Outcomes of Patients who survived Treatment on an Intensive Care unit for COVID-19 in England and Wales: a comparative retrospective cohort study

1. Introduction

1.1. Background and rationale

1.1.1. Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019. By mid-July 2020 14 million people globally had been infected, of which over 600,000 died of coronavirus disease 2019 (COVID-19) (1). In the UK, nearly 20% of patients hospitalised with COVID-19 were transferred to an intensive care unit (ICU) or high dependency ward (2). In total, over 10,000 patients have been treated for COVID-19 on an ICU in England and Wales. On average, 50% of these patients survived to hospital discharge, although survival rates appeared to increase over this period (3,4). The long-term impact on the health of survivors is unknown.

Previous studies have shown that critically ill patients who survive ICU treatment are at greater risk of death and report lower health-related quality of life when compared with population norms (5–7). While pre-existing comorbidities partially account for these differences, organ damage caused by critical illness and the impact of intensive organ support given in the ICU likely also play a role (8). Analysis by the Intensive Care National Audit and Research Centre (ICNARC) suggests that patients admitted with COVID-19 receive higher intensity organ support and suffer more complications than observed in other viral respiratory infections (4). For example, nearly all COVID-19 patients required respiratory support, with nearly 60% receiving mechanical ventilation (compared to 43% with viral pneumonias) (4). Around one third of patients also required advanced cardiovascular or renal support (4,9). Cardiac (myocarditis, heart failure, arrhythmias, acute coronary syndrome) and venous thrombotic complications (e.g. pulmonary embolism) were not uncommon (10–12). Although rare, some patients developed neurological complications such as stroke, encephalitis and Guillain-Barré syndrome (13).

1.1.2. Aim

This statistical analysis plan describes a retrospective cohort study aiming to characterise outcomes for patients treated on an ICU with COVID-19 in England and Wales, one year after discharge from hospital. The study will use existing national audit data linked to routine healthcare datasets.

1.2. Objectives and outcome measures

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To estimate the risk of death for patients who survived to hospital discharge after treatment on an ICU for COVID-19 and compare these risks to patients treated on ICU as an emergency for other conditions	**Primary outcome** • Death as recorded in the Civil Registration -- Deaths	1 year after discharge from ICU
Secondary Objectives To estimate the risk of adverse events for patients who survived to hospital discharge after treatment on an ICU for COVID-19 and compare these risks to	**Secondary outcomes** • Emergency hospital admission • Emergency hospital admission for respiratory infection • Emergency hospital admission for a major adverse cardiac	180 days after discharge from ICU AND 1 year after discharge from ICU

patients treated on ICU as an emergency for other conditions	event (myocardial infarction, stroke, heart failure) • Emergency hospital admission for a venous thrombotic event (deep vein thrombosis or pulmonary embolism) • Development of end stage renal failure treated by renal replacement therapy	
Exploratory Objectives To compare the risks in patients treated in ICU for COVID-19 to patients who survived to hospital discharge after treatment on an ICU for other bacterial or viral respiratory infections during the same period (January to June 2020) To compare the risks in pregnant patients treated in ICU for COVID-19 with an age-matched control group	**Primary outcome** • Death as recorded in the Civil Registration -- Deaths **Secondary outcomes** • Emergency hospital admission • Emergency hospital admission for respiratory infection • Emergency hospital admission for a major adverse cardiac event (myocardial infarction, stroke, heart failure) • Emergency hospital admission for a venous thrombotic event (deep vein thrombosis or pulmonary embolism) • Development of end stage renal failure treated by renal replacement therapy	180 days after discharge from ICU AND 1 year after discharge from ICU

2. Study methods

2.1. General study design and plan

This is a retrospective cohort study of outcomes for patients treated on an ICU in England and Wales, one year after discharge from hospital. Our primary group will include patients admitted to ICU with confirmed COVID-19 between 1st January and 1st July 2020, who were discharged alive from hospital. We will use the ICNARC Case Mix Programme (CMP) to identify comparator groups of emergency ICU admissions, to which outcomes in the primary group can be compared. Once identified, each cohort will be linked to the national data sets to obtain information on subsequent hospitalisations, and longer-term mortality, cardiac and renal outcomes.

The study will be reported using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) (14).

2.2. Sample size, power, and detectable difference

The study size will be determined by the number of ICU survivors available from the CMP. The CMP currently holds around 10,000 patients admitted with confirmed COVID-19 between January and July 2020, of which ≈5,000 survived to hospital discharge. Of the survivors, we expected 90% (4,600) to have been admitted to an ICU in England or Wales.

Prior to the COVID-19 pandemic, there were around 130,000 emergency ICU admissions per annum in the CMP. Of these, around 100,000 survived to hospital discharge. We expect ≈90,000 to have been admitted to an ICU in England or Wales.

Study participants will include around 3.5 years of pre-pandemic admissions (90,000 x 3.5 = 315,000) and 4,600 COVID admission during the pandemic giving a total sample size of 319,600.

