal was 2.9 days (± 1.1 ; $n = 18$ participants) in the study population. Only 3/18 (16.7%) participants had their chest tube removed after 24 hours (that is, on day 1) as part of usual clinical care. Had a thoracic ultrasound-based decision-making process been applied using the cut-off value for the total pleural adherence score described above, this would have risen to 13/18 (72.2%) participants ($p = 0.002$, Fisher's exact test) having their chest tube removed on day 1 following talc slurry instillation.

3.1.4 Exploratory analyses

In light of the primary data showing that longer-term pleurodesis success appeared to be associated with a higher total pleural adherence score on day 1, an exploratory analysis was undertaken to see if the anatomical window in which pleurodesis occurred could be identified. Ultrasound data for individual (bedside only) and combined (bedside plus blinded) scorers were sub-divided into anatomical regions – anterior, lateral, and posterior chest; and upper, middle, and lower chest – and the pleural adherence scores on day 0 and day 1 in each region compared for successful versus failed pleurodesis to look for any differences. The data (**table 3**) suggest that the pleural adherence score posteriorly and laterally, rather than anteriorly; and in the upper and middle chest, as opposed to lower; was more predictive of a successful long-term pleurodesis.

The presence of a residual pleural effusion either immediately prior to (day 0) or 24 hours following (day 1) talc slurry instillation did not have any predictive value for longer-term pleurodesis success (**table 4**).

Table 3 Pleural adherence scores (minimum 0, maximum 6 in each region) on days 0 and 1 sub-divided according to anatomical region for study participants ($n = 15$) with either successful or failed pleurodesis at 1-month follow-up; data are presented as mean (SD)

Individual (original) scorer		Pleurodesis success $n = 11$	Pleurodesis failure $n = 4$	p-value (unpaired t -test)
DAY 0	Anterior	3.18 (2.18)	2.00 (2.71)	0.398
	Lateral	3.36 (1.80)	2.25 (2.87)	0.380
	Posterior	4.18 (0.87)	2.25 (1.26)	0.005
DAY 1	Anterior	3.73 (2.05)	3.50 (2.65)	0.863
	Lateral	4.36 (1.50)	1.00 (0.82)	0.001
	Posterior	5.27 (1.01)	2.25 (0.50)	<0.001
DAY 0	Upper	4.64 (1.36)	2.75 (0.50)	0.020
	Middle	4.18 (1.60)	2.25 (0.50)	0.037
	Lower	1.91 (1.58)	1.50 (1.91)	0.680
DAY 1	Upper	4.91 (1.30)	3.25 (2.06)	0.083
	Middle	4.91 (1.22)	1.75 (1.26)	0.001
	Lower	3.55 (1.69)	1.75 (1.26)	0.078
Combined (original + blinded) scorers		Pleurodesis success $n = 11$	Pleurodesis failure $n = 4$	p-value (unpaired t -test)
DAY 0	Anterior	3.09 (2.12)	1.63 (1.82)	0.017
	Lateral	3.30 (1.75)	2.38 (2.50)	0.115
	Posterior	3.93 (1.30)	1.81 (1.11)	<0.001
DAY 1	Anterior	3.73 (1.98)	2.69 (2.06)	0.080
	Lateral	4.00 (1.73)	1.50 (1.63)	<0.001
	Posterior	5.05 (1.20)	2.25 (1.06)	<0.001
DAY 0	Upper	4.09 (1.61)	2.13 (1.09)	<0.001
	Middle	3.98 (1.81)	2.19 (1.38)	0.001
	Lower	2.25 (1.69)	1.50 (1.71)	0.135
DAY 1	Upper	4.64 (1.42)	2.75 (1.88)	<0.001
	Middle	4.68 (1.38)	1.81 (1.17)	<0.001
	Lower	3.45 (1.72)	1.88 (1.26)	0.002

Table 4 Association of the presence of a residual pleural effusion in study participants ($n = 15$) on days 0 and 1 with longer-term pleurodesis success or failure

		Pleurodesis success $n = 11$	Pleurodesis failure $n = 4$	
DAY 0	Effusion present	6	2	p = 1.0 (Fisher's exact test)
	Effusion absent	5	2	
DAY 1	Effusion present	8	3	p = 1.0 (Fisher's exact test)
	Effusion absent	3	1	

3. RESULTS

3.2 Thoracic ultrasound as a predictor of unexpandable lung and symptomatic improvement prior to pleural intervention

3.2.1 Subjects

A total of 92 patients were included in the study; baseline characteristics for the study population are provided in **table 5**.

All patients who had their in-depth thoracic ultrasound examination performed prior to a therapeutic thoracentesis had sufficient large-volume drainage during either their initial and/or a subsequent pleural procedure within the four-month follow-up period specified in the study methodology to allow an assessment of whether or not the lung was expandable. The primary diagnosis for each patient was taken from their clinical records and confirmed by the independent respiratory physicians at the same time as making the diagnosis of unexpandable lung.

Table 5 Baseline characteristics of the study population (total $n = 92$ patients); data are presented as either n (%age) or mean (SD; 95% CI)

Sex	- Male - Female	48 (52.2%) 44 (47.8%)
Age, years		70.6 (11.8; 68.2 to 73.1)
Side of effusion / intervention	- Right - Left	55 (59.8%) 37 (40.2%)
Procedure undertaken	- Thoracentesis - Medical thoracoscopy - Tube thoracostomy - Indwelling pleural catheter insertion	55 (59.8%) 18 (19.6%) 11 (12.0%) 8 (8.7%)
Primary clinical diagnosis		
Malignant effusion		59 (64.1%)
	- Breast	16 (17.4%)
	- Lung	15 (16.3%)
	- Mesothelioma	14 (15.2%)
	- Gynaecological	10 (10.9%)
	- Other	4 (4.3%)
Paramalignant effusion		6 (6.5%)
Benign effusion		27 (29.3%)
	- Cardiac failure	10 (10.9%)
	- Parapneumonic	4 (4.3%)
	- Post-cardiac surgery	3 (3.3%)
	- Post-trauma	3 (3.3%)
	- Benign asbestos-related	2 (2.2%)
	- Tuberculous pleuritis	2 (2.2%)
	- Other	3 (3.3%)
Volume of pleural fluid drained, mL		1360 (661; 1223 to 1497)

3.2.2 Unexpandable lung

The presence of unexpandable lung was observed in 27/92 (29.3%) patients. Static and dynamic thoracic ultrasound features prior to pleural intervention were assessed individually for their potential association with the presence of unexpandable lung (**table 6**) and to facilitate pre-selection for the subsequent regression model.

In light of the small sample size Fisher's exact test was chosen (rather than the chi-squared test) as the primary method of analysing categorical data, using the Freeman-Halton extension where applicable. Data pertaining to the presence of septations were analysed both according to the original categorisation (that is, absent, mild, moderate, or severe septations) and as a dichotomous variable (that is, septations either absent or present). Motion (M-) mode ultrasound assessment of the transmission of cardiac pulsation through the atelectatic lung was analysed both as a continuous (*t*-test) and dichotomous (Fisher's exact test) variable; with the cut-off values for the latter analysis chosen using receiver operating characteristic (ROC) curves generated using the study dataset (**figure 6**) and according to desired sensitivity and specificity thresholds.

Of the static thoracic ultrasound features, the presence of septated pleural fluid, visceral pleural thickening (both $p = <0.01$), and anechoic pleural fluid ($p = 0.02$) were associated with unexpandable lung in the study population. Of the dynamic ultrasound features, the free movement of underlying atelectatic lung within the effusion, a greater degree of cardiac pulse transmission through the atelectatic lung as measured with motion (M-) mode ultrasound (both $p = <0.01$), and lung expansion with inspiratory effort ($p = 0.02$) were associated with lung expansion following pleural drainage.

Motion (M-) mode ultrasound assessment of cardiac pulse transmission through the underlying atelectatic lung (**figure 6**) within an effusion appeared to be capable of predicting the presence of unexpandable lung, regardless of when measurements were taken during the respiratory cycle (**tables 6 and 7**). A significant difference in

lung excursion with cardiac pulse transmission between expandable and unexpandable lung was seen with both end-tidal inspiratory (difference 1.2 mm, 95% CI 0.5 to 1.9) and expiratory (difference 1.9 mm, 95% CI 0.8 to 3.0) breath hold manoeuvres.

Receiver operating characteristic (ROC) curves (**figure 7**) for M-mode assessment demonstrated a similar area under the curve to that reported in previous work (Salamonsen et al., 2014). Applying a cut-off value of >1.0 mm for M-mode assessment during an end-tidal expiratory breath hold manoeuvre in order to distinguish expandable from unexpandable lung, as proposed in this prior work, gave a positive predictive value (PPV) of 80.0% (95% CI 44.2 to 96.5) and negative predictive value (NPV) of 76.8% (95% CI 66.0 to 85.1). However, per the analysis plan described in the study methods above, a greater priority was to be placed on sensitivity for the detection of unexpandable lung as opposed to specificity in this study. As such, a new cut-off value of >1.5 mm was taken from the ROC curve, providing a PPV 63.3% (95% CI 43.9 to 79.5) and NPV 87.1% (95% CI 75.6 to 93.9) (**table 7**).

Figure 6 Example of sonographic assessment of lung using motion (M-) mode performed for this study: (a) pre-and post-drainage chest X-ray with unexpandable lung (top panel); corresponding pre-drainage thoracic ultrasound with consolidated, poorly collapsing lung (middle panel) and poor transmission of cardiac impulse (bottom panel); (b) pre-and post-drainage chest X-ray with normally expanding lung (top panel); corresponding pre-drainage thoracic ultrasound with normal atelectatic lung (middle panel) and good transmission of cardiac impulse (bottom panel, note arterial waveform with diastolic notch)

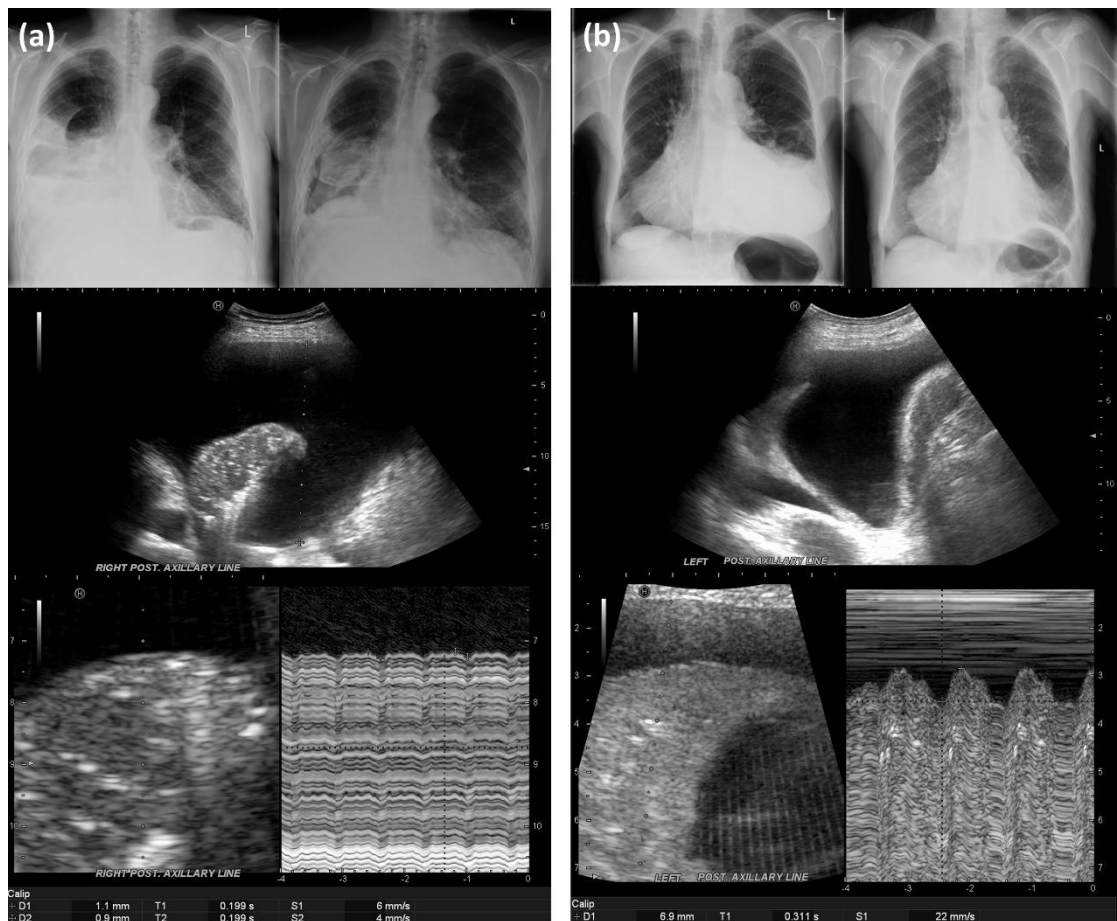
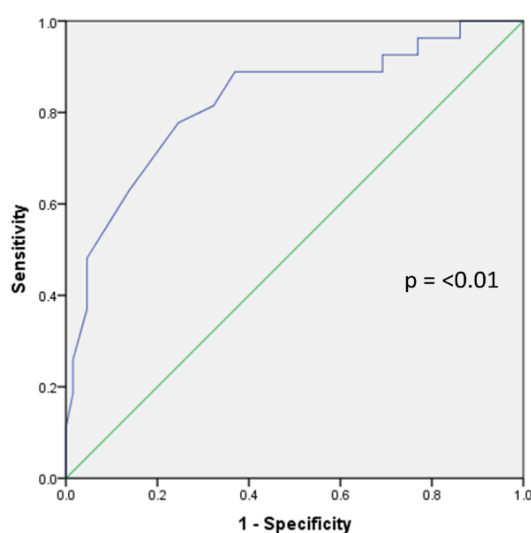


Table 6 Unexpandable lung: association with in-depth thoracic ultrasound (TUS) findings prior to large-volume pleural drainage; data are presented as either *n* (%age) or mean (SD; 95% CI)

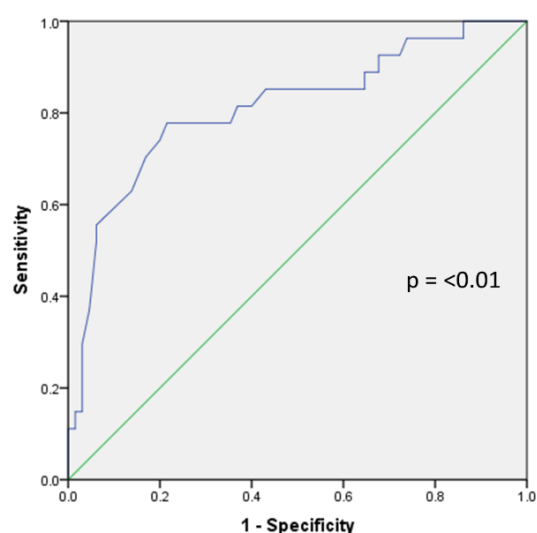
	Post-drainage lung characterisation		
	Expandable <i>n</i> = 65 (70.7%)	Unexpandable <i>n</i> = 27 (29.3%)	
Clinical features			
Malignant or paramalignant effusion	45/65 (69.2%)	20/27 (74.1%)	<i>p</i> = 0.80 (Fisher's exact test)
Benign effusion	20/65 (30.8%)	7/27 (25.9%)	
Volume of pleural fluid drained, mL	1321 (612; 1169 to 1472)	1456 (773; 1150 to 1761)	<i>p</i> = 0.38 (<i>t</i> -test)
Static TUS features			
Effusion side - Right	38/65 (58.5%)	17/27 (63.0%)	<i>p</i> = 0.82 (Fisher's exact test)
- Left	27/65 (41.5%)	10/27 (37.0%)	
Effusion size - Large	42/65 (64.6%)	19/27 (70.4%)	<i>p</i> = 0.64 (Fisher's exact test)
- Moderate	23/65 (35.4%)	8/27 (29.6%)	
Septations - None	61/65 (93.8%)	12/27 (44.4%)	<i>p</i> = <0.01 (Fisher-Freeman-Halton test)
- Mild	3/65 (4.6%)	10/27 (37.0%)	
- Moderate	1/65 (1.5%)	3/27 (11.1%)	
- Severe	0/65	2/27 (7.4%)	
Septations - Absent	61/65 (93.8%)	12/27 (44.4%)	<i>p</i> = <0.01 (Fisher's exact test)
- Present	4/65 (6.2%)	15/27 (55.6%)	
Echogenic pleural fluid	44/65 (67.7%)	11/27 (40.7%)	<i>p</i> = 0.02 (Fisher's exact test)
Parietal pleural thickening visible	3/65 (4.6%)	3/27 (11.1%)	<i>p</i> = 0.35 (Fisher's exact test)
Visceral pleural thickening visible	0/65	7/27 (25.9%)	<i>p</i> = <0.01 (Fisher's exact test)
Pleural nodularity visible	12/65 (18.5%)	7/27 (25.9%)	<i>p</i> = 0.41 (Fisher's exact test)
Lung consolidation visible	4/65 (6.2%)	4/27 (14.8%)	<i>p</i> = 0.23 (Fisher's exact test)
Dynamic TUS features			
Paradoxical motion of hemidiaphragm seen	24/65 (36.9%)	16/27 (59.3%)	<i>p</i> = 0.07 (Fisher's exact test)
Atelectatic lung moving freely within fluid	62/65 (95.4%)	15/27 (55.6%)	<i>p</i> = <0.01 (Fisher's exact test)
Lung expansion seen with inspiratory effort	21/65 (32.3%)	2/27 (7.4%)	<i>p</i> = 0.02 (Fisher's exact test)
Expiratory hold – cardiac pulse transmission visible	64/65 (98.5%)	24/27 (88.9%)	<i>p</i> = 0.07 (Fisher's exact test)
Inspiratory hold – cardiac pulse transmission visible	64/65 (98.5%)	24/27 (88.9%)	<i>p</i> = 0.07 (Fisher's exact test)
Expiratory hold - M-mode measurement of cardiac pulse transmission through lung, mm	3.6 (2.7; 2.9 to 4.2)	1.6 (1.3; 1.2 to 2.1)	<i>p</i> = <0.01 (<i>t</i> -test)
Inspiratory hold - M-mode measurement of cardiac pulse transmission through lung, mm	2.4 (1.7; 1.9 to 2.8)	1.2 (0.9; 0.8 to 1.5)	<i>p</i> = <0.01 (<i>t</i> -test)

