**Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies.**

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**Summary**

The emergence of coronavirus disease 2019 (COVID-19) has led to high demand for intensive care services world-wide. However, the mortality of patients admitted to intensive care units (ICU) with COVID-19 is unclear. Here, we perform a systematic review and meta-analysis, in line with PRISMA guidelines, to assess the reported ICU mortality for patients with confirmed COVID-19. We searched MEDLINE, EMBASE, PubMed and Cochrane databases up to 31 May 2020 for studies reporting ICU mortality for adult patients admitted with COVID-19. The primary outcome measure was death in intensive care as a proportion of completed intensive care unit admissions, either through discharge from the ICU or death. The definition excluded patients still alive on ICU. Twenty-four observational studies including 10 150 patients were identified from centres across Asia, Europe, and North America. In-ICU mortality in reported studies ranged from 0% to 84.6%. Seven studies reported outcome data for all patients. In the remaining studies, the proportion of patients discharged from ICU at the point of reporting varied from 24.5% to 97.2%. In patients with completed ICU admissions with COVID-19 infection, combined ICU mortality was 41.6% (95% CI 34.0% - 49.7%, $I^2$ = 93.2%). Subgroup analysis by continent showed that mortality is broadly consistent across the globe. As the pandemic has progressed the reported mortality rates have reduced from above 50% to close to 40%. The in-ICU mortality from COVID-19 is higher than usually seen in ICU admissions with other viral pneumonias. Importantly, the mortality from completed episodes of ICU differs considerably from the crude mortality rates in some early reports.

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The pandemic of coronavirus 19 (COVID-19) has greatly impacted international health and health-care delivery [1]. The rapid spread of the virus, high case load and the high proportion of patients requiring respiratory support has placed unprecedented demand on intensive care unit (ICU) services, necessitating rapid expansion of intensive care infrastructure, capacity and staffing in many countries [2]. There is concern that patients admitted to ICU with COVID-19 have a high mortality, but the current literature is largely composed of small case-series and cohort analyses. Further, headline survival rates are inconsistently reported due to variable follow-up periods, and many publications are complicated by patients who may still be receiving intensive care support at the point of publication. In this paper we aim to establish the mortality occurring within ICUs amongst patients admitted with COVID-19. Our objectives include performing a systematic review and meta-analysis to generate a point estimate of mortality in patients admitted to intensive care with COVID-19 where there is a definitive outcome (either died or discharged alive from ICU). We also explore how this in-ICU mortality rate may be influenced by geography and the different phases of the pandemic.

**Methods**

The review was prospectively registered with PROSPERO (CRD42020180671) and conducted according to PRISMA guidelines [3]. No ethical approval was required. We searched MEDLINE, EMBASE, PubMed and The Cochrane Library up until 31 May 2020 using the search terms “coronavirus”, “covid19”, “sars-cov-2” or “2019-ncov”; and “intensive care”, “mortality”, or “disease course”. Exact terms used were adapted to each database (Table S1). Manual searching was used to identify additional results. Articles published before the first report of COVID-19 (31 December 2019) were excluded. Studies were eligible for inclusion where the study group included adult patients (18 years or older) admitted to an ICU with COVID-19, and the outcome of ICU admission was reported (i.e. reported as died or discharged from ICU alive). Patients in intensive care and high dependency units were included. Studies were excluded if the primary outcome was not reported; all patients were under 18 years old; or the report was a single case report.

Screening of titles and abstracts was performed in Microsoft Excel. All articles were screened independently by two authors (RAA, ADK) to identify studies potentially meeting inclusion criteria. The full text of potentially eligible studies was independently assessed for eligibility with disagreements resolved by discussion with a third reviewer (TMC). The pre-specified primary outcome was the mortality rate in patients with completed ICU admission. Data were only included when this outcome was clearly reported. Other pre-defined data items extracted included study setting and design,

including information for risk of bias assessment, patient characteristics, clinical features, and rates of organ support delivered. A modified version of the Newcastle-Ottawa Scale was used to assess the quality of included studies (Table S2). The Newcastle-Ottawa Scale is an eight point scale that assesses patient selection (3 points), comparability of cohorts (2 points) and the ascertainment of outcomes (3 points) [4]. Funnel plot asymmetry was used to assess heterogeneity and risk of publication bias.

Meta-analysis was conducted using the 'meta' package (Version 4.12.0, 2019) in R (The R Foundation for Statistical Computing; Version 3.6.1, 2019. An inverse variance random effects model was used for all analyses. Between-study heterogeneity was assessed using the $I^2$-test. Results are presented as percentages with associated 95% confidence interval (CI), *p*-values, and forest plots [5,6]. Funnel plots were produced using the Public Health England tool [7]. To further explore heterogeneity, we performed subgroup analyses based on study methodology (single- or multi-centre, number of participants, censoring of ICU outcomes) and geographical location. Meta-regression was used to explore the effects of population characteristics (proportion ventilated, average age), publication date, and proportion of patients with outcomes reported. Additions to and deviations from the PROSPERO record are described below.