2.3. Timing of analysis

An initial analysis will be carried out after six months follow-up has been achieved for all patients, therefore including data up until 1st January 2021. A further analysis will include data up to one year, i.e. 1st July 2021.

2.4. Timing of outcome assessments

The primary outcome will be at 1 year after discharge from ICU. Secondary outcome assessments will be made at 30, 60, 90 and 180 days after discharge.

3. Statistical principles

3.1. Multiplicity

We do not plan to make any adjustments to p-values or confidence intervals. To reduce the impact of multiple testing, we will only report p-values for the primary outcome measure (i.e. death). All analyses of secondary outcomes will only present the effect size and the 95% confidence interval.

3.2. Statistical significance and confidence interval

We will consider a p-value < 0.05 as statistically significant, and therefore we will present 95% confidence intervals.

3.3. Adherence and protocol deviations

Any deviations from the protocol and this analysis plan will be described in the subsequent manuscript where the results of the study are presented.

4. Study populations

4.1. Eligibility

4.1.1. Inclusion Criteria

- Age ≥16 years
- Admitted to an adult, general ICU in England or Wales as an emergency (i.e. unplanned)
- Admitted to ICU for either:
    - confirmed COVID-19 between 1st January to 1st July 2020
    - without confirmed COVID-19 between 1st July 2016 and 1st July 2020 (patients admitted prior to 2020 are included to account for seasonal variation and identify specific impacts of the pandemic on patient follow-up)

4.1.2. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patients who died in hospital after treatment on an ICU

We chose to exclude ICU admissions after 1st July 2020 to account for a possible three-month delay in patient data being registered in hospital episode statistics (HES) and national audit databases. Linking data sources in July and October 2021 will maximise the chance that complete data will be available for outcomes at 180 and 365 days respectively.

4.2. Recruitment

Participants will be recruited from general adult ICUs across England and Wales who participate in the ICNARC CMP audit. All ICUs in England and Wales have participated in the CMP audit since 2015.

4.3. Withdrawal/follow-up

This is an observational study. Participants can request their data to be deleted at any time in accordance with GPDR and the study privacy policy. The number of participants who do withdraw their data will be summarised.

4.4. Cohort definitions

4.4.1. Patients with confirmed COVID-19 between 1st January to 1st July 2020

This group will consist of all individuals who were admitted to an intensive care unit between 1st January and 1st July 2020 with a confirmed diagnosis of COVID-19.

4.4.2. ICU admissions 1st July 2016 – 1st July 2019

All emergency ICU admissions between 1st July 2016 and 1st July 2019. The 1st July 2019 cut-off is intended to allow 6 months follow-up of all patients before the COVID-19 pandemic had opportunity to influence healthcare provision.

4.4.3. ICU admissions 1st July 2016 – 1st January 2020

All emergency ICU admissions between 1st July 2016 and 1st January 2020 where the primary diagnosis was not COVID-19. The cohort is the same as the previous one, with an additional 5 months' of ICU admissions. To allow for admissions which are closer in time to be included, and therefore to check the robustness of analyses involving the previous cohort.

4.4.4. Non-COVID ICU admissions 1st January 2020 – 1st July 2020

All emergency ICU admissions between 1st January 2020 and 1st July 2020 where the primary diagnosis was not COVID-19. This cohort includes patients admitted to ICU concurrently to the primary COVID-19 cohort. While this cohort will likely be small, it will possibly provide a fairer comparison of outcomes if the pandemic did affect the healthcare provision during follow-up (i.e. if there were a reduction in the number of hospital admissions for non-Covid causes during the period of the pandemic due to restrictions).

5. Analysis

5.1. Baseline patient characteristics

We will describe the characteristics of patients at the time of ICU admission, including demographics and clinical characteristics (listed in Section 5.2). These will be presented for each cohort separately. Data will be presented as mean with standard deviation (SD) when normality distributed or median and interquartile range for skewed variables. Categorical variables will be presented as number and proportion.

5.2. Assumed confounding covariates

The following variables are assumed to be related to the risk of experiencing one or more of the outcomes, and will therefore be included in the baseline characteristics table, be included as covariates in the multivariable regression models, and be included as covariates in the propensity scores.

- Patient demographics: age, sex, ethnicity, index of multiple deprivation (IMD), body mass index (BMI), clinical frailty score, smoking status, month of admission, dependency prior to ICU admission (fully/partial/total assistance with activities of daily living), geographical region
- Medical history: comorbidities (as per Elixhauser (14)), dialysis-dependent, total length of previous hospital admissions in year prior to ICU admission.
- Hospital/ICU stay characteristics: Length of hospital stay prior to ICU transfer, Length of ICU stay, length of hospital stay after discharge from ICU, hospital region, month of admission.
- Acuity: APACHE-II/ICNARC severity score at admission, length of mechanical ventilation, length of advanced organ support (cardiovascular, respiratory, renal, liver, neurological)

5.3. Outcome definitions

5.3.1. Primary outcome

Death – death from any cause, as recorded in the civil registrations data set. As per Section 2.4 the primary analysis will be at one-year post-discharge. Comparisons at 30, 60, 90 and 180 days will be secondary analyses of the primary outcome.