Figure 7 Receiver operating characteristic (ROC) curve and selected coordinates for motion (M-) mode thoracic ultrasound assessment pre-drainage as a predictive tool for the diagnosis of unexpandable lung



Inspiratory hold M-mode TUS measurement of lung pulse transmission: ROC area 0.83 (95% CI 0.73 to 0.93)

Inspiratory hold M-mode measure of lung pulse transmission		
Measured excursion, mm	Sensitivity	Specificity
0.6	22%	99%
0.8	37%	95%
1.0	48%	95%
1.2	78%	75%
1.4	89%	63%
1.6	89%	54%
1.8	89%	43%
2.0	89%	37%



Expiratory hold M-mode TUS measurement of lung pulse transmission: ROC area 0.81 (95% CI 0.71 to 0.92)

Expiratory hold M-mode measure of lung pulse transmission		
Measured excursion, mm	Sensitivity	Specificity
0.6	15%	99%
0.8	15%	97%
1.0	30%	97%
1.2	52%	94%
1.4	63%	86%
1.6	74%	80%
1.8	78%	72%
2.0	78%	69%
2.2	82%	63%

Table 7 Comparison of different cut-off thresholds for motion (M-) mode thoracic ultrasound measurement of cardiac pulse transmission through atelectatic lung prior to large volume pleural drainage for distinguishing expandable from unexpandable lung; data presented as n (%age) unless otherwise stated

	Post-drainage lung characterisation			Sensitivity (95% CI)	Specificity (95% CI)
	Expandable n = 65 (70.7%)	Unexpandable n = 27 (29.3%)			
Expiratory hold – M-mode measurement of cardiac pulse transmission through lung tissue, mm					
> 1.0 mm	63/65 (96.9%)	19/27 (70.4%)	p = <0.01 (Fisher’s exact test)	29.6% (14.5 to 50.3)	96.9% (88.4 to 99.5)
> 1.5 mm	54/65 (83.1%)	8/27 (29.6%)	p = <0.01 (Fisher’s exact test)	70.4% (49.7 to 85.5)	83.1% (71.3 to 90.9)
> 2.0 mm	45/65 (69.2%)	6/27 (22.2%)	p = <0.01 (Fisher’s exact test)	77.8% (57.3 to 90.6)	69.2% (56.4 to 79.8)
Inspiratory hold – M-mode measurement of cardiac pulse transmission through lung tissue, mm					
> 1.0 mm	62/65 (95.4%)	14/27 (51.9%)	p = <0.01 (Fisher’s exact test)	48.1% (29.2 to 67.6)	95.4% (86.2 to 98.9)
> 1.5 mm	39/65 (60.0%)	3/27 (11.1%)	p = <0.01 (Fisher’s exact test)	88.9% (70.0 to 97.1)	60.0% (47.1 to 71.7)
> 2.0 mm	24/65 (36.9%)	3/27 (11.1%)	p = 0.01 (Fisher’s exact test)	88.9% (69.7 to 97.1)	36.9% (25.6 to 49.8)

Based on the initial analysis of individual thoracic ultrasound parameters and their association with unexpandable lung, six parameters (expiratory hold M-mode measurement of cardiac pulse transmission through lung; pleural fluid septations; pleural fluid echogenicity; visceral pleural thickening; free movement of atelectatic lung within the effusion; and lung expansion with inspiratory effort) were considered for inclusion in the subsequent regression analysis. Expiratory hold M-mode measurement of cardiac pulse transmission through lung was included as a dichotomous variable with a cut-off threshold of >1.5 mm. This would prioritise sensitivity in the detection of unexpandable lung as outlined above, and potentially allow the development of a pragmatic prediction model for use in real-life clinical practice, which analysis of M-mode measurement as a continuous variable might not. Pleural fluid septations were also included as a dichotomous variable (that is, present or absent) because of the small number of events in the individual categories (that is, mild, moderate, or severe septation), and to simplify both the regression analysis in this study and development of any prediction model that might be validated in future research by limiting the subjectivity of this particular ultrasound parameter. Inspiratory hold M-mode measurement of cardiac pulse transmission through lung was excluded as it was felt to duplicate the findings on expiratory hold M-mode measurement that were already under consideration in this study and had been evaluated in previous work (Salamonsen et al., 2014).

A correlation matrix (**figure 8**) was developed to look for collinearity between the individual ultrasound parameters that had been pre-selected as above. Visceral pleural thickening, and free movement of atelectatic lung within the effusion were subsequently excluded from the planned regression analysis. The free movement of atelectatic lung within the effusion was strongly associated with a number of other parameters being taken forward and felt to be a surrogate for M-mode measurement of cardiac pulse transmission through lung tissue. Visceral pleural thickening, with the physical restriction it was likely to place on both expandability and free movement of the affected lung, was felt to be accounted for in the planned regression analysis by both M-mode measurement of cardiac pulse transmission and lung expansion with inspiratory effort.

Figure 8 Cramér's V (phi-) correlation hemi-matrix showing inter-relationship between thoracic ultrasound parameters, calculated using 2x2 contingency tables (not shown here); the darkest shaded cells represent the six autocorrelations, with lighter shading representing a reduction in any association between individual parameters

Expiratory hold M-mode > 1.5 mm	1.0					
Pleural fluid echogenicity	0.14	1.0				
Lung expansion with inspiration	0.24	0.04	1.0			
Visceral pleural thickening	0.32	0.27	0.17	1.0		
Pleural fluid septations	0.45	0.07	0.17	0.36	1.0	
Atelectatic lung moving freely	0.57	0.24	0.25	0.65	0.43	1.0
	Expiratory hold M-mode > 1.5 mm	Pleural fluid echogenicity	Lung expansion with inspiration	Visceral pleural thickening	Pleural fluid septations	Atelectatic lung moving freely

The four remaining ultrasound parameters (expiratory hold M-mode measurement of cardiac pulse transmission through lung; pleural fluid septations; pleural fluid echogenicity; and lung expansion with inspiratory effort) to be included in the regression analysis meant the outcome event per variable was 6.75 and therefore within the acceptable range specified in the statistical analysis plan (Vittinghoff & McCulloch, 2007).

The logistic regression analysis utilised a sequential (hierarchical) approach to model building with expiratory hold M-mode measurement of cardiac pulse transmission through lung tissue in block 1 (**table 8 (a)**), as a previously described means of delineating expandable from unexpandable lung (Salamonsen et al., 2014), applying the dichotomous cut-off threshold of 1.5 mm as described above. The remaining ultrasound parameters were then introduced in block 2 (**table 8 (b) and (c)**) as unproven variables, utilising a backward stepwise (determined by likelihood ratio) regression to ascertain which of these novel parameters, if any, might improve the prediction model's performance. No concerns were identified during the regression analysis regarding significant multicollinearity, with calculated tolerance coefficients all ≥ 0.5 .

TABLE 8: Results of sequential (hierarchical) logistic regression predicting the presence of unexpandable lung using thoracic ultrasound parameters; overall success of model with intercept only was 70.7% (assuming lung always expandable)

(a) Model (step) 1: expiratory hold M-mode measurement of lung excursion with cardiac pulse transmission through lung < 1.5 mm added to model

(b), (c) Models (steps) 2 & 3: other parameters incorporated using backward stepwise selection to identify any that might improve model performance

(a)	Model (step) 1			
	Overall success 79.3%; $\chi^2(1) = 24.3$, $p = < 0.01$ (vs. intercept only)			
Parameter	B (SE)	Wald χ^2	p value	OR (95% CI)
Expiratory M-mode measurement of cardiac pulse transmission through lung < 1.5 mm	2.46 (0.54)	21.01	< 0.01	11.66 (4.08 to 33.32)

(b)	Model (step) 2 Overall success 84.8%; $\chi^2(4) = 44.3$, $p = < 0.01$ (vs. intercept only)			
Parameter	B (SE)	Wald χ^2	p value	OR (95% CI)
Expiratory M-mode measurement of cardiac pulse transmission through lung < 1.5 mm	1.65 (0.64)	6.63	0.01	5.22 (1.48 to 18.35)
Anechoic pleural fluid seen	1.40 (0.65)	4.69	0.03	4.06 (1.14 to 14.42)
Pleural fluid septations seen	2.55 (0.77)	10.96	< 0.01	12.74 (2.82 to 57.51)
No lung expansion seen with inspiratory effort	1.33 (0.89)	2.20	0.14	3.76 (0.65 to 21.71)

(c)	Model (step) 3 Overall success 85.9%; $\chi^2(3) = 41.7$, $p = < 0.01$ (vs. intercept only)			
Parameter	B (SE)	Wald χ^2	p value	OR (95% CI)
Expiratory M-mode measurement of cardiac pulse transmission through lung < 1.5 mm	1.87 (0.62)	9.16	< 0.01	6.48 (1.93 to 21.76)
Anechoic pleural fluid seen	1.31 (0.63)	4.31	0.04	3.71 (1.08 to 12.76)
Pleural fluid septations seen	2.53 (0.74)	11.63	< 0.01	12.57 (2.93 to 53.87)

Expiratory hold M-mode measurement of cardiac pulse transmission through atelectatic lung tissue, using the cut-off threshold of 1.5 mm displacement, was shown to be a consistent predictor of unexpandable lung when considered in both isolation (that is, in model 1), and in subsequent regression analyses alongside the other novel ultrasound parameters (that is, in models 2 and 3). Of the novel ultrasound parameters evaluated in the regression analysis, the presence of pleural fluid septations appeared to have the strongest association with unexpandable lung (odds ratio 12.57, 95% CI 2.93 to 53.87). The final model (**table 8 (c)**) correctly classified 85.9% of the whole study population (92.3% of those with expandable lung; 70.4% of those with unexpandable lung) as compared to 70.7% of the whole study population when using a null model with intercept only (that is, assuming all study participants have expandable lung); a difference that reached statistical significance and appeared to indicate that the predictors as a set could reliably distinguish between expandable and unexpandable lung (chi-square = 41.7, $p = < 0.01$ with 3 df). Nagelkerke's R^2 was 0.52 for the final model, suggesting a moderately strong relationship between prediction and grouping.

3.2.3 Symptomatic response to pleural drainage

56/92 (60.9%) patients completed the voluntary post-procedural questionnaire (**figure 2**) relating to their experience of and symptomatic response following pleural intervention. Of these, 45/56 (80.4%) patients were attending for a day-case procedure and therefore returned their questionnaire on the same day as they underwent intervention. 16/56 (28.6%) patients had unexpandable lung as defined by the study methodology.

There was no significant difference between the mean reported visual analogue scale procedural pain score for patients with either unexpandable lung (mean 22.7 mm; SD 21.2) or expandable lung (mean 16.5 mm; SD 19.6) ($p = 0.30$; difference 6.2 mm, 95% CI -18.0 to 5.7). Dyspnoea was evaluated using a Likert-type scale and visual analogue scale score, with a reduction in dyspnoea of ≥ 19 mm on the visual analogue scale considered significant (Mishra et al., 2015). There was no significant difference between those patients with expandable or unexpandable lung with respect to the

likelihood of reporting an improvement in dyspnoea following pleural drainage (**table 9**).

No characteristic on pre-procedure thoracic ultrasound examination, either static or dynamic, was identified that appeared to be significantly associated with change in dyspnoea following pleural drainage (**tables 10 and 11**).

Table 9 Association of the presence of either expandable or unexpandable lung with symptomatic improvement following pleural drainage based on (a) change in visual analogue scale dyspnoea score; and (b) Likert-type rating of change in dyspnoea

		Post-drainage lung characterisation	
		Expandable <i>n</i> = 40 (71.4%)	Unexpandable <i>n</i> = 16 (28.6%)
(a) Change in VAS dyspnoea score			
≥19mm (<i>n</i> = 42; 75.0%)	30/40	12/16	χ ² (1) = <0.01 (<i>p</i> = 1.0)
<19mm (<i>n</i> = 14; 25.0%)	10/40	4/16	
(b) Likert-type rating of change in dyspnoea			
Better (<i>n</i> = 43; 76.8%)	30/40	13/16	χ ² (1) = 0.25 (<i>p</i> = 0.62)
Not better (<i>n</i> = 13; 23.2%)	10/20	3/16	

TABLE 10 Association of pre-drainage in-depth static thoracic ultrasound findings and symptomatic improvement following pleural intervention based on (a) change in visual analogue scale dyspnoea score; and (b) Likert-type rating of change in dyspnoea. Data presented as either *n* (%age) or mean (SD; 95% CI)

	(a) Change in VAS dyspnoea score		(b) Likert-type rating of change in dyspnoea	
	≥19mm <i>n</i> = 42 (75.0%)	<19mm <i>n</i> = 14 (25.0%)	Better <i>n</i> = 43 (76.8%)	Not better <i>n</i> = 13 (23.2%)
Clinical features				
Malignant or paramalignant effusion	30	9	X ² (1) = 0.25 (<i>p</i> = 0.62)	8
Benign effusion	12	5		5
Volume of pleural fluid drained, mL	1433 (778; 1191 to 1676)	1161 (471; 889 to 1433)	<i>p</i> = 0.22 (<i>t</i> -test)	1215 (493; 917 to 1513)
Static TUS features				
Effusion side - Right	28	5	X ² (1) = 4.16 (<i>p</i> = 0.04)	6
- Left	14	9		7
Effusion size - Large	28	9	X ² (1) = 0.03 (<i>p</i> = 0.87)	7
- Moderate	14	5		6
Septations - None	36	10	X ² (2) = 5.12 (<i>p</i> = 0.08)	9
- Mild	3	4		4
- Moderate	3	0		0
Echogenic pleural fluid	26	6	X ² (1) = 1.56 (<i>p</i> = 0.21)	8
Parietal pleural thickening visible	3	2	X ² (1) = 0.66 (<i>p</i> = 0.42)	1
Visceral pleural thickening visible	3	2	X ² (1) = 0.66 (<i>p</i> = 0.42)	2
Pleural nodularity visible	8	0	X ² (1) = 3.11 (<i>p</i> = 0.08)	0
Lung consolidation visible	4	2	X ² (1) = 0.25 (<i>p</i> = 0.62)	3

TABLE 11 Association of pre-drainage in-depth dynamic thoracic ultrasound findings and symptomatic improvement following pleural intervention based on (a) change in visual analogue scale dyspnoea score; and (b) Likert-type rating of change in dyspnoea. Data presented as either *n* (%age) or mean (SD; 95% CI)

	(a) Change in VAS dyspnoea score		(b) Likert-type rating of change in dyspnoea	
	≥19mm <i>n</i> = 42 (75.0%)	<19mm <i>n</i> = 14 (25.0%)	Better <i>n</i> = 43 (76.8%)	Not better <i>n</i> = 13 (23.2%)
Dynamic TUS features				
Paradoxical motion of hemidiaphragm	19	6	21 $\chi^2(1) = 0.02$ (<i>p</i> = 0.88)	4 $\chi^2(1) = 1.32$ (<i>p</i> = 0.25)
Atelectatic lung moving freely within fluid	35	11	35 $\chi^2(1) = 0.16$ (<i>p</i> = 0.69)	11 $\chi^2(1) = 0.07$ (<i>p</i> = 0.79)
Lung expansion seen with inspiratory effort	13	4	12 $\chi^2(1) = 0.03$ (<i>p</i> = 0.87)	5 $\chi^2(1) = 0.53$ (<i>p</i> = 0.47)
Inspiratory hold - lung pulse visible	41	13	42 $\chi^2(1) = 0.69$ (<i>p</i> = 0.41)	12 $\chi^2(1) = 0.84$ (<i>p</i> = 0.36)
Expiratory hold - lung pulse visible	41	13	42 $\chi^2(1) = 0.69$ (<i>p</i> = 0.41)	12 $\chi^2(1) = 0.84$ (<i>p</i> = 0.36)
Inspiratory hold - M-mode measurement of lung pulse transmission, mm	2.4 (1.8; 1.8 to 2.9)	2.1 (1.6; 1.2 to 3.1)	2.2 <i>p</i> = 0.65 (<i>t</i> -test)	2.4 <i>p</i> = 0.76 (1.6; 1.5 to 3.4) (<i>t</i> -test)
Expiratory hold - M-mode measurement of lung pulse transmission, mm	3.5 (3.0; 2.6 to 4.5)	3.0 (2.3; 1.7 to 4.3)	3.4 <i>p</i> = 0.54 (<i>t</i> -test)	3.5 <i>p</i> = 0.85 (2.1; 2.2 to 4.8) (<i>t</i> -test)

3. RESULTS

3.3 Thoracic ultrasound in the assessment of extravascular lung water in patients with end-stage renal failure undergoing haemodialysis

3.3.1 Subjects

A total of 30 participants were recruited to the study. This was below the intended recruitment target of 50 participants; however, as this target was pragmatic and not mandatory, being based on the recruitment timeframe available as opposed to any formal power calculation, it was not felt to be a barrier to study completion and data analysis. Baseline characteristics of the study population are provided in **table 12**. All study participants completed their planned haemodialysis session (between 3 and 4 hours in duration, depending on clinical need), and all study-related procedures without any complications.