**Results**

Initial searching found 1923 articles, including 183 duplicates, leaving 1740 to be screened. After exclusion by title or abstract of 1654 articles, 86 full text articles were reviewed, of which 25 reported primary endpoints. Six of these studies were from Wuhan, China: due to overlap of both data collection period and hospital location three early and smaller studies were excluded to avoid data duplication in later publications [8-10]. One study reported both adult and paediatric populations: only data for adult patients were included in this analysis [11]. Two further articles were found by manual searching resulting in 24 articles for analysis [11-34] (Table 1, Figure 1). These studies reported ICU outcome data for a total of 10 150 patients admitted to ICU with a COVID-19 diagnosis. The median (IQR [range]) number of patients in each study was 30 (19 – 134 [1 – 9347]); the very small series were from reports of larger cohorts including non-ICU patients. Recruitment in these 24 studies was from 16 December 2019 to 28 May 2020 with publication dates from 24 January 2020 to 29 May 2020 (Figure 2). Studies reported on patients from China (8 studies), United States of America (USA, 6), France (2), Canada, Denmark, the Netherlands, Hong Kong, Italy, Singapore, Spain, and the United Kingdom (UK) (1 each). Reported ICU mortality rates ranged from 0%, in small case series, to 84.6% (Table 1).

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The proportion of included patients who had completed their ICU stay (being dead or discharged) at the point the study was reported varied between studies. Seven studies reported outcome data for all participants and in the remaining 17 studies the percentage varied from 24.5% to 97.2% (Table 1, Figure S1). All studies were observational cohort series with varying durations of patient follow-up. Median quality score for risk of bias was 5/8 while only two studies scored at 4 and none below (Table S3). Details of ICU treatments were variably reported making further analysis of the impact of treatment on outcome, other than invasive mechanical ventilation, impractical (Table S4).

The ICU mortality rate across all studies included in the quantitative analysis was 41.6% (95% CI 34.0 - 49.7), $I^2$ = 93.2%; Figure 3). The largest patient group was in the Intensive Care National Audit and Research Centre (ICNARC) study from the UK [34]. A sensitivity analysis with this group removed did not substantially affect mortality rate or heterogeneity (40.2% (95% CI 30.4 – 50.9%, $I^2$ = 92.5%) and Egger's test of funnel plot asymmetry was negative (0.08, $p$ = 0.92; Figure 4).

Subgroup analyses by geographical location and study characteristics (single or multiple centres; sample size; complete outcome reporting) showed no significant between-group differences or substantial reduction in heterogeneity (Table S5).

Meta-regressions based on patient characteristics (age, proportion of invasively ventilated patients) and proportion of patient outcomes reported were not significant (Table S6). Meta-regression by month of publication was significant, with a reduction in reported mortality over time (Treatment effect (logit transformed proportion) -0.46 per 1-month increment, $p$ = 0.02; Figure S2). This remained significant after adjusting for geographical location and proportion of outcomes reported (Treatment effect (logit transformed proportion) -0.62 per 1-month increment, $p$ = 0.01) (Table S6).

**Discussion**

This is the first systematic review and meta-analysis of outcomes of patients admitted to ICU with COVID-19. Data from 24 studies involving 10 150 patients demonstrate an ICU mortality rate in those with a completed ICU stay of 41.6% (95% CI 34.0 - 49.7%). This mortality is broadly consistent across the globe. As the pandemic has progressed the reported mortality rates have reduced from above 50% in March 2020 to close to 40% at the end of May 2020. This in-ICU mortality from COVID-19 is higher than usually seen in ICUs. The overall mortality from completed episodes of ICU differs considerably from the crude mortality rates in some early reports.

The pandemic of COVID-19 disease has been challenging, not least due to the large number of patients who have required advanced respiratory support, including high flow nasal oxygen, non-invasive and invasive mechanical ventilation. In this systematic review and meta-analysis, the pooled ICU mortality rate of above 40% is notably higher than the 22.0% seen in other patients admitted to intensive care with viral pneumonia [34,35]. This may be attributable to the disease process itself, or to difficulty in providing reliable services in a pandemic setting. Of note, it is likely that due to pandemic pressures on intensive care services there has been widespread use of advanced respiratory support (non-invasive ventilation or high flow nasal oxygen) outside of ICUs, and this may have led to increased acuity of patients admitted to ICU. The observed ICU mortality rate is notably lower than crude mortality rates in some reports early in the pandemic, which exceeded 90% for patients undergoing invasive ventilation [15], and led to fears that patients requiring intensive care had an unacceptably high rate of death. The huge burden on health services and high mortality rates in ICU raised questions about when ICU admission is merited and whether, and at what point, tracheal intubation and invasive ventilation are indicated [36].