5.3.2. Secondary outcomes

Cause-specific readmissions will be identified by combining HES (ICD-10) and GDPPR coding, using coding sets defined in Ayoubkhani et al. (15). For a venous thrombotic event, we will include the following ICD-10 codes: I80.0-I80.3, I80.8-I80.9, I82.9, O22.2-O22.3, O87.0-O87.1, I26.0, and I26.9.

- Emergency hospital admission – any non-elective hospital admission. Recorded in the hospital episode statistics data set.

- Emergency hospital admission for respiratory infection – any emergency hospital admission for a respiratory infection.
- Emergency hospital admission for a major adverse cardiac event (myocardial infarction, stroke, acute heart failure)
- Emergency hospital admission for a venous thrombotic event (deep vein thrombosis or pulmonary embolism)
- Development of end stage renal failure treated by renal replacement therapy

5.4. Analysis methods

5.4.1. Descriptive analysis of incidence

The incidence of each of the primary and secondary outcomes will be summarised within each cohort. Kaplan-Meier curves will be used to graphically display the number of patients who die in the follow-up period, whilst cumulative incidence function curves will be used to display all of the secondary outcomes (treating death as a competing risk). The number and proportion of patients experiencing each event will be tabulated at each of the outcome assessment time points. Further analyses will investigate the event rates within relevant subgroups (described in Section 5.5). For continuous variables (such as age) we will additionally consider regression modelling with non-linear terms (e.g. fractional polynomials or restricted cubic splines) to describe the impact of the variable on the patient's risk of experiencing the outcome events.

5.4.2. Comparison of COVID-19 cohort to other cohorts using standard regression modelling

To compare the risk of the primary outcome (death) between the COVID-19 cohort and the other cohorts, we will use Cox proportional hazards regression models to estimate the hazard ratio (and 95% confidence interval). The hazard ratio (HR) will be calculated at each of the outcome assessment time points. For the secondary outcomes, a competing risk approaches will be used, with death as the competing risk. We will use the cause-specific Cox proportional hazards regression approach to estimate the cause-specific hazard ratio (and associated 95% confidence interval). The Fine-and-Gray approach will be used as a sensitivity analysis to estimate the sub-distribution hazard ratio. For each of these analyses we will report unadjusted results.

5.4.3. Comparison of COVID-19 cohort to other cohorts using propensity score matching

For each comparison of the COVID-19 cohort to a non-COVID cohort we will use propensity score matching to create cohorts that are similar in terms of baseline characteristics and confounding variables. We will construct a propensity score using logistic regression where the outcome is the cohort status, and the covariates will be those previously defined in Section 5.2. The model will allow for non-linear relationships between continuous variables and the outcome. The propensity score will then be estimated for each patient. One to one matching will be performed based on the

propensity score, initially using a nearest neighbour (greedy) approach. We will assess the balance achieved through the matching process using standard approaches, such as Q-Q plots, and assessments of the absolute standardised mean difference. If the covariates are not well balanced after nearest neighbour matching, alternative approaches will be tested, such as full matching, until sufficient balance is achieved. If sufficient balance cannot be achieved or too many patients from the COVID cohort are removed by the matching algorithm, we will consider using the propensity score for inverse probability weighting in our Cox regression models.

Once matched cohorts have been identified, we will analyse the outcomes with the standard regression modelling as described in Section 5.4.2– using Cox regression for the death outcome, and competing risk approaches for the secondary outcomes. However, since the data will now be clustered due to the matching, we will need to account for this in the regression models. We will therefore use cluster-robust standard errors.

5.5. Subgroup analyses

For both the unadjusted and propensity-matched analyses, we will investigate the following subgroups: age, sex, ethnicity and length of advanced organ support.

5.6. Sensitivity analyses

To assess the robustness of the propensity-matched analysis, we will also fit multivariable regression models. We will use restricted cubic splines or fractional polynomials to allow for potentially non-linear relationships between continuous covariates and outcomes. The adjustment variables will be those listed in Section 5.2.

5.7. Missing data

The proportion of missing data for each of the outcome measures and variables of interest will be described. In addition, we will describe the patterns of missingness.

We anticipate that missing data will be minimal, in which case we will use a complete case analysis, i.e. omitting any patients with missing data. However, if the amount of missing data is relatively high (more than 5% of patients have missing data) we will use multiple imputation . In this case we would also perform a complete case analysis as a sensitivity analysis.

5.8. Statistical software

It is expected that all analysis will be carried out using R statistical software.

6. Conclusion

The intention of this study is to understand the long-term consequences of being admitted to ICU with COVID-19. Initially analyses will be descriptive in nature. We will then go on to summarise whether these long-term consequences are different from those that are associated with admission to ICU for other causes. We will use different comparison cohorts and different analysis methods to check the robustness of our conclusions.

This statistical analysis plan presents the principles of the analysis that we intend to follow in the OPTIC-19 study. We hope that by pre-specifying our analyses we will minimise the risk of reporting bias and data driven results.

7. References

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