3.3.2 Routine clinical measures of fluid status during haemodialysis

Data were collected to assess the relationship between clinical measurements used routinely to monitor changes in fluid status during haemodialysis in everyday practice. As expected, this demonstrated a strong positive correlation between change in weight pre- to post-haemodialysis, and the volume of fluid removed during haemodialysis as measured by the dialyzer (Pearson's $r = 0.92$, $p = <0.01$) (**figure 9.a**). There was a weaker negative correlation between the change in haematocrit pre- to post-haemodialysis, and the volume of fluid removed during haemodialysis (Pearson's $r = -0.47$, $p = 0.01$) (**figures 9.b**).

Table 12: Baseline characteristics of the study population (total $n = 30$ participants); data are presented as either n (%age) or median (IQR)

Sex	Male	22 (73.3%)
	Female	8 (26.7%)
Age, years		63.6 (52.8 - 76.4)
Aetiology of ESRF	Diabetes	9
	Hypertension	4
	Adult polycystic kidney disease	4
	IgA nephropathy	3
	Autoimmune vasculitis	2
	Postinfectious GN	2
	Obstructive uropathy	2
	Idiopathic / unknown	2
	Mesangial proliferative GN	1
	Nephrectomy (malignancy)	1
Other medical history	COPD	12 (40%)
	Interstitial lung disease	3 (10%)
	Cardiac failure	6 (20%)
Fluid removed on dialysis, mL		2562 (2019 - 3531)

Abbreviations: *IQR = interquartile range; ESRF = end-stage renal failure; IgA = Immunoglobulin A; GN = glomerulonephritis; COPD = chronic obstructive pulmonary disease*

3.3.3 Primary analysis

As there was an extremely strong positive correlation between change in weight pre- to post-haemodialysis and the volume of fluid removed during haemodialysis as measured by the dialysis machine, the primary analysis utilised the latter measurement alone as it potentially allowed three readings to be matched with contemporaneous lung ultrasound examinations (that is, from before, midway through, and following haemodialysis).

An initial analysis using just two timepoints (before and after haemodialysis) did not appear to demonstrate any correlation between the volume of fluid removed during haemodialysis and the reduction in total lung ultrasound B-line score recorded by either the primary bedside ultrasound operator (Pearson's $r = 0.20$, $n = 30$, $p = 0.28$) (**figure 10.a**) or the independent blinded scorers (Pearson's $r = 0.08$, $n = 60$, $p = 0.55$) (**figure 10.b**). However, this initial analysis included several study participants who had a minimal number of B-lines prior to haemodialysis; and therefore, by extension, no sonographic evidence of excess extravascular lung water that could be measured.

A post-hoc decision was therefore made to re-analyse the data, this time excluding those study participants who had a minimal number of B-lines on their baseline (that is, pre-dialysis) ultrasound scan to see if this revealed any sonographic signal. The exclusion criteria were based on a version of the sonographic categorisation of extravascular lung water accumulation used in prior work (Frassi et al., 2007; Mallamaci et al., 2010), modified to reflect this study's use of a 20-point (as opposed to 28-point in the prior published work) ultrasound examination protocol. On this basis, participants with a total of 10 or fewer B-lines according to their baseline ultrasound scan score were considered to have no or minimal extravascular lung water. At least two of the three sonographers assessing the ultrasound imaging had to report a total lung ultrasound B-line score of 10 or below on the baseline (pre-dialysis) scan for a patient to be excluded from the post-hoc analysis. Once these criteria were applied, 8/30 (26.7%) study participants were excluded on the basis that they had no or minimal sonographic evidence of

extravascular lung water. Analysis of data from the remaining 22 (73.3%) participants demonstrated at least moderate positive correlation between the reduction in total lung ultrasound B-line score and volume of fluid removed during haemodialysis (**figure 11**).

3/30 (10%) patients recruited to the study had concomitant interstitial lung disease, recognised as a potential confounder to the assessment of any change in B-lines on lung ultrasound as specified in the introduction. None of the patients were known to have interstitial lung disease prior to study recruitment, with the diagnosis only being made following cross-sectional (CT) imaging for study purposes. All three patients were included in the post-hoc analysis detailed above, having more than 10 B-lines on their baseline ultrasound scan. When these three patients with interstitial lung disease were excluded from any analysis of the data, the correlation between reduction in total lung ultrasound B-line score and volume of fluid removed during haemodialysis improved; this was evident both for the entire study population and once participants with minimal B-lines on their pre-dialysis baseline scan per the post-hoc definition had been removed (**figure 12 and table 12**).

When looking at data from three timepoints (before, during, and after haemodialysis), whilst the positive correlation between reduction in total lung ultrasound B-line score and volume of fluid removed during haemodialysis was evident, the relationship did not appear to be purely linear (**figures 13, 14 and 15**). This would suggest other factors having an influence on how changes in intravascular volume status affected extravascular fluid status in different individuals. It was, however, also noted that no study participant had an increase in their total B-line score from pre- to post-dialysis reported by either the primary bedside or blinded scorers (**figure 15**).

Figure 9 Relationship between (a) change in weight, kg, pre- to post-dialysis and volume of fluid, mL, removed during haemodialysis; and (b) change in haematocrit pre- to post-dialysis and volume of fluid removed

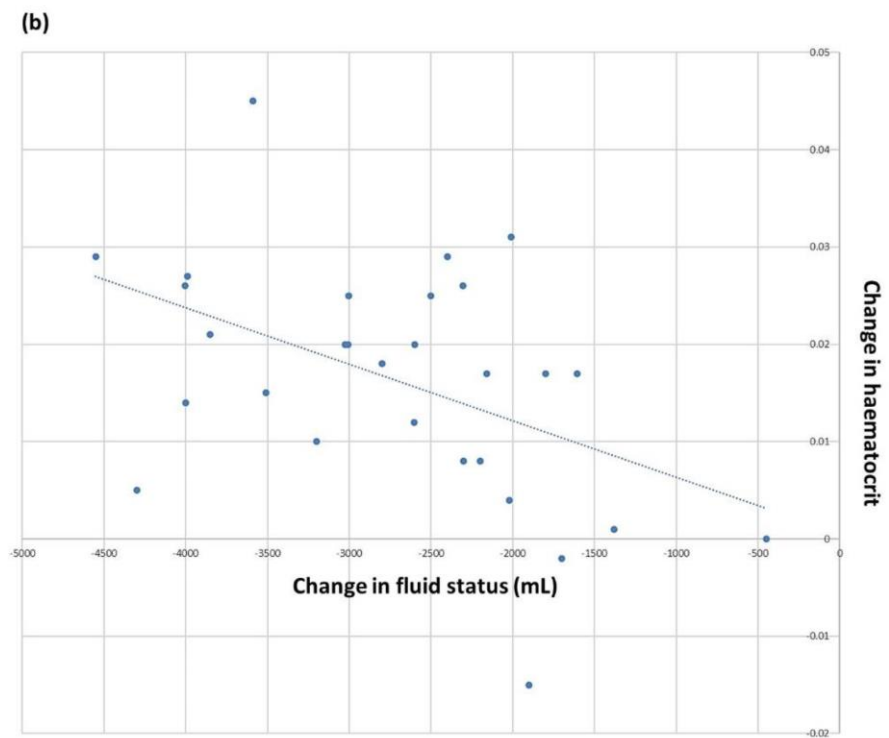
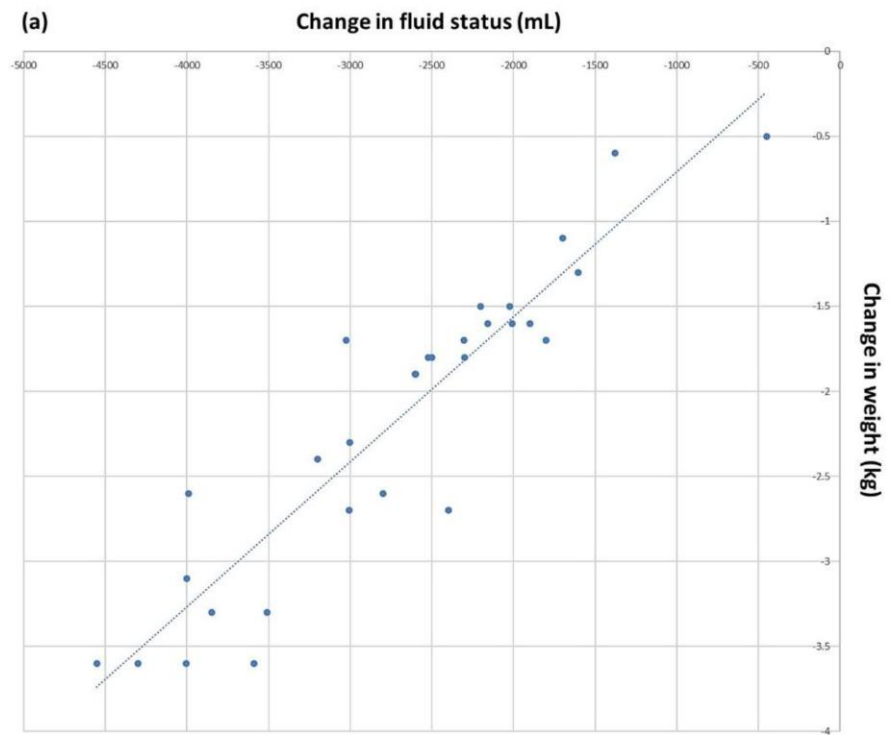


Figure 10 Relationship between volume of fluid (mL) removed during haemodialysis and change in total lung ultrasound B-line score for all study participants; **(a)** data for primary (bedside) scorer, **(b)** data for combined blind scorers

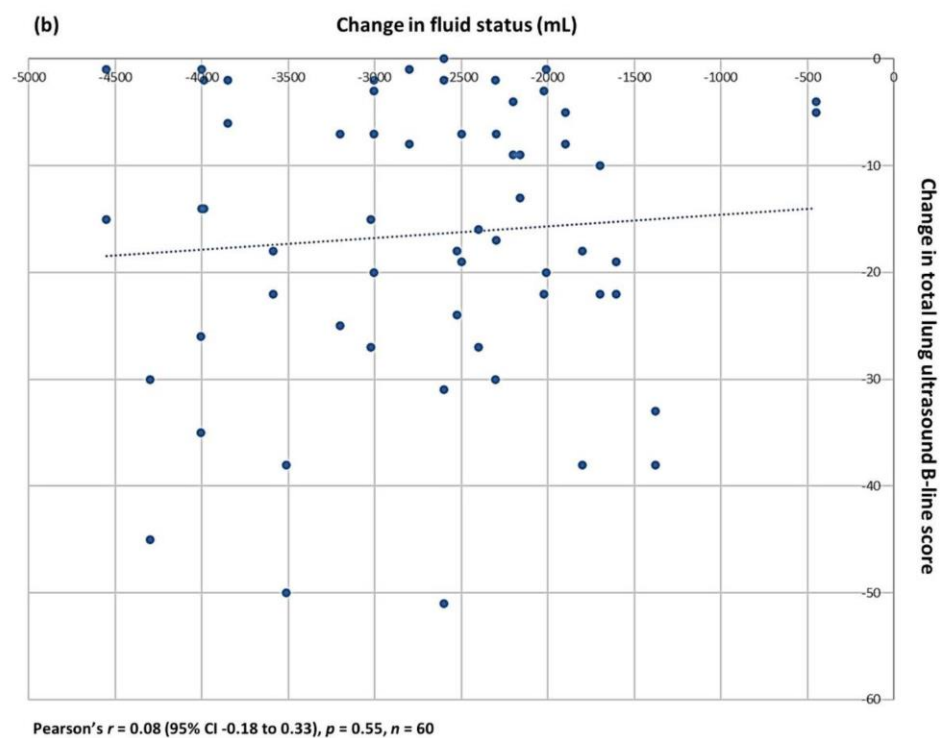
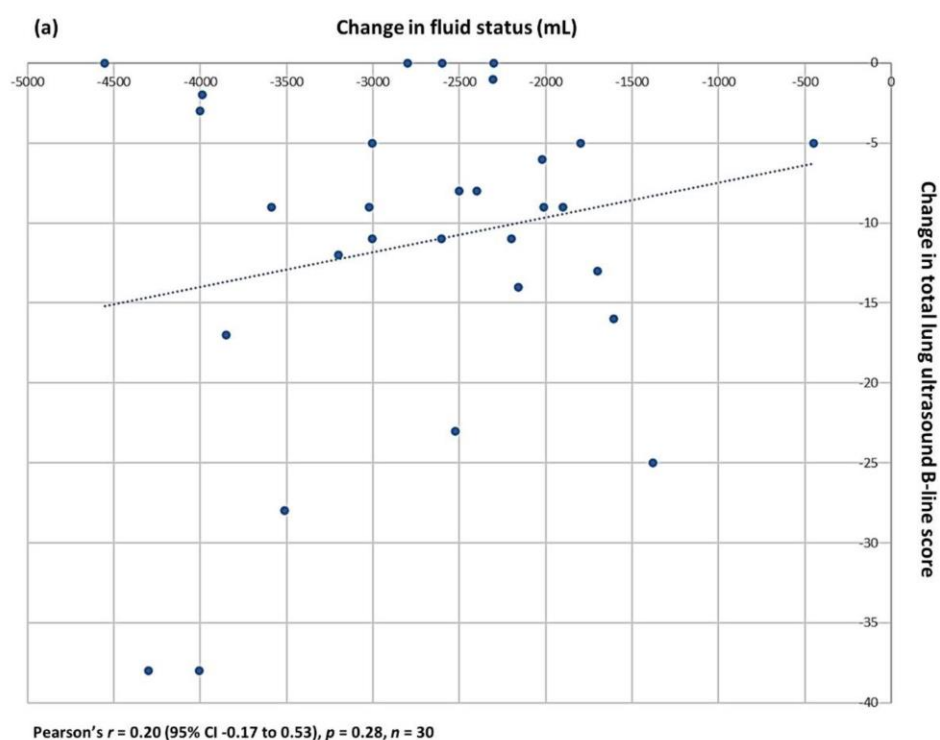


Figure 11 Relationship between volume of fluid (mL) removed during haemodialysis and change in total lung ultrasound B-line score excluding patients with minimal B-lines on baseline ultrasound;
(a) data for primary (bedside) scorer, **(b)** data for combined blind scorers