We chose in-ICU mortality as our primary outcome measure as a useful metric of the efficacy of ICU care. In this rapidly evolving pandemic, many studies have reported incomplete data in which ICU outcomes for a considerable majority of patients were unknown. Reporting those patients still on ICU as 'surviving' leads to potentially distorted data. We therefore chose as our outcome measure a completed episode of ICU which included death or survival to ICU discharge. The consequence of this is that it may bias towards early mortality. However, subgroup analysis comparing studies with full outcome reporting to those with incomplete outcome data, and meta-regression by proportion of patients with outcome data reported, did not reveal significant differences in mortality rates. Conversely, a proportion of patients surviving ICU will die before hospital discharge and the survival rate we report will modestly overestimate survival to hospital discharge. To put this in context, the long-running ICNARC case mix registry reports a 5.7% in-hospital mortality rate for patients after discharge from ICU [35]. Whether this finding is replicated after ICU admission with COVID-19 is worthy of future research, as are the longer-term outcomes of these patients. Several studies were excluded as they did not specifically report ICU outcome data; rather they included outcome data for the entire inpatient population, or outcome data were not yet available. It is possible that the ICU outcomes in these studies may have differed from the studies we were able to include in this analysis.

A clinically important finding is that meta-regression by month of publication revealed a significant reduction in reported mortality rates over time. The earliest reports came from Asia, in particular

China, followed by reports from Europe and latterly from North America; however, the reduction over time was still present after adjusting for geographical location. This echoes the reduction in reported mortality in serial reports from ICNARC, which peaked at 51.6% in the 10th April report [37], reducing to 43.2% in the latest version included in this analysis . There are several explanations for this finding. It may reflect rapid learning that has taken place on a global scale due to the rapid publication of clinical reports early in the pandemic. It may be that ICU admission criteria have changed over time, for example with more non-invasive ventilatory management outside of ICU. It is also likely to reflect the fact that prolonged admissions, for example due to prolonged respiratory weaning, take time to be reflected in the data. Critical illness associated with COVID-19 is prolonged with approximately 20% of UK ICU admissions lasting more than 28 days and 9% more than 42 days [34]. Despite this our meta-regression indicated that the proportion of outcomes reported did not affect mortality, and this may hint at ongoing risk of mortality long into the disease pathway. There is a possibility that early studies, which were smaller, were prone to overestimate mortality. Funnel plot analysis does not strongly support this as there was no significant asymmetry and smaller studies appeared to report lower mortalities. The important message, however, is that early reports of in-ICU mortality appear to have over-estimated mortality as now calculated.

The ICU mortality did not differ significantly across continents despite some evidence of variations in admission criteria, treatments delivered and the thresholds for their application. For instance, where reported, proportions of patients receiving non-invasive or invasive respiratory support varied with more non-invasive ventilation in reports from Asia. Similarly antivirals, corticosteroids, immunoglobulins and other immunomodulatory treatments were in widespread use in many reports from China but may be less frequently used in Europe and North America [10,15,34,38]. This is consistent with research findings to date of no specific therapy that reduces ICU mortality. Mortality from COVID-19 is highly age-dependent and variations in population age or the age of admitted patients would likely significantly impact mortality [34]. Similar arguments may apply for comorbidities. Further, there is much interest in ethnicity and mortality from COVID-19 and it is plausible that differences in ethnicity between populations, particularly in the proportion of patients of Black African and Black Caribbean ethnicity, may contribute to the outcomes [34,39-41]. As we have only summary statistics, with variable reporting, we were unable to explore these factors in detail, though meta-regression by the crude measure of average age was not significantly associated with reported mortality. Reporting of such data in future cohort studies and trials would be beneficial.