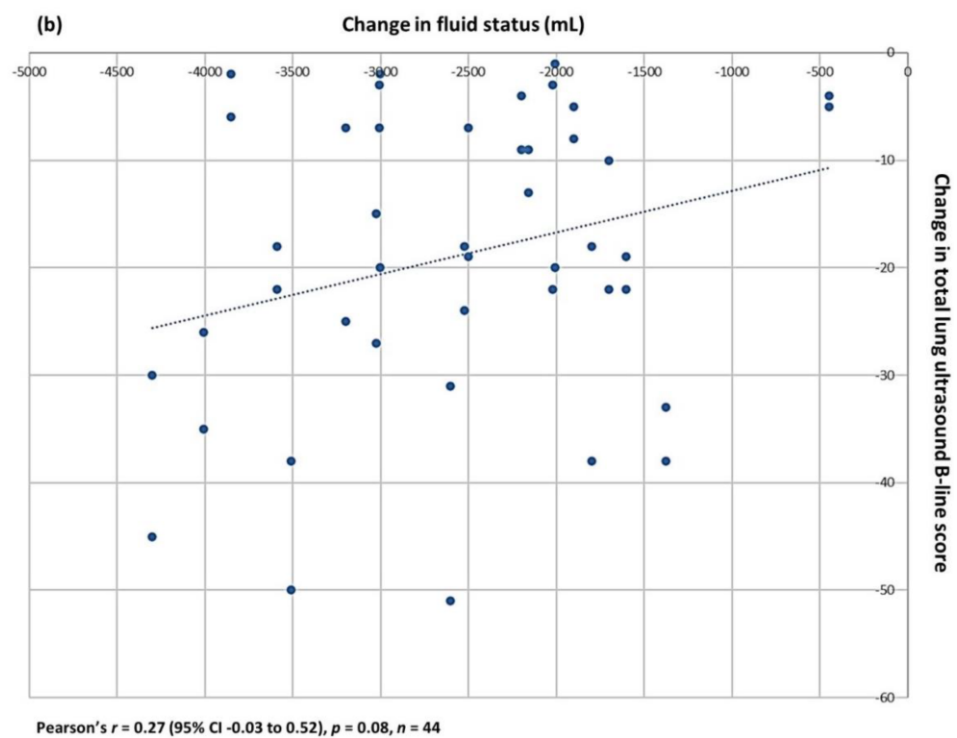
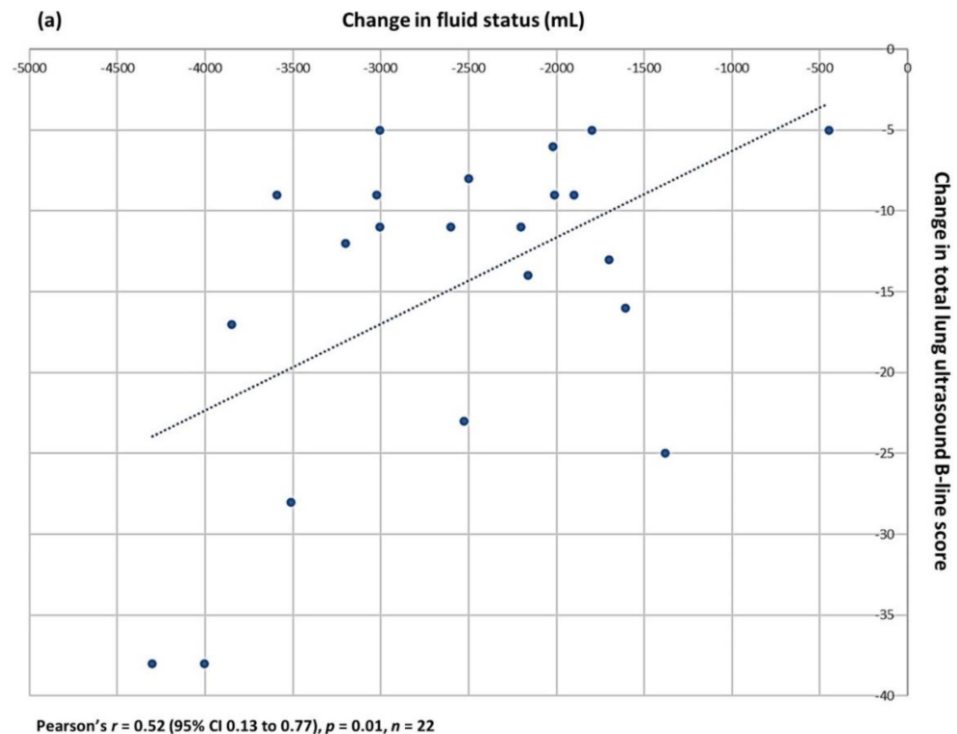


Figure 12 Relationship between volume of fluid (mL) removed during haemodialysis and change in total lung ultrasound B-line score excluding patients with minimal B-lines on baseline ultrasound and/or with interstitial lung disease; **(a)** data for primary (bedside) scorer, **(b)** data for combined blind scorers

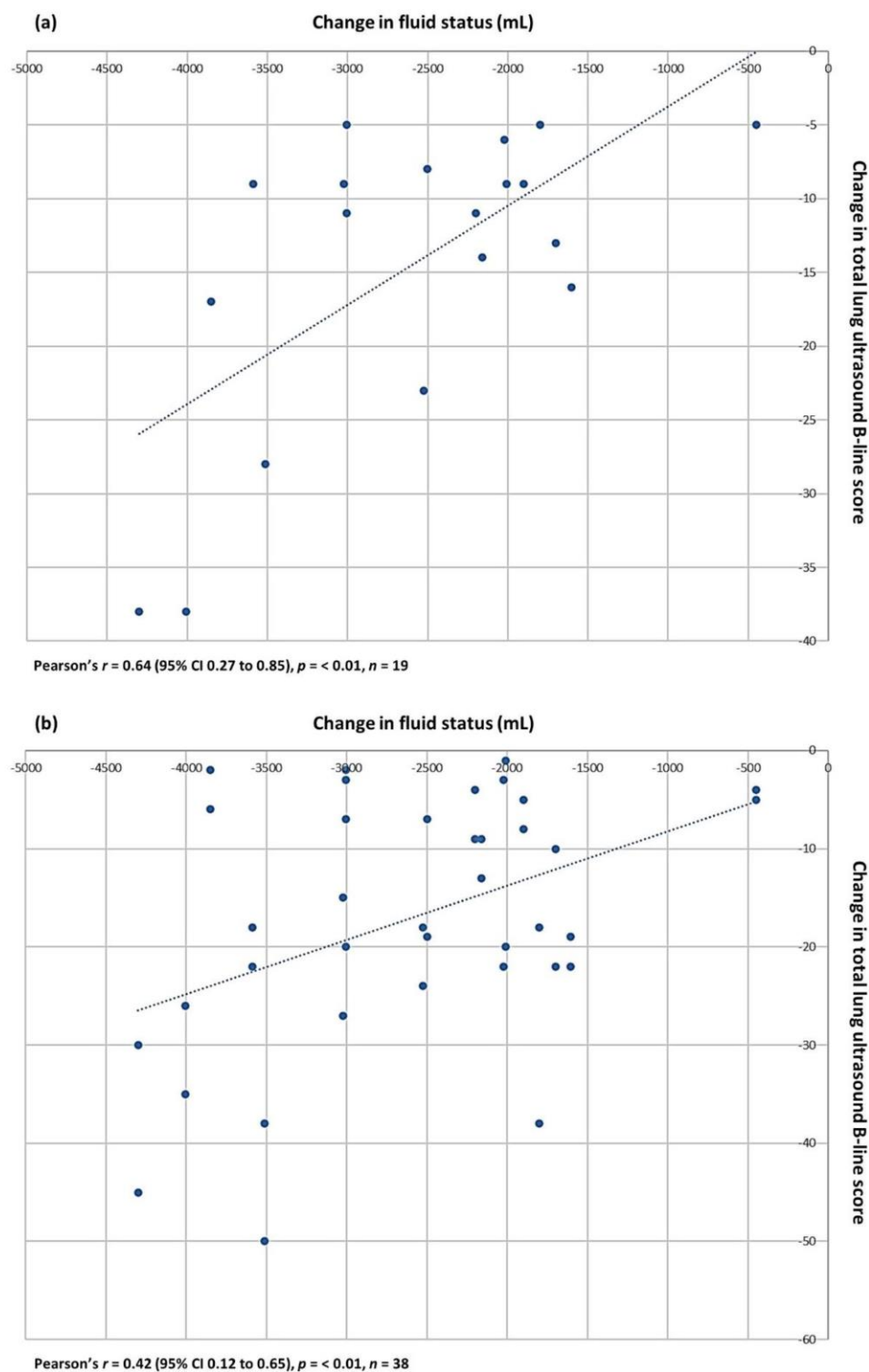


Table 13

Relationship between volume of fluid (mL) removed during haemodialysis and change in total lung ultrasound B-line score (BLS) pre-to post-dialysis for primary (bedside) operator and independent (blinded) scorers – Pearson's correlation coefficient (r) reported with 95% confidence intervals and p value (two-tailed)

	All participants	ILD patients excluded	Q4 patients (low baseline BLS) excluded	ILD & Q4 patients (low baseline BLS) excluded
Data for primary (bedside) scorer	$r = 0.20$ (-0.17 to 0.53) $p = 0.28$, $n = 30$	$r = 0.29$ (-0.10 to 0.60) $p = 0.14$, $n = 27$	$r = 0.52$ (0.13 to 0.77) $p = 0.01$, $n = 22$	$r = 0.64$ (0.27 to 0.85) $p = < 0.01$, $n = 19$
Combined data for blind scorers	$r = 0.08$ (-0.18 to 0.33) $p = 0.55$, $n = 60$	$r = 0.19$ (-0.08 to 0.43) $p = 0.17$, $n = 54$	$r = 0.27$ (-0.03 to 0.52) $p = 0.08$, $n = 44$	$r = 0.42$ (0.12 to 0.6) $p = < 0.01$, $n = 38$
- Blind scorer 1	$r = 0.06$ (-0.42 to 0.51) $p = 0.81$, $n = 18$	$r = 0.30$ (-0.23 to 0.69) $p = 0.25$, $n = 16$	$r = 0.21$ (-0.39 to 0.68) $p = 0.50$, $n = 13$	$r = 0.51$ (-0.14 to 0.85) $p = 0.11$, $n = 11$
- Blind scorer 2	$r = -0.20$ (-0.61 to 0.29) $p = 0.42$, $n = 18$	$r = -0.18$ (-0.63 to 0.37) $p = 0.52$, $n = 15$	$r = 0.19$ (-0.40 to 0.67) $p = 0.52$, $n = 13$	$r = 0.38$ (-0.33 to 0.82) $p = 0.27$, $n = 10$
- Blind scorer 3	$r = 0.33$ (-0.24 to 0.73) $p = 0.24$, $n = 14$	$r = 0.43$ (-0.16 to 0.79) $p = 0.14$, $n = 13$	$r = 0.37$ (-0.34 to 0.81) $p = 0.29$, $n = 10$	$r = 0.52$ (-0.22 to 0.88) $p = 0.15$, $n = 9$
- Blind scorer 4	$r = 0.33$ (-0.38 to 0.79) $p = 0.35$, $n = 10$	$r = 0.33$ (-0.38 to 0.79) $p = 0.35$, $n = 10$	$r = 0.45$ (-0.38 to 0.88) $p = 0.27$, $n = 8$	$r = 0.45$ (-0.38 to 0.88) $p = 0.27$, $n = 8$

3.3.4 Comparison of lung ultrasound and computed tomography findings

4/30 (13.3%) participants were reported as having evidence of fluid overload on the pre-dialysis computed tomography (CT) scan of their chest. In two cases the reporting radiologist described this as “clear fluid overload”, with features including cardiomegaly, small bilateral pleural effusions, and widespread interlobular septal thickening throughout the lung parenchyma. In two cases the changes were described as “subtle fluid overload”, with interlobular septal thickening towards the lung bases only and favouring more dependent areas of the lung parenchyma. The remaining 26/30 (86.7%) participants were reported as having no evidence of fluid overload on their pre-dialysis CT scan; this was unchanged on their post-dialysis CT scans.

Of the four participants with fluid overload on their pre-dialysis CT scan, only one (initially described as “clear fluid overload”) was reported as showing evidence of improvement on their post-dialysis CT scan with resolution of one pleural effusion and almost complete clearance of the previous interlobular septal thickening. The other three participants with evidence of fluid overload on their pre-dialysis CT scan were reported as showing no change in appearances on their post-dialysis CT scan.

The 4/30 (13.3%) study participants with evidence of fluid overload on pre-dialysis CT scan of their chest all had a reduction in their total lung ultrasound B-line score during haemodialysis (**figures 13.a & 14.a**) that was consistently observed by both the primary (bedside) and blinded scorers. The mean absolute reduction in B-line score was 28.3 (SD 13.7), and the mean percentage reduction pre- to post-dialysis was 69.5% (SD 10.4; 95% CI 53 to 86) for the primary (bedside) scorer. The mean absolute reduction in B-line score was 31.1 (SD 14.0), and the mean percentage reduction pre- to post-dialysis was 61.6% (SD 15.9; 95% CI 48 to 75) for the combined blinded scorers.

For the remaining study participants with no evidence of fluid overload on pre-dialysis CT scan, once those with minimal B-lines on their baseline (pre-dialysis) lung ultrasound examination had been excluded per the approach taken for the primary

analysis, there was also evidence of a reduction in total lung ultrasound B-line score during haemodialysis (**figures 13.b & 14.b**), that was again observed by both the primary (bedside) and blinded scorers. The mean absolute reduction in B-line score was 11.6 (SD 5.8), and the mean percentage reduction pre- to post-dialysis was 52.3% (SD 25.4; 95% CI 40 to 65) for the primary (bedside) scorer. The mean absolute reduction in B-line score was 16.5 (SD 12.1), and the mean percentage reduction pre- to post-dialysis was 50.6% (SD 28.5; 95% CI 41 to 60) for the combined blinded scorers.

There was no significant difference in the mean percentage reduction in total lung ultrasound B-line score pre- to post-dialysis between the study participants who had evidence of fluid overload on their pre-dialysis CT scan, and the study participants with no evidence of fluid overload on their pre-dialysis CT scan. This was the case for both the primary (bedside) scorer ($p = 0.21$, t -test) and the combined blinded scorers ($p = 0.30$, t -test).

In terms of a direct comparison between CT and ultrasound for both the detection of extravascular lung water and identification of subsequent change following haemodialysis, CT was able to detect lung water in 4/30 (13.3%) participants and a change following haemodialysis in 1/30 (3.3%) participants. Ultrasound was able to detect lung water (defined *a priori* as an excess of B-lines) in 22/30 (73.3%) participants and a change following haemodialysis in all these same individuals, whether assessed by the primary bedside or blinded scorers.

Figure 13 Change in absolute total lung ultrasound B-line score vs. volume of fluid removed during haemodialysis (mL) for study participants with **(a)** evidence of fluid overload, and **(b)** no evidence of fluid overload on pre-dialysis CT. Dashed line represents best fit for each group. Ultrasound data presented for primary (bedside) scorer.

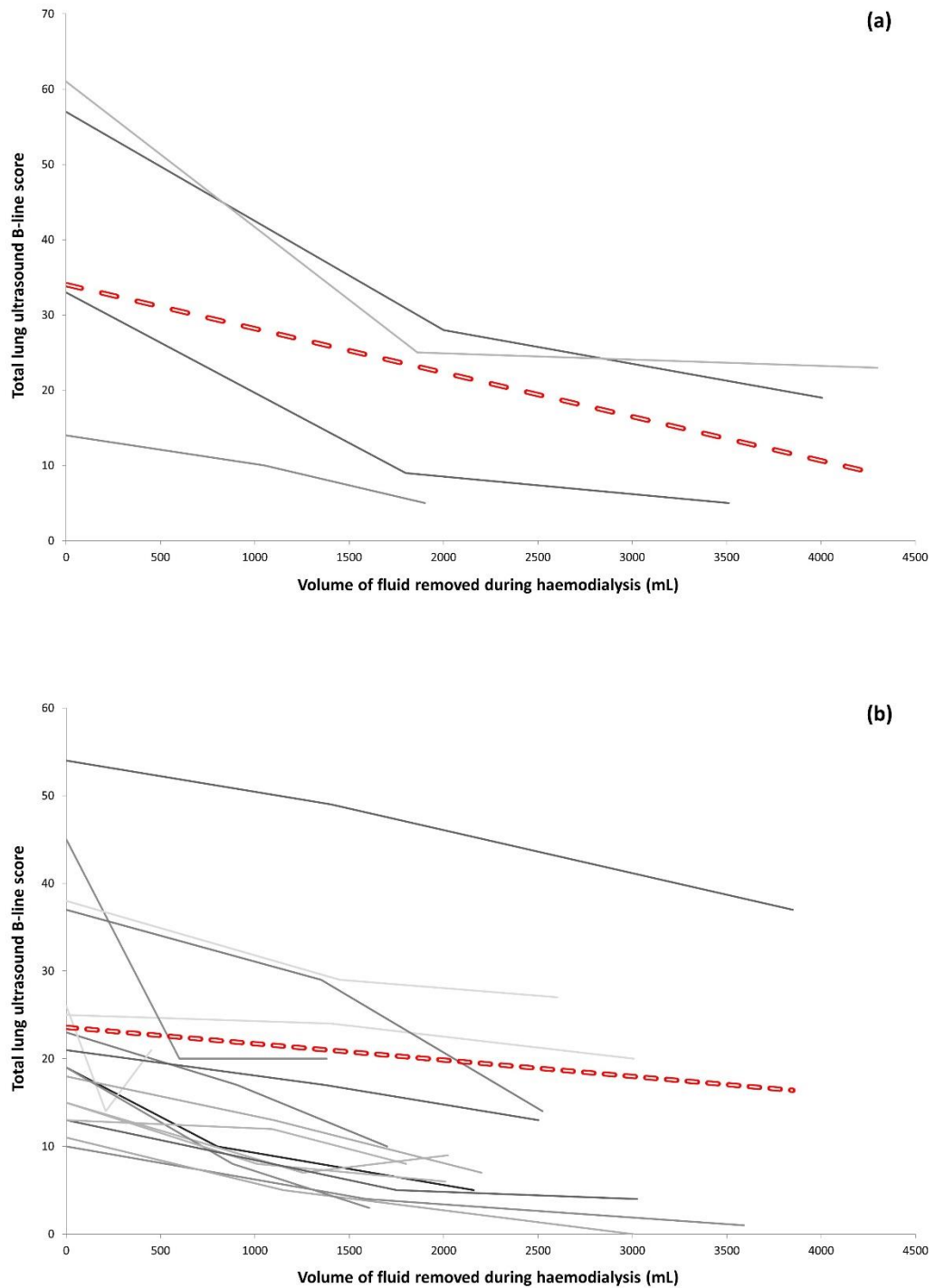


Figure 14 Change in absolute total lung ultrasound B-line score vs. volume of fluid removed during haemodialysis (mL) for study participants with **(a)** evidence of fluid overload, and **(b)** no evidence of fluid overload on pre-dialysis CT. Dashed line represents best fit for each group. Ultrasound data presented for combined blind scorers.

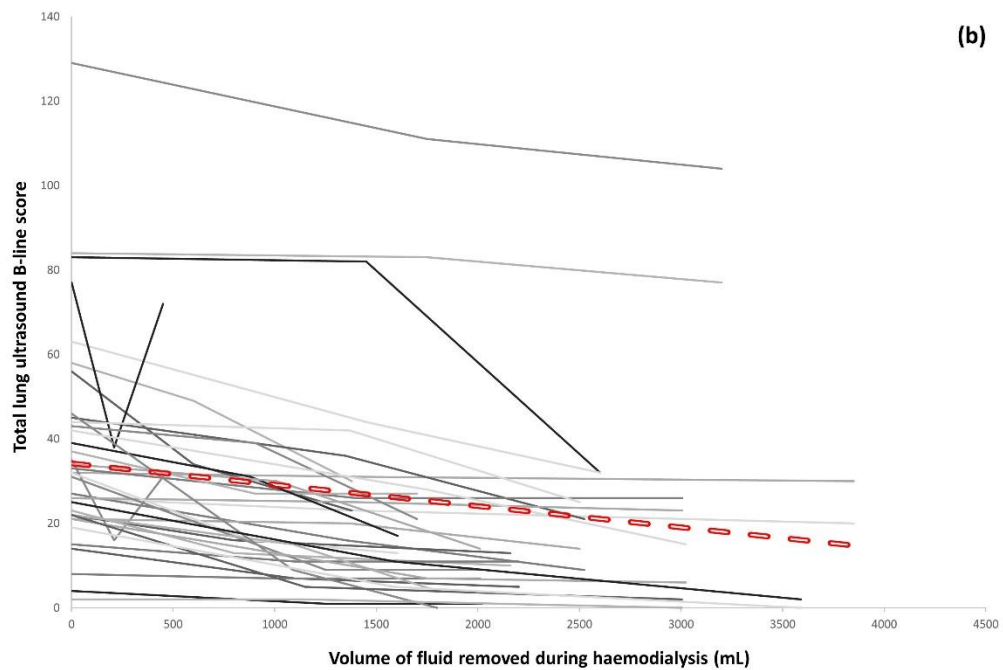
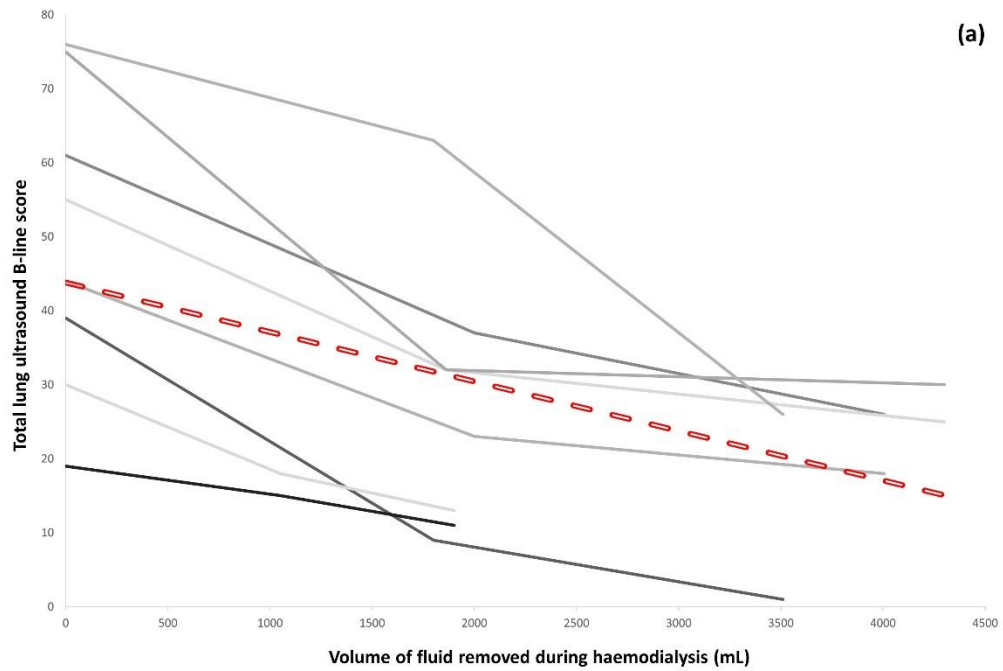
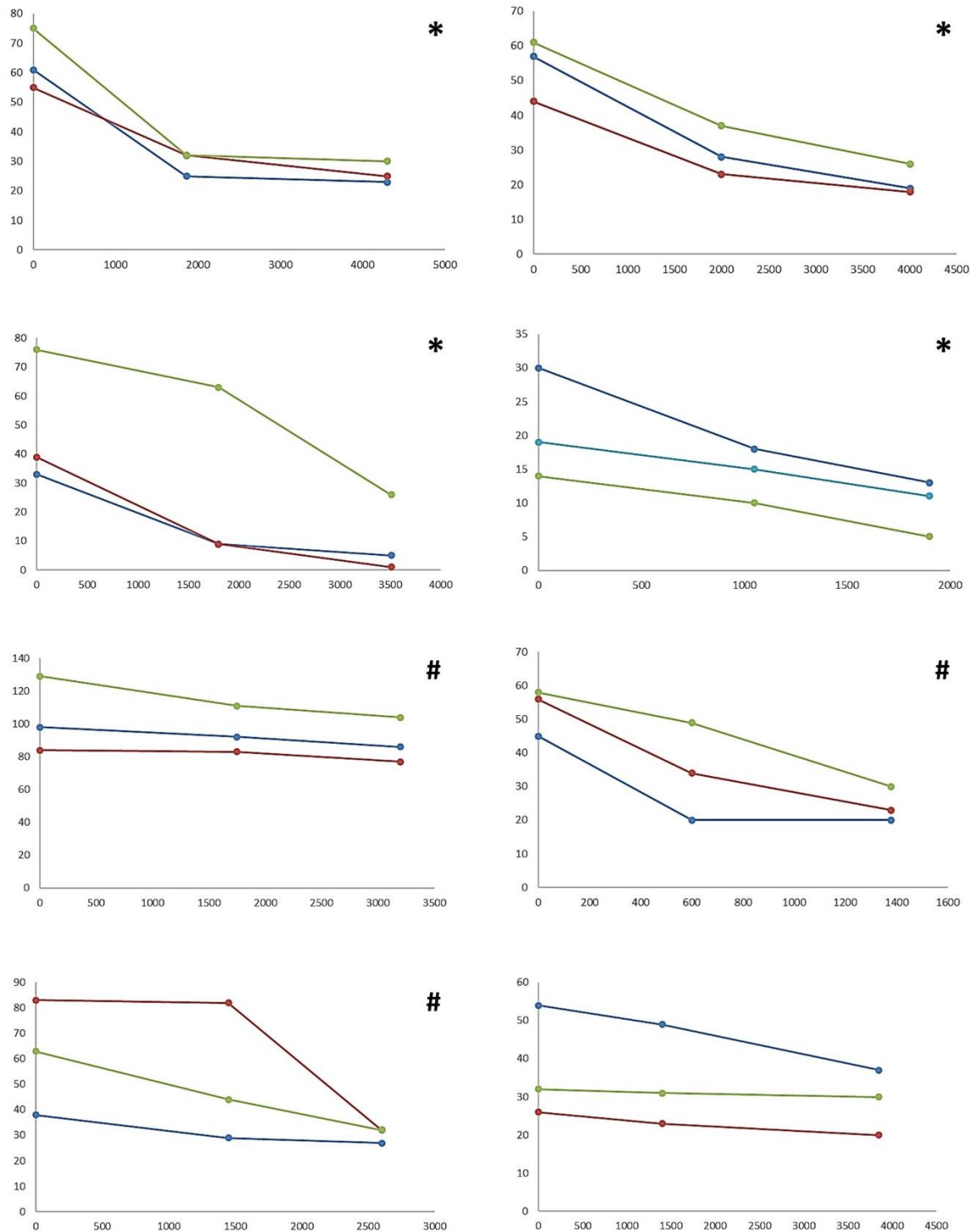
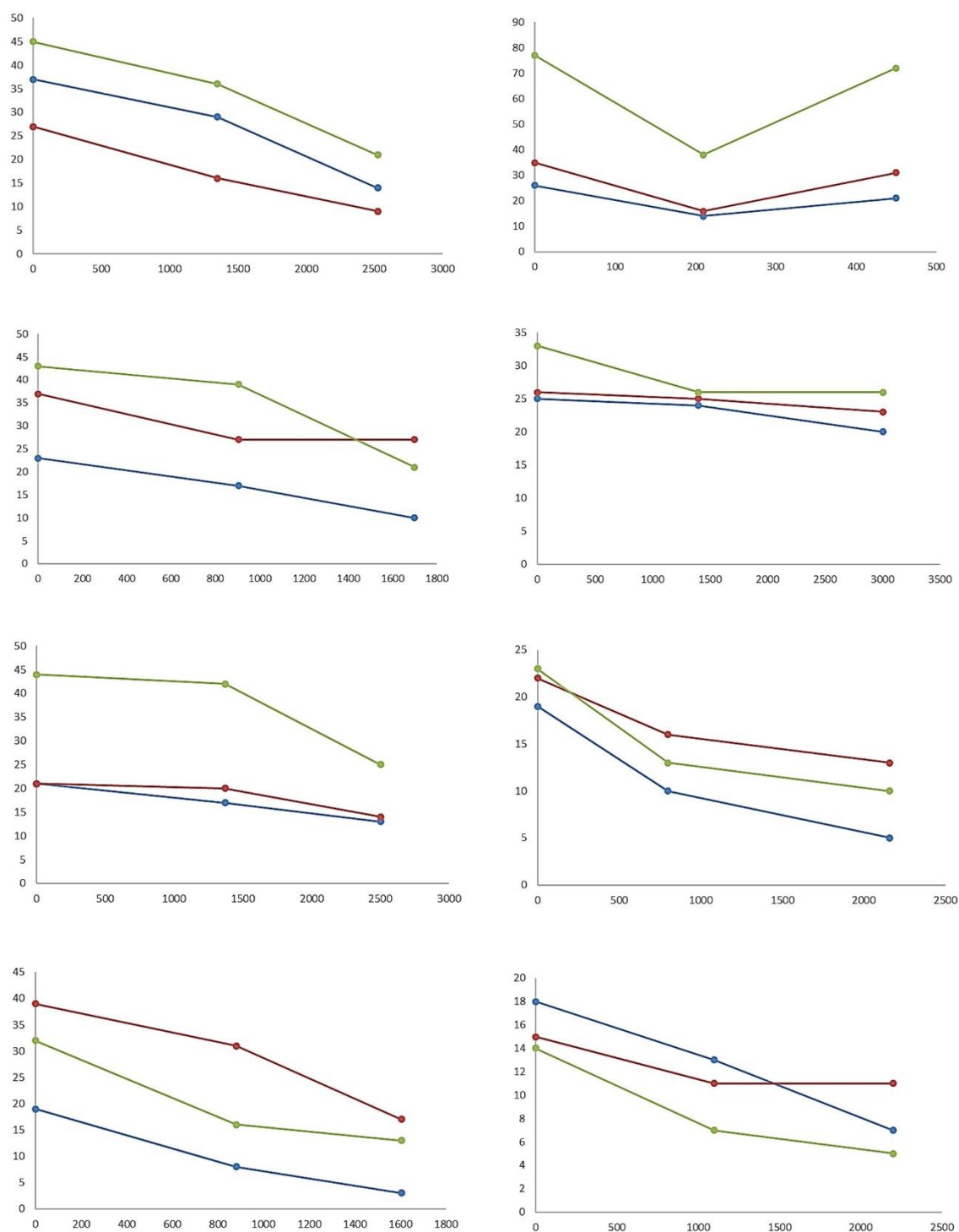


Figure 15 Individual patient data (n = 22; excludes patients with minimal B-lines on baseline (pre-dialysis) ultrasound) showing change in total B-line score (y-axis) vs. fluid removed during dialysis (x-axis) with similar trends but variation in absolute scores from different scorers.
 (* patients with evidence of fluid overload on pre-dialysis CT scan;
 # patients with interstitial lung disease)



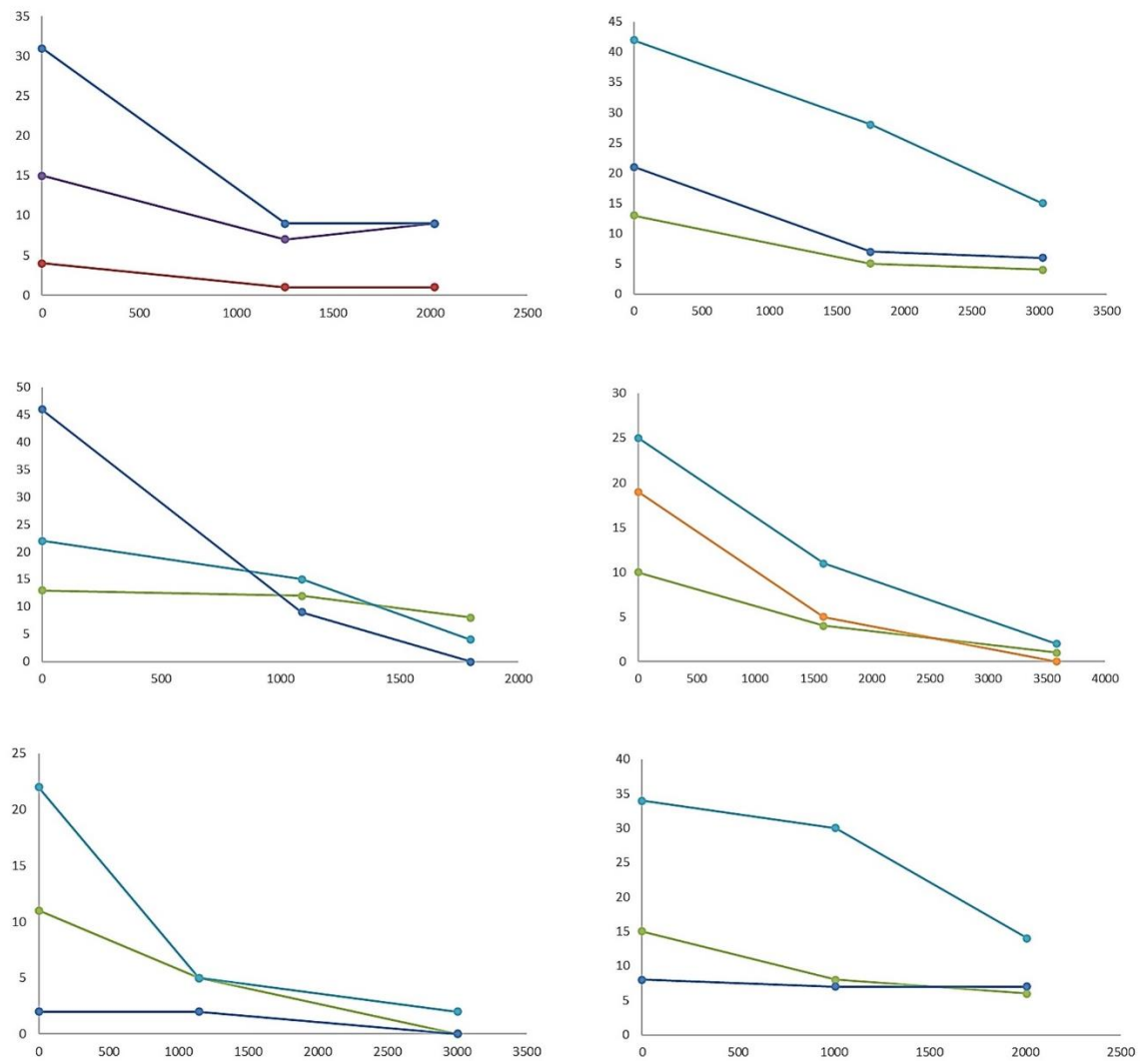
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Figure 15 Individual patient data (n = 22; excludes patients with minimal B-lines on baseline (pre-dialysis) ultrasound) showing change in total B-line score (y-axis) vs. fluid removed during dialysis (x-axis) with similar trends but variation in absolute scores from different scorers.



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Figure 15 Individual patient data (n = 22; excludes patients with minimal B-lines on baseline (pre-dialysis) ultrasound) showing change in total B-line score (y-axis) vs. fluid removed during dialysis (x-axis) with similar trends but variation in absolute scores from different scorers.



3.3.5 Correlation of changes in total lung ultrasound B-line score with patient-reported breathlessness

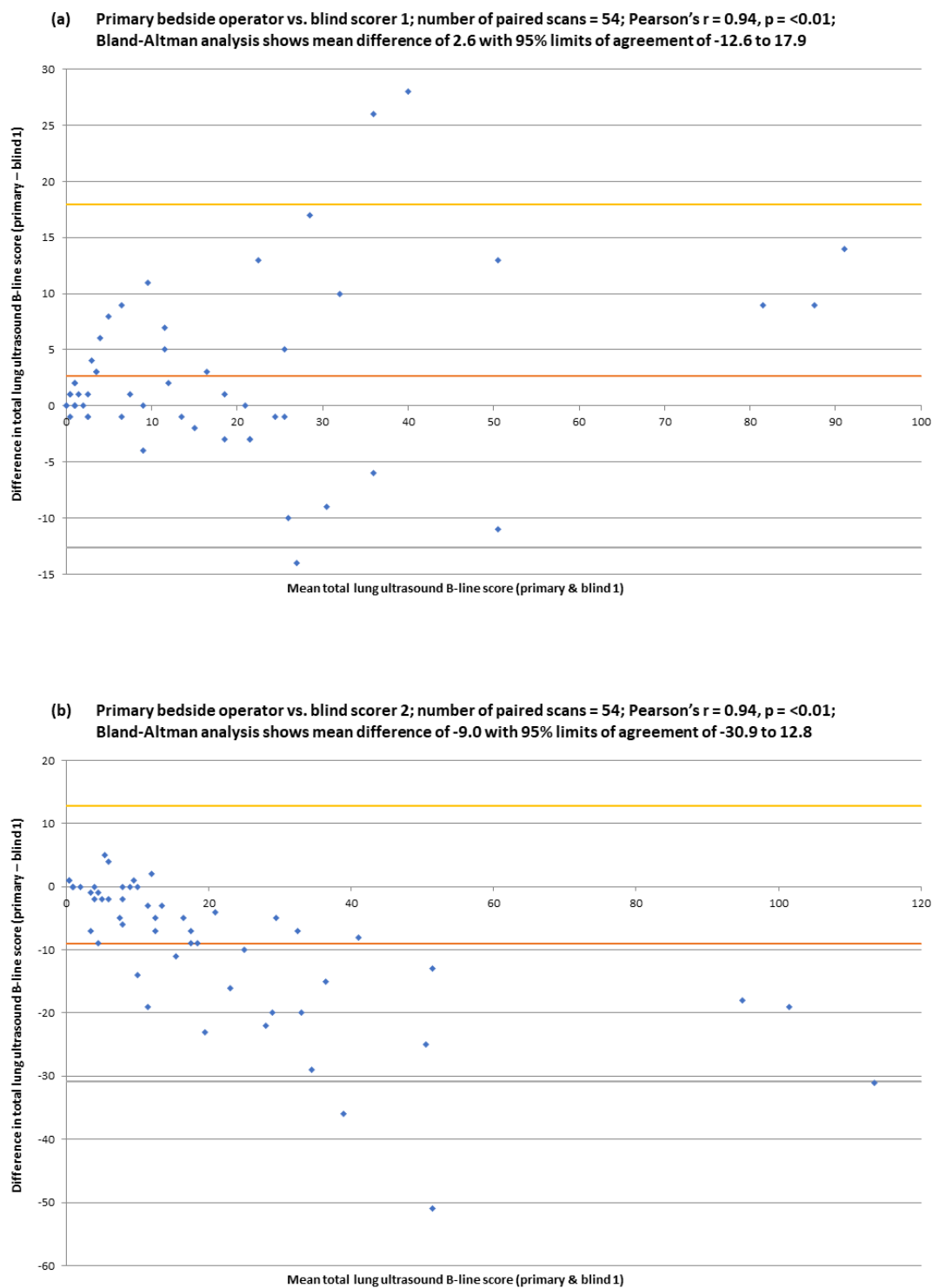
Patient-reported change in breathlessness following haemodialysis was measured using a Likert-type scale and visual analogue scale score, with a reduction in breathlessness of ≥ 10 mm on the visual analogue scale considered clinically significant based on data from a general population (Booth, 2006) in the absence of any large population reference data for haemodialysis patients. The mean change in the visual analogue scale breathlessness score following haemodialysis was -4.8 mm (SD 10.1; 95% CI -8.6 to -1.0), with 5/30 (16.7%) participants reporting a significant reduction in breathlessness according to the pre-specified threshold. 11/30 (36.7%) participants reported an improvement in their breathing (4 slightly, 3 moderately, 4 significantly) using the Likert-type scale.

The mean reduction in the total lung ultrasound B-line score for any study participant reporting an improvement in breathlessness following haemodialysis was 15.3 (SD 11.3; 95% CI 8.1 to 22.5), whilst the reduction in B-line score for study participants without any improvement in breathlessness was 8.5 (SD 8.8; 95% CI 4.1 to 12.9). The difference between the two groups did not reach significance (mean difference -6.8; 95% CI -14.3 to 0.8; $p = 0.07$, unpaired t-test).

3.3.6 Consistency of lung ultrasound scoring between clinicians

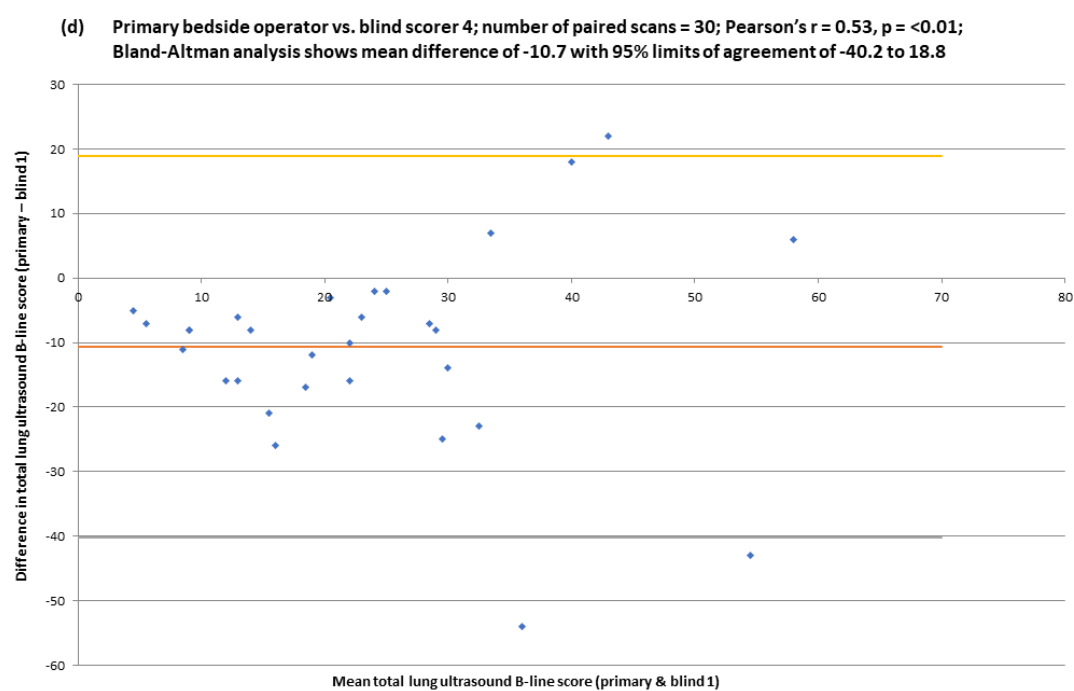
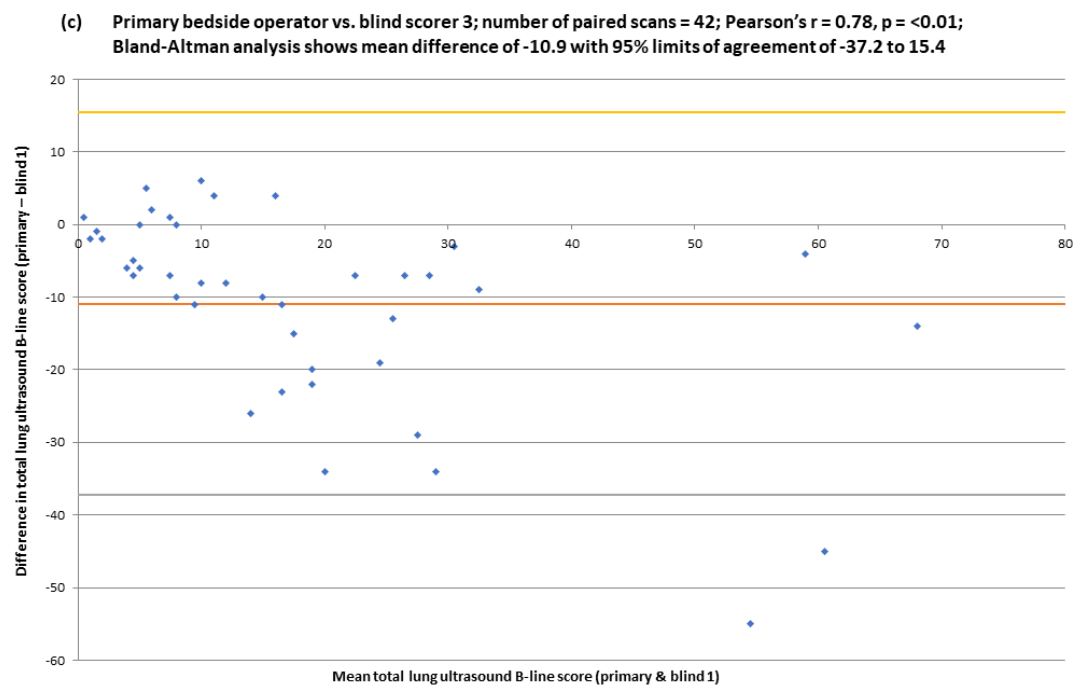
Each ultrasound scan was scored by the primary (bedside) operator and two independent clinicians blinded to the patient's clinical condition and the time at which the ultrasound scan had been performed during haemodialysis. Inter-rater agreement for the diagnosis of interstitial syndrome (a binary choice between present or absent) was moderate to good, with free-marginal kappa 0.61 (95% CI 0.47 to 0.73, $p = <0.01$) and 80% overall agreement between the three raters. Whilst there was at least moderate agreement between the primary (bedside) operator and individual blinded clinicians as measured by the correlation coefficient, Bland-Altman analysis demonstrated poor agreement between the individual total lung ultrasound B-line scores awarded by different raters (**figure 16**).

Figure 16 Bland-Altman plots assessing pairwise agreement for total lung ultrasound B-line scores (primary operator vs. blinded scorers 1-4)



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Figure 16 Bland-Altman plots assessing pairwise agreement for total lung
(continued) ultrasound B-line scores (primary operator vs. blinded scorers 1-4)



3.3.7 Patient satisfaction with lung ultrasound examination

All the study participants reported their willingness to have the same ultrasound scans performed again in future if it were deemed to be clinically appropriate.

15/30 (50%) participants did not find the ultrasound examination time-consuming at all; 14/30 (46.7%) reported it to be slightly time-consuming, whilst 1/30 (3.3%) found it very time-consuming. The mean visual analogue pain score reported in association with the ultrasound examination was 4.8 mm (SD 5.9; 95% CI 2.6 to 7.0).

4. DISCUSSION

4.1 Thoracic ultrasound as an early predictor of pleurodesis success in malignant pleural effusion

This feasibility study addressed whether the findings on thoracic ultrasound examination immediately before and 24 hours after chemical pleurodesis (talc slurry instillation) for malignant pleural effusion could predict longer-term success or failure of the procedure.

The results of this study appear to show that thoracic ultrasound has utility in the early detection of pleural adhesion formation following talc slurry instillation, as manifest in the loss of the normal lung sliding artefact on thoracic ultrasound. This finding is consistent with prior published data (Cassanelli et al., 2012; Sasaki et al., 2005) demonstrating the same sonographic and anatomical features in a different clinical setting. The extent of loss of lung sliding on thoracic ultrasound at 24 hours following talc slurry instillation, as measured by a total pleural adherence score, appears to be associated with longer-term pleurodesis success. Those study participants with a successful pleurodesis at one-month follow-up had a higher mean total pleural adherence score on thoracic ultrasound at 24 hours post-talc slurry instillation compared to those whose pleurodesis went on to fail (mean difference of 6.27; 95% CI 3.94 to 8.59; $p = <0.001$).

Thoracic ultrasound examination for this clinical purpose appears acceptable to patients, and deliverable at the bedside by appropriately trained physicians with the potential to impact positively on decision making around timing of chest tube removal. No thoracic ultrasound examination took longer than five minutes, meaning the technique could be easily incorporated into everyday clinical practice. This was reflected in patient feedback; none of whom found the ultrasound examination overly time consuming, and all of whom would be willing to have the same examination again if indicated for these clinical purposes. The interpretation of thoracic ultrasound findings was consistent across the different clinicians who

viewed the scans, with good inter-rater reliability. This is an important observation as thoracic ultrasound has the potential to be highly operator dependent and subjective. The fact that the scoring of thoracic ultrasound scans by the bedside operator and two remote blinded observers not involved in any of the original data collection was similar means both the technique used, and outcomes observed in this study can be confidently regarded as reliable and robust.

This study is the first to establish a proof of principle for thoracic ultrasound as an outcome prediction tool following talc (chemical) pleurodesis in humans with recurrent symptomatic malignant pleural effusion. It is additionally novel in assessing and demonstrating the ability of thoracic ultrasound to detect the early loss of lung sliding, a sonographic marker of pleural adhesion formation, and thereby predict longer-term pleurodesis success. However, the loss of lung sliding on ultrasound examination is not unique to the presence of pleural adhesions and may be seen with other thoracic pathology; most notably pneumothorax which may develop ex-vacuo in the same patient population as a consequence of unexpandable lung secondary to underlying malignant pleural disease.

In this particular study and clinical context, however, one would expect the presence of unexpandable lung to be associated with subsequent pleurodesis failure due to inadequate apposition of the visceral and parietal pleural surfaces prior to talc slurry instillation. If the absence of lung sliding on ultrasound were indeed the result of pneumothorax ex-vacuo as opposed to early pleural adhesion formation, any signal for a higher ultrasound adherence score to be associated with longer-term pleurodesis success would most likely be lost. It is reasonable, therefore, to assume that the observations made on ultrasound examination in this study, with a loss of normal lung sliding, do indeed reflect the formation of early pleural adhesions that predate a subsequent successful pleurodesis. The case for there being an active pleural process ongoing around the time of talc slurry instillation in those patients who went on to have long-term pleurodesis success is further supported by the increase seen in total mean pleural adherence score from day 0 to day 1 (mean difference of 2.91; 95% CI 0.97 to 4.85; $p = 0.004$) in this

patient group, as opposed to the absence of any significant change over the same timeframe in those patients whose pleurodesis failed (mean difference of 1.08; 95% CI -1.10 to 3.26; $p = 0.32$).

Prior data in both animals (Zhu et al., 2005) and humans (Leo et al., 2005) describing thoracic ultrasound assessment of pleurodesis were obtained at a delayed interval of two and four weeks following the administration of a sclerosing agent respectively. A thoracic ultrasound assessment of pleurodesis success that required a delay of up to a month after the use of talc or another chemical sclerosant would have little or no clinical utility in the real-world context of intended definitive treatment for malignant pleural effusion, since those patients with a failed pleurodesis would most likely already have had fluid recurrence diagnosed and/or a further therapeutic intervention. However, the ability to identify early on those patients at a higher risk of pleurodesis failure would allow clinicians to put appropriate measures into place; for example, discussion of and planning for alternative strategies such as indwelling pleural catheter insertion. Equally, the development and validation of a total pleural adherence score cut-off that allows earlier chest drain removal and, by extension, discharge from hospital without concern that doing so might compromise the likelihood of longer-term pleurodesis success would benefit patients and clinicians alike. Whilst the data from this study suggest that such a benefit might be achievable, this was identified from a post-hoc analysis and should be considered only with caution accordingly. A further large-scale study adequately powered to address this outcome among others is necessary before any change in clinical practice should be considered.

An interesting and unexpected observation from this study was the signal seen for the total pleural adherence score at day 0 (that is, prior to talc slurry instillation) to predict longer-term pleurodesis success. Although the combined thoracic ultrasound results for the original bedside and blinded scorers at day 0 reached significance for detecting a difference between the two patient groups (that is, pleurodesis success or failure at one-month follow-up), this was not the case for individual scorers' data and therefore cannot be considered a reliable finding.

Nonetheless, this observation may be linked to the concept of spontaneous or auto-pleurodesis in malignant pleural effusion; most frequently described in the current literature in the context of indwelling pleural catheters (Davies et al., 2012; Wahidi et al., 2017; Muruganandan et al., 2018) where up to 50% of the patient population may develop a pleurodesis after 6 to 12 months without the use of a chemical sclerosant such as talc.

There are limited data available to describe auto-pleurodesis rates following chest tube drainage of malignant pleural effusion without the subsequent use of a sclerosant agent, with the available studies reporting rates of anywhere between 11 and 60% (Groth et al., 1991; Shaw & Agarwal, 2013; Sorensen, Svendsen, & Enk, 1984; Zaloznik, Oswald, & Langin, 1983). However, the ability of the pleural space to form adhesions spontaneously in the context of prolonged or recurrent inflammatory stimuli, as occurs following repeated thoracentesis for recurrent symptomatic effusions, is well recognised (Roberts et al., 2010). The importance of a dry pleural space to this same process, as demonstrated by the increased rate of auto-pleurodesis seen in patients managed with a more aggressive and frequent drainage regime with indwelling pleural catheters in-situ (Wahidi et al., 2017; Muruganandan et al., 2018) is also recognised.

Bearing these facts in mind it is unclear whether the observations made in this study, with a reduction in normal lung sliding already evident prior to talc administration, can be taken as proof that another phenomenon promoting pleural adhesion formation is already at work in a proportion of cases and to which the arrival of talc in the pleural space is simply a late adjunct. The length of time (4.3 days) between chest tube insertion and subsequent talc slurry instillation in this study reflects real-world and not necessarily optimal practice (Roberts et al., 2010; Davies et al., 2012), but may have allowed the process of adhesion formation to begin of its own accord in a consistently dry pleural space during this unintentional delay. The anatomical mechanism of auto-pleurodesis is likely to be similar to that seen with talc though with pleural adhesion formation leading on to obliteration of the pleural space; potentially with the drain itself acting as an inflammatory

stimulus, or an as yet unrecognised physical, biochemical, or immunological characteristic of the malignant pleural effusion or the diseased pleural surface(s) predisposing to spontaneous pleurodesis. Regardless, it may be that thoracic ultrasound can identify those patients who are likely to develop auto-pleurodesis following complete drainage of a malignant pleural effusion without the need for intrapleural talc or another sclerosant, saving time and resources in turn.

An exploratory analysis of the ultrasound data collected during this study suggest the development of pleural adhesions laterally, posteriorly, and more superiorly in the affected hemithorax may be of relevance to longer-term pleurodesis success following treatment for malignant pleural effusion. It is important to note this analysis was exploratory, post-hoc, and vulnerable given the small number of cases and multiple comparisons performed. Hypothetically, however, this anatomical location would appear to make sense clinically and physiologically. Any residual or recurrent pleural fluid will usually find its way to the base of the hemithorax with gravity; however, symptoms are only likely to arise if the volume of fluid is sufficient to involve the more superior part of the pleural cavity. The development of pleural adhesions in the upper and middle part of the chest would prevent this from happening. An alternative explanation is that diaphragmatic excursion at the base of the hemithorax may confound the assessment of lung sliding by giving a false impression of movement and increasing scorer's uncertainty.

This study has several limitations. Being a feasibility study, the number of participants was small and recruited from a single centre with specific expertise in both pleural disease and the use of thoracic ultrasound. Thoracic ultrasound is a highly operator-dependent technique with the accurate evaluation of lung sliding vulnerable to factors including probe orientation in relation to the visceral-parietal pleural interface and the use of noise reduction software (Lichtenstein, 2007). As a result, the findings may not necessarily be replicated elsewhere in centres with less familiarity with the technique and/or ultrasound expertise, and must therefore be validated as part of a large-scale multicentre randomised trial before the technique described can be adopted as part of routine clinical practice. This process of

assessing the validity of thoracic ultrasound-guided management of patients undergoing talc instillation as a therapeutic intervention for malignant pleural effusion is already underway (Psallidas et al., 2017). 3/18 (16.7%) participants died before reaching one-month follow-up, and 9/18 (50%) participants failed to survive to the later three-month follow-up point. This is not unexpected given the nature of the population being studied and malignant pleural effusion being a recognised marker of advanced metastatic disease (Clive et al., 2014; Roberts et al., 2010). The study methodology was, however, strong; in particular, the use of independent blinded assessors for and demonstration of consistency in thoracic ultrasound scoring, something which has not been a feature of previous work in this area of practice.

There has also been a shift in clinical practice towards the use of indwelling pleural catheters to manage malignant pleural effusions over the past few years, potentially meaning that the use of chemical pleurodesis and need for outcome prediction through ultrasound markers may become less important. However, this instead raises the possibility of future work looking at whether the same ultrasound technique described in this study can identify those patients who are most likely to have a successful outcome from accelerated treatment protocols for indwelling pleural catheters; whether this is through a more aggressive daily drainage routine (Wahidi et al., 2017; Muruganandan et al., 2018) or the use of talc slurry instillation (Bhatnagar et al., 2018).

In conclusion, a pleural adherence score obtained using thoracic ultrasound at 24 hours post-talc slurry instillation in the context of symptomatic malignant pleural effusion was associated with longer-term pleurodesis success or failure in this pilot study. Thoracic ultrasound examination for this purpose appears to be reliable, deliverable at the bedside, and acceptable to patients. These findings have implications for the individualised management of patients with malignant pleural effusion; a population that is growing in number on an annual basis and will continue to do so for the foreseeable future. Further research is now needed to further evaluate the role of thoracic ultrasound as an early outcome prediction tool

for patients with malignant pleural effusion undergoing definitive treatment with intrapleural talc or another chemical sclerosant.

4. DISCUSSION

4.2 Thoracic ultrasound as a predictor of unexpandable lung and symptomatic improvement prior to pleural intervention

This study addressed whether the findings of an in-depth thoracic ultrasound examination prior to intervention for a symptomatic pleural effusion could predict the presence of unexpandable lung, and the patient's subsequent response to that intervention in terms of any procedure-associated discomfort and improvement in breathlessness.

The results of this study demonstrate the potential value of thoracic ultrasound as a non-invasive means of identifying unexpandable lung prior to pleural intervention. As well as showing similar results to the previously published data relating to the use of motion (M-) mode measurement of cardiac pulse transmission through atelectatic lung (Salamonsen et al., 2014), this study has also identified a number of more commonly observed sonographic features that might be of potential interest in future research designed to develop and validate an expanded thoracic ultrasound prediction model for unexpandable lung. The study is additionally novel in evaluating key patient-related outcome measures; that is, procedure-associated pain and post-procedural change in breathlessness; following drainage of a symptomatic pleural effusion in the context of unexpandable versus expandable lung. The observation that patients with unexpandable lung are as likely to see a symptomatic improvement in their breathing following pleural drainage as those patients with expandable lung, and without a significant difference in procedure-associated pain, is important to physicians responsible for counselling these individuals about the risks and benefits of pleural intervention.

This study builds on previous work (Salamonsen et al., 2014) by demonstrating the feasibility of delivering an in-depth thoracic ultrasound assessment as part of routine care. Measurements including M-mode evaluation (**figure 6**) were taken prospectively in real-time by a number of different thoracic physicians with

varying individual experience and expertise, and without access to more specialised (notably, echocardiographic) training or equipment. These same physicians were all operating within the time constraints and pressures of a busy clinical service, as opposed to a more controlled research-dedicated environment. A more pragmatic definition of unexpandable lung was adopted, combining easily available radiographic and clinical data, and focusing on the likely impact of this diagnosis on future interventions for recurrent symptomatic pleural fluid in such a way that it would be directly relevant to physicians and patients during the continued clinical decision-making process.

M-mode measurement of cardiac pulse transmission through atelectatic lung was demonstrated to be a significant predictor of unexpandable lung, with an area under the receiver operating characteristic curve (AUROC) of 0.81 (95% CI 0.71 to 0.92, $p = <0.01$) in this study that compares favourably to the AUROC of 0.79 reported in previous work (Salamonsen et al., 2014). A number of other thoracic ultrasound parameters were identified as being associated with unexpandable lung during this study, all of which were biologically and physiologically plausible with respect to why this might be the case (**table 13**). Furthermore, a subsequent regression analysis incorporating some of these other thoracic ultrasound parameters identified as being of potential interest in the identification of unexpandable lung showed the predictive capability of M-mode, using a cut-off threshold of 1.5 mm to distinguish between expandable and unexpandable lung, to be preserved with an odds ratio of approximately 6 in the final prediction model. This same regression analysis also identified two other sonographic parameters, pleural fluid septations (OR approximately 12) and pleural fluid echogenicity (OR approximately 4), that appear to be associated with and potentially predictive of unexpandable lung in their own right. A larger prospective study will be necessary to distinguish what might be real as opposed to chance findings, although this study has helped by identifying which sonographic parameters are likely to be of greatest interest and allowing the original in-depth thoracic ultrasound examination protocol to be refined prior to any future evaluation.

Table 14 Thoracic ultrasound parameters associated with unexpandable lung in this study, and proposed mechanism(s) by which this might occur

Thoracic ultrasound parameter	Possible mechanism of association with presence of unexpandable lung
Motion (M-) mode measure of cardiac pulse transmission through atelectatic lung	Reduction in cardiac pulse transmission thought to correlate with a greater restriction of free lung movement within an effusion, and more likely to occur in the context of unexpandable lung
Lung expansion with inspiratory effort	Limited lung expansion may be caused by either a lung parenchymal abnormality (e.g. fibrotic lung disease increasing elastic recoil of the lung, or an obstructing endobronchial lesion) or more subtle visceral pleural thickening not visible on ultrasound
Visceral pleural thickening	Pleural inflammation (either active or remote) causing fibrous thickening of the visceral pleura that is visible on ultrasound examination, restricting lung expansion and causing an effusion ex-vacuo
Pleural fluid septations	More likely to be seen as part of an active inflammatory process, and in the context of increasing chronicity of an effusion; as such may be associated with developing lung entrapment
Pleural fluid echogenicity	Anechoic pleural fluid (associated with unexpandable lung in this study) usually seen with transudative effusions, which can develop ex-vacuo in the context of long-term trapped lung; the majority of patients in this study had conditions more commonly associated with exudative effusions

Unexpandable lung occurs in around 30% of patients with malignant pleural effusion (Dresler et al., 2005; Huggins et al., 2018); a patient group that continues to grow as the prevalence of cancer in an aging population steadily increases (Maddams et al., 2012; Taghizadeh, Fortin, & Tremblay, 2017). The diagnosis of unexpandable lung has previously relied on the drainage of an effusion to facilitate either the use of pleural manometry (Feller-Kopman, 2013; Grabczak, Krenke, Zielinska-Krawczyk, & Light, 2018) and/or the identification of pneumothorax *ex-vacuo* on a post-procedural chest radiograph. However, both of these methods are dependent on an invasive procedure taking place first. The early identification of patients with or without unexpandable lung in the context of a symptomatic pleural effusion, using a non-invasive technique such as thoracic ultrasound, would allow their care to be streamlined as patients could be directed towards the appropriate therapeutic intervention at first presentation; for example, indwelling pleural catheter insertion for patients with unexpandable lung, rather than pleural drainage with a view to subsequent chemical pleurodesis.

It is worth noting that as the first-line use of indwelling pleural catheters to manage recurrent symptomatic malignant pleural effusion becomes increasingly common (Davies et al., 2012; Penz et al., 2014; Porcel et al., 2017), the future development of a predictive model using thoracic ultrasound may favour a higher sensitivity rather than specificity for the detection of unexpandable lung. In this study, a higher cut-off threshold value for lung excursion on M-mode with cardiac pulse transmission of 1.5 mm (sensitivity 70%, specificity 83%) was chosen for this reason, as opposed to the 1.0 mm cut-off (sensitivity 50%, specificity 85%) proposed in previous work (Salamonsen et al., 2004). This approach may be preferable given the outcome of a number of studies focusing on shortening the length of time that indwelling pleural catheters need to be left in-situ (Bhatnagar, Keenan et al., 2018; Bhatnagar, Zahan-Evans et al., 2018; Muruganandan et al., 2018; Wahidi et al., 2017), meaning the additional use of resources and delay in definitive treatment that might otherwise be incurred by a failure to immediately identify a patient with unexpandable lung will become the greater burden on all those involved.

The decision to intervene in any patient with a pleural effusion is heavily driven by the desire to provide symptomatic benefit, most commonly a reduction in breathlessness. The observation in this study that the presence of either expandable or unexpandable lung had no significant impact on either pain or breathlessness post-intervention is an important one, supporting a general principle of offering a trial of drainage to any patient with a sizable and symptomatic pleural effusion. Although none of the thoracic ultrasound parameters evaluated as part of this study reached significance in predicting the change in patient-reported breathlessness following pleural drainage, pleural nodularity (presence predictive of a positive outcome) and septated pleural fluid (presence predictive of a negative outcome) were close to doing so. The latter observation makes physiological sense since increasing septations are likely to result in incomplete drainage of the pleural space, and is of interest given similar findings in a recently published randomised trial of intrapleural fibrinolytic therapy in this specific patient cohort (Mishra et al., 2018). Once more, a larger study will allow this relationship to be explored in greater detail. The mechanisms underpinning breathlessness in patients with pleural effusion are complex and likely to be multifactorial and different in each individual; it may simply be that ultrasound alone cannot collect all the data necessary to explain the differences in symptomatic response from one patient to another.

There were limitations to the design and delivery of this study. Data were collected at a single centre with specific expertise in pleural disease and the clinical use of thoracic ultrasound; as such, it may be difficult to extrapolate the findings to wider use. However, as none of the thoracic ultrasound operators had prior experience in the everyday clinical use of M-mode ultrasonography and measurement, it suggests the technique can be learned quickly for this specific indication. The number of patients included in the study was small; as such, appropriate caution should be taken with the interpretation of any data since there will have been a greater risk of chance findings occurring whilst the power of the subsequent regression analysis and prediction modelling will have been reduced. As data were collected in real-time in the context of a busy clinical service, this had to be done on a convenience

sampling basis; it cannot be guaranteed that this process was entirely random, and bias may have been introduced into the results as a consequence. It was also not practical or feasible for multiple ultrasound operators to examine the same individual patients; this prevented an assessment of inter- or intra-observer variability in the measurements being taken. Future work will need to address this limitation through the use of multiple assessors, and/or blinded evaluation of ultrasound video clips. However, the nature of this study does allow us to consider how a similar in-depth thoracic ultrasound examination could be delivered in real life as opposed to a more protected research environment.

The study relied on the accurate diagnosis of unexpandable lung which can be challenging when using imaging studies alone (Martin et al., 2020) as, for example, incomplete drainage of the pleural space may leave uncertainty as to whether the lung would have fully expanded had all the fluid been removed. Individual clinicians may not necessarily agree on what chest X-ray appearances represent truly unexpandable lung; whilst any imaging study can only provide information from a single point in time and may therefore miss lung which is slow to re-expand as opposed to being truly unexpandable. The study methodology compensated for this by using multiple clinical assessors and a combination of clinical and radiological parameters to define unexpandable lung; with data, including serial thoracic imaging and the outcome of more than one pleural procedure, acquired over a longer-term follow-up period used to inform the diagnosis. Interpretation of this same data was reliant on the assessors' sub-specialist expertise and might therefore be more challenging in a centre seeing a lower volume of patients with pleural disease. There is also the possibility that the use of multiple imaging studies, including those taken a number of months after the original thoracic ultrasound assessment and pleural intervention, might act as a confounder in any cases where the nature and biology of a patient's pleural disease has evolved over time.

The voluntary nature of the patient questionnaire, a consequence of data being collected as part of service evaluation and development, meant the response rate was limited to 61% of patients undergoing intervention. For the same reasons, data

regarding symptomatic response could only be reasonably collected at a single time point no more than 24 hours following intervention, and in the majority of cases within the first four to six hours. Whilst some patients will have noticed a change in their symptoms (certainly procedure-associated pain, and possibly breathlessness) within this timeframe, there will inevitably have been patients who were not able to provide realistic feedback until the days after their pleural intervention. A future study will need to take this into account, collecting patient-related outcome data on pain, breathlessness, physical activity levels, and other quality of life measures for a longer period (potentially up to a week) following drainage of a pleural effusion to get a fuller picture of the consequences of the intervention. This more detailed data may also unmask a feature of thoracic ultrasound examination that can predict key patient-related outcomes such as improvement in breathlessness.

In conclusion, these results demonstrate that thoracic ultrasound can be used to identify unexpandable lung using M-mode measurement of cardiac pulse transmission through atelectatic lung underlying a pleural effusion, confirming the observations made by a separate group in previously published work (Salamonsen et al., 2014). A number of other more conventional sonographic parameters, in particular pleural fluid septations and pleural fluid echogenicity, have also been identified that might be associated with the presence of unexpandable lung, and which should be explored in future studies. There was no significant difference in symptomatic benefit following pleural drainage for patients with unexpandable as opposed to expandable lung, and as such this diagnosis should not be considered a reason to counsel against intervention. A larger multicentre study is now needed to better characterise those thoracic ultrasound parameters that might allow the non-invasive diagnosis of unexpandable lung prior to pleural intervention, and explore whether a cohort of patients less likely to obtain symptomatic benefit from pleural fluid drainage can be identified concurrently. The development of a prospectively validated thoracic ultrasound prediction model would have implications for the management of patients with pleural effusions by informing the responsible clinician on how and whether to intervene, reducing the burden on healthcare providers and patients alike.

4. DISCUSSION

4.3 Thoracic ultrasound in the assessment of extravascular lung water in patients with end-stage renal failure undergoing haemodialysis

This study addressed whether thoracic ultrasound could detect the presence of, and identify changes in extravascular lung water; using a stable outpatient population of patients with end-stage renal failure undergoing routine haemodialysis who would transition from a hyper- to euvolaemic state over a few hours in a closely monitored environment.

The results of this study demonstrate that thoracic ultrasound can both identify the presence of extravascular lung water and monitor its resolution in real-time, as manifest in a reduction in the total lung ultrasound B-line score from before to after haemodialysis. We can be confident that this is a genuine finding, since the study participants acted as their own controls with the change in total body fluid status incurred by haemodialysis being the only physiological intervention that took place during the period of observation and ultrasound assessment. This reduction in the total lung ultrasound B-line score was observed not only by the primary bedside operator, but independent blinded clinicians with access to the scans only and no knowledge of either the patient's physiological state or timing of the imaging in relation to haemodialysis. There appeared to be moderate correlation between the total lung ultrasound B-line score and volume of fluid removed during haemodialysis over time, evident again in the data available from both the primary (bedside) and independent blinded scorers. The change in total lung ultrasound B-line score and its association with the volume of fluid removed during dialysis appear to at least match the performance of change in haematocrit, which is already a well-established means of monitoring change in fluid status during haemodialysis. The results of this study are consistent with prior published data (Mallamaci et al., 2010; Noble et al., 2009), and add to the evidence base by further demonstrating that thoracic ultrasound appears to outperform computed tomography in both identifying lung changes that would be consistent with the

presence of extravascular lung water, and showing the resolution of these same changes over time.

Despite the ultrasound examination being a detailed study taking measurements from 20 points across the thorax, patients found it to be an acceptable intervention. Minimal pain was reported in association with ultrasound assessment, and all study participants indicated they would be willing to have the same scans again in future if it were felt to be clinically necessary. An assessment of the change in patient-reported breathlessness following haemodialysis did not demonstrate a clear association between a reduction in total lung ultrasound B-line score and improved symptoms; however, it is worth noting that half the study population were not particularly breathless even before dialysis, with 15/30 (50%) participants reporting a pre-dialysis visual analogue scale breathlessness score of 10 mm or less. This may be a consequence of the study using a stable and therefore tightly controlled outpatient population; these patients will be monitored closely and any reported change in symptoms (such as increasing breathlessness) is likely to be evaluated and responded to swiftly by the responsible renal physician. Despite this, there appeared to be a signal for the reduction in total B-line score to predict an improvement in breathing that might reach statistical significance in a larger study of more symptomatic patients. The study findings also suggest that changes on lung ultrasound may precede the development of symptoms, and that its use as a screening tool in this and other populations prone to the development of extravascular lung water may be worth exploring in future studies.

One of the strengths of this study was the use of multiple and blinded scorers when assessing lung ultrasound findings, since the technique is vulnerable to an individual operator's ability to both acquire and interpret images. Some tests of inter-rater reliability were reassuring, with 80% agreement for the diagnosis of interstitial syndrome and at least moderate correlation between the primary (bedside) operator and blinded scorers for total lung ultrasound B-line score across different timepoints. However, a more appropriate evaluation of agreement on individual scores between the ultrasound raters using the Bland-Altman analysis

demonstrated poor agreement. This is an important observation since it suggests that whilst the dynamic changes observed on lung ultrasound during dialysis may have a common trend between different raters, the approach to scoring is unique to that individual clinician. This means that if lung ultrasound is to be used as a surveillance tool for monitoring change in fluid status over time, the findings will only be valid and of clinical use if the same assessor carries out each examination. This in turn has implications for how lung ultrasound might be used in this clinical setting, since a single assessor who is likely to already be aware of a patient's physiology and fluid status at any given point in time will inevitably be subject to a degree of bias in how they interpret any ultrasound images. Having either multiple assessors and/or blinded scoring, as used in this study, is equally impractical in a real-life clinical setting.

The removal of this potential for human error is therefore likely to be critical if lung ultrasound is to gain credibility as a tool for monitoring patients for change in extravascular lung water over time, whether in the context of end-stage renal failure or other clinical scenarios. Work is ongoing to see if artificial intelligence and computer-aided scoring can solve this problem (Brattain, Telfer, Liteplo, & Noble, 2013; Corradi et al., 2013; Moshavegh et al., 2019), but until this kind of software is both widely available and validated in real-life practice clinicians will need to remain aware of the limitations of lung ultrasound examination for this specific purpose.

The observation in this study that lung ultrasound appears to outperform computed tomography in the evaluation of extravascular lung water is a novel one that raises several questions. B-lines are classically regarded as a ring-down artefact of ultrasound seen in various pathologies outside the lung, and most commonly associated with abnormal foci of air that generate resonant vibrations and a continuous soundwave returning to and from the ultrasound transducer (Avruch & Cooperberg, 1985). The precise physiological and anatomical changes that underpin the development of B-lines on lung ultrasound are incompletely understood, although it was another study comparing thoracic ultrasound with computed tomography that first associated their formation with increased

subpleural interlobular septal thickening secondary to either pulmonary oedema or fibrotic lung disease (Lichtenstein et al., 1997). It is theorized that as lung water increases, the difference in acoustic impedance between the aerated lobular parenchyma and fluid-filled interstitium creates a highly reflective interface, reverberation of ultrasound waves, and B-lines on ultrasound imaging. It was the same study (Lichtenstein et al., 1997) that prompted the adoption of computed tomography as a gold standard for comparison with lung ultrasound in this study, alongside clinical experience in other lung parenchymal conditions where computed tomography is also widely regarded as the gold standard imaging test.

For this study, in the majority of patients who were observed to have an excess of B-lines on lung ultrasound examination that subsequently resolved during haemodialysis, in keeping with a reduction in lung water, no correlating abnormality (either initial, or evolving from pre- to post-dialysis imaging) could be identified on computed tomography despite these scans being reported by unblinded radiologists with sub-specialist expertise in thoracic imaging. Only 4/30 (13.3%) study participants had evidence of fluid overload and pulmonary oedema on this pre-defined gold standard radiologic investigation (that is, pre-dialysis computed tomography); and only one of these participants was felt to have any noticeable change on their post-dialysis CT scan. This is in stark contrast to lung ultrasound, where a clear reduction in total lung ultrasound B-line score from pre- to post-dialysis was documented in all four of these study participants by each of the three scorers reviewing these scans (**figure 15**). These findings imply that either computed tomography is insufficiently sensitive to show what was expected; and/or, more likely, that what is being seen on lung ultrasound may not represent pulmonary oedema or excess lung water in the way that clinicians and radiologists would conventionally expect to see and diagnose this condition on other imaging modalities.

It is, however, difficult to simply dismiss the presence of and variation in B-lines on lung ultrasound as not being intrinsically related to total body fluid status in some way, given the clear association between the total lung ultrasound B-line score and

volume of fluid being removed during haemodialysis that was demonstrated in this study by independent blinded assessors; and with no other physiological intervention occurring at the same time. As such, if alveolar oedema and/or subpleural interstitial thickening that one might expect to identify on computed tomography are not an adequate explanation for excess B-lines on lung ultrasound, then what are the alternatives? The findings of this study suggest that extravascular lung water may induce a change in lung anatomy and physiology that is either beyond the level of the interlobular septa and/or the resolution of computed tomography, but which remains detectable on lung ultrasound through the formation of B-lines as a sonographic artefact. This finding will need to be both replicated and evaluated in greater detail in future studies that use other means of monitoring total body fluid status but for now appears to suggest that, in this clinical context at least, lung ultrasound may be the gold standard radiologic test.

The findings of this, and previous studies of lung ultrasound in this patient population have potential implications for clinical practice. It is well recognized that chronic volume expansion in patients with end-stage renal failure is associated with increased long-term morbidity and mortality (Kalantar-Zadeh et al., 2009; Zoccali et al., 2013), and may develop insidiously over time without symptoms ever becoming obvious as a result. As already outlined above, lung ultrasound surveillance may allow the identification of patients with features of pulmonary congestion before they develop any breathlessness or other features of physiological decompensation, and earlier modification of their treatment as a result. Whilst dry weight remains the benchmark by which fluid status in haemodialysis is measured and managed, lung ultrasound may prove complementary as a more nuanced way of monitoring patients in real-time during dialysis and allowing clinicians to better judge when a euvolaemic state has been achieved. Outside the haemodialysis population and considering other conditions where fluid overload and pulmonary congestion are commonplace, it is easy to see how similar techniques could be applied to modify the management of in- and outpatients with, for example, congestive cardiac failure. In all these scenarios, well-designed and robust clinical trials are needed to

demonstrate that lung ultrasound can modify hard clinical outcomes of relevance to patients and clinicians before its wider uptake can be recommended.

There were limitations to the design and delivery of this study. The population was small and recruited from a single centre with experience in the delivery of clinical studies in both renal and respiratory medicine; whilst several participants did not have any evidence of excess extravascular lung water prior to commencing haemodialysis. There were a limited number of participants with co-morbidities that might impact on lung ultrasound findings; including interstitial lung disease, severe emphysema, and congestive cardiac failure. The former of these is of particular relevance since interstitial lung disease is widely recognized as a cause of interstitial syndrome and excess B-lines on lung ultrasound examination in its own right. However, the observation of a reduction in total B-line score with increasing fluid removal during haemodialysis in these participants by all three scorers reviewing the ultrasound scans regardless probably only adds to the credibility of lung ultrasound as a tool for monitoring changes in extravascular lung water. Whilst the patients in this study will have acted as their own controls, and the observed changes on lung ultrasound examination can therefore be reliably attributed to changing fluid status alone, it is uncertain what impact these other co-morbidities might have; for example, how does the presence of significant left and/or right ventricular dysfunction impact on the rate of B-line resolution during haemodialysis? These questions will need to be addressed as part of a larger multi-centre study. All the ultrasound scans were acquired by a single bedside operator with extensive experience in the use of thoracic ultrasound; future work will need to build on the robust methodology of using multiple blinded raters to score ultrasound images by also having different bedside operators examine patients to ensure reproducibility of findings at the point of acquisition.

In conclusion, these results demonstrate that lung ultrasound can identify the presence of and changes in extravascular lung water in patients with end-stage renal failure undergoing haemodialysis. The scoring of B-lines on ultrasound appear at the absolute level to be dependent on the individual operator, whereas the more

global trends observed are consistent between different clinicians. Lung ultrasound appears in this study at least to be more sensitive than computed tomography for detecting changes in extravascular lung water, and future studies should utilise other recognized methods of monitoring total body and intravascular fluid status alongside these imaging modalities to validate the hypothesis that lung ultrasound may be considered the gold standard radiologic test for this particular condition. These observations have potential implications for clinical care and further research is now needed to better characterize the role that thoracic ultrasound might play in the management of patients on haemodialysis and with other conditions that result in pulmonary congestion, with the long-term aim of reducing morbidity and mortality in these different populations.

5. CONCLUSIONS AND FUTURE DIRECTIONS

As the use of thoracic ultrasound by physicians becomes ever more commonplace, so those same clinicians will look for new ways in which it can be used to advance patient care. The three studies described above represent a beginning in terms of thinking about how ultrasound might change the way that patients are managed in each of these different areas of practice.

A feasibility study looking at the association between the loss of the normal lung sliding artefact (taken to represent early pleural adhesion formation) following the drainage of malignant pleural effusion and administration of talc via chest tube, and longer-term pleurodesis success found that an increased ultrasound adherence score was linked to a better outcome. This finding represents a potential opportunity to influence patient care by using ultrasound as a decision-making adjunct in chest tube management, through both the timing of talc administration and subsequent chest tube removal; as well as allowing the earlier identification of those patients whose attempted pleurodesis is more likely to fail and therefore warrant closer follow up. This could be extended to other forms of malignant effusion management, such as observing patients with indwelling pleural catheters for signs of auto-pleurodesis and/or to monitor any attempt at an accelerated pleurodesis through either daily drainage (Wahidi et al, 2017) or the use of a sclerosing agent (Bhatnagar et al, 2018). A larger multi-centre study (Psallidas et al, 2017) is looking to answer some of these questions and may allow the role of thoracic ultrasound in this area of practice to be better defined moving forwards.

The signal that was seen in the same feasibility study for the ultrasound pleural adherence score prior to talc administration to also predict long-term pleurodesis success is of particular interest, and not something the ongoing multi-centre study (Psallidas et al, 2017) mentioned above will address specifically. It may be that the longer than expected interval (mean of 4.3 days) between chest tube insertion and subsequent talc slurry administration contributed to this, by allowing more time for early adhesion formation with the tube itself acting as an inflammatory stimulus.

However, it may also be telling us something about the biology of the pleural space in those individuals and some pre-existing physiological or biochemical feature that already predisposes them to early adhesion formation and subsequent auto-pleurodesis without the need for any sclerosant. This observation is something that will warrant evaluation in a future study of patients with malignant pleural effusion undergoing intervention for diagnostic and therapeutic purposes, potentially correlating sonographic with biochemical parameters as part of further exploratory work and hypothesis generation.

There are other scenarios in which the loss of lung sliding may prove to be of prognostic interest. Approximately 30% of patients presenting with a first episode of primary spontaneous pneumothorax go on to have recurrent events (Walker et al, 2018), with no means identified of predicting which individual patient is at more or less risk. If adhesion formation following the index pleural injury is a protective factor, it may be possible to identify this with thoracic ultrasound. An exploratory observational study in this patient population may allow this hypothesis to be explored in more detail.

A further observational study was undertaken in patients undergoing large-volume thoracentesis for symptomatic pleural effusion in order to explore whether any thoracic ultrasound parameters might be associated with the presence of unexpandable lung, and/or with patient-related outcomes such as pain or relief of breathlessness post-procedure. This study demonstrated that reduced motion (M-) mode measurement of atelectatic lung excursion with cardiac pulse transmission was associated with the presence of unexpandable lung, consistent with the findings of previous work in this area of clinical practice (Salamonsen et al, 2014). It also identified other sonographic parameters that were associated with unexpandable lung in this study population, including the presence of pleural fluid septations and anechoic fluid. The findings of this study now need to be taken forward in a larger multi-centre study that utilizes additional scorers to assess both intra- and interobserver variability in order to validate both the technique and sonographic findings.

Unexpandable lung is found in a significant minority of patients with pleural effusions; being able to identify its likely presence prior to any intervention could inform discussions with the affected patient and subsequent clinical decision making about the most appropriate therapeutic intervention. In making this decision, given the increasing use of indwelling pleural catheters in the management of patient with recurrent symptomatic effusions, it is likely that any predictive sonographic model should favour sensitivity for the detection of unexpandable lung over specificity. In turn, the sonographic findings may help guide clinicians when deciding which patients are most likely to benefit from a more aggressive management strategy if early pleurodesis and catheter removal is the ultimate objective.

There is, alongside this, interest in understanding which patients are most likely to benefit symptomatically from any pleural intervention. It is understood that the improvement seen following drainage of an effusion varies greatly from patient to patient, but it is incompletely understood why this is the case and there are certainly no prospective means of determining this. This study failed to identify any sonographic parameters that were associated with patient-related outcome measures following pleural drainage, but the limitations of this study – in particular, a short follow-up period addressing patient-reported symptoms following the index intervention – mean further and more comprehensive work is likely to be needed to allow a more robust and definitive answer to this question. This is important since any ultrasound model that sought to predict symptomatic benefit, particularly a failure to improve following pleural drainage, would need to be reliable and comprehensively validated before clinicians might consider not intervening on the basis of an ultrasound examination in this clinical scenario.

A future study addressing some of the issues outlined above would need to have sufficient patient numbers to ensure power to detect a significant difference in the outcomes of interest; for example, distinguishing between expandable and unexpandable lung, and those patients with significant as opposed to limited symptomatic benefit following pleural intervention. It should recruit from multiple

centres, use multiple ultrasound assessors to ensure validity and reproducibility of the ultrasound parameters being tested, and ensure an adequate follow-up period to allow any change in patient-reported symptoms over time to be better understood. A recently published study (Muruganandan et al, 2020) has identified diaphragm shape and motion as being predictive of symptomatic outcome in patients undergoing large-volume therapeutic pleural drainage, and it may be possible to refine this further by better characterizing the three-dimensional behaviour of the diaphragm with M-mode evaluation to assess its dynamic qualities pre- and post-drainage.

The third and final study described above assessed the utility of ultrasound to detect the presence of, and changes in extravascular lung water in a population of patients undergoing haemodialysis. This study showed that ultrasound was not only capable of doing this, but also appeared to identify changes in total body fluid status and extravascular lung water that could not be discerned on computed tomography. However, this potential utility may be restricted by the finding that there appears to be a lack of consistency between individual ultrasound assessors. It may be possible to overcome this through the use of automated B-line scoring or more straightforward scoring methodology for human assessors, grading the number of B-lines according to a series of ranges (and thereafter as, for example, none, mild, moderate, or severe) as opposed to relying on an absolute count.

The inconsistency between the ultrasound and computed tomography findings in this study population also needs to be considered. It is difficult to suggest that B-lines can be associated with anything other than extravascular lung water and total body fluid status on the basis of the observations made during this study, and yet only 13% of the study population had evidence of fluid overload reported on their pre-dialysis CT scan. It may be that the reporting radiologists were looking for the wrong features when reviewing these CT scans, and any future comparative study between lung ultrasound and CT should utilise other means of assessing body fluid status with the latter modality. The inferior vena cava diameter may provide one means of doing this; whilst a quantitative evaluation using lung density analysis

(Barile et al, 2020) may be more sensitive than traditional qualitative methods of reporting the presence of pulmonary oedema on CT.

The relationship between fluid removal during haemodialysis and change in total lung ultrasound B-line score was not linear, and there are likely to be other patient characteristics that have an impact on intra- and extravascular fluid status. It would be a natural extension of ultrasound evaluation to look at other markers of fluid status alongside B-line identification; for example, focused echocardiography to quantify left and right ventricular function, and measurements of inferior vena cava diameter and collapsibility. Future studies of lung ultrasound and extravascular lung water will also need to look at patient populations beyond the haemodialysis unit, with the greatest potential gains likely to be in hospital admissions units and patients presenting with breathlessness secondary to cardiogenic pulmonary oedema. The early identification and treatment of these patients, potentially using lung ultrasound as a diagnostic and surveillance tool to guide both acute offloading of excess fluid and subsequent maintenance therapy, will need detailed evaluation to determine whether the addition of lung ultrasound to the traditional clinical evaluation has a meaningful impact on key clinical outcomes such as mortality and length of hospital stay.

In conclusion, the three studies of novel and emerging uses for thoracic ultrasound described above have all shown promise and the potential for patient and clinician benefit. Future research should build on these findings with a view to refining and validating the techniques described to develop a robust evidence base for their wider use in everyday clinical practice.

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