Limitations of our analysis include the high heterogeneity of reported outcomes, the lack of data from many countries and deviations from our published protocol. The high degree of heterogeneity ($I^2$ = 93.2%) in the meta-analysis suggests that survival rates between studies are highly variable. Whilst this may reflect true variability in outcomes between the studies included in the analysis, it needs to be interpreted with caution [42]. First, there are only 24 studies in the meta-analysis, and, despite a few large data sets, several have low numbers of patients. In the random effects model used here, the relatively large number of small studies, which because of small numbers are inevitably prone to more variable results, may contribute towards a (predictable) high degree of heterogeneity. To characterise this further we assessed the variability of ICU mortality by patients in each study by funnel plot analysis (Figure 4). Seventeen of the 24 studies fell within the 3-standard deviation (SD) confidence interval limits of the funnel plot. There were three studies with higher than expected mortality (>3 SD above mean) [11,15,19], and four with lower than expected mortality (>3 SD below mean) [30-33]. The studies that appear to have excess mortality include early reports from Lombardy and the United States at points where local health systems may have been stretched [11,15,19]. Indeed it is known in Lombardy that there were high rates of non-invasive ventilation in patients outside of intensive care due to severe demand for critical care beds [43], therefore patients receiving intensive care were more likely to have a higher rate of invasive mechanical ventilation and increased mortality. Intensive care provision and admission criteria likely differ across global healthcare systems and as such the definition of 'intensive care' is unlikely to be consistent in all studies. This may also contribute to explain the high observed degree of heterogeneity between studies, but as stated above, outcome by geographical region did not differ. Further exploration of heterogeneity through subgroup analyses and meta-regression did not result in significant reductions. With most studies falling within the funnel plot we suggest the pooled estimate of mortality is still of value despite the acknowledged high heterogeneity.

It is notable that we could locate no data from many countries. By contrast the UK ICNARC registry reports on a national scale [34], in near real-time and is an exemplar of good practice that would be of benefit in other countries. While this study accounts for most cases in this analysis, a sensitivity analysis which removed ICNARC data did not affect our findings. We note that Brazil has a large cohort of COVID-19 patients, which is partially reported, but it was not possible to extract the primary endpoint from the available data [44]. Except for the ICNARC dataset, all other studies are from single centres, or small local clusters of hospitals. In the future it will be of great benefit if national results are published which include not only outcomes, but also in-depth analysis of patient characteristics, acuity of illness, admission criteria and interventions undertaken. It is therefore possible that there is

publication bias towards worse outcomes being reported. More case series and registries may be in preparation and/or currently undergoing peer review.

Elements of the final analysis varied from the pre-specified plan as registered on PROSPERO. This was in part unavoidable as the available published data, resultant subgroups and reported variables could not be predicted. In view of the paucity of reports and the known differences between the effect of COVID-19 in adult and paediatric populations we made an early decision to only analyse adult patients (over 18 years of age). We were not able to distinguish reliably between HDU and ICU settings of care, and so this separation was not possible. Secondary outcome measures and organ support were not consistently reported and as such could not be investigated further. At the time of registration the global progression and time course of the pandemic were unknown. As such, the analyses over time and by geographical location were not pre-specified.

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In summary, this systematic review and meta-analysis of ICU outcome in patients with COVID-19 found an in-ICU mortality rate of 41.6% across international studies. There were no significant effects of geographical location but reported ICU mortality fell over time. Optimistically, countries in the later phase of the pandemic may be coping better with COVID-19. In the future it is important that such outcome data are collected and reported in a more systematic manner and that this is supplemented by data on what defines intensive care, the admission criteria, patient status on admission and treatments delivered while in ICU. Our analysis is reassuring in that in-ICU mortality is lower than early reports suggested.

**Competing interests and declarations**

No funding was received for this study and ethical approval was not required. The authors confirm no conflicts of interest. All authors contributed to study design, data extraction, analysis and drafting of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RAA and ADK are Health Services Research Centre Clinical Research Fellows at the Royal College of Anaesthetists, UK.

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**Table 1** Included studies arranged by publication date. NR – not reported.

| Study | Centres | Country | Area | First admission | Last admission | Last follow-up | Publication date | Proportion of patients with ICU outcome; *n* (%). | Patients who died in ICU: *n* (%) |
|---|---|---|---|---|---|---|---|---|---|
| Huang et al., [12] | Single | China | Wuhan | 16 Dec 2019 | 02 Jan 2020 | 02 Jan 2020 | 24 Jan 2020 | 12/13 (92.3) | 5/12 (41.7) |
| Stoecklin et al., [13] | Multiple | France | - | 10 Jan 2020 | 24 Jan 2020 | 12 Feb 2020 | 13 Feb 2020 | 1/1 (100) | 0/1 (0) |
| Young et al., [14] | Multiple | Singapore | - | 23 Jan 2020 | 03 Feb 2020 | 25 Feb 2020 | 03 Mar 2020 | 2/2 (100) | 0/2 (0) |
| Zhou, F et al., [15] | Multiple | China | Wuhan | 29 Dec 2019 | 31 Jan 2020 | 31 Jan 2020 | 09 Mar 2020 | 50/50 (100) | 39/50 (78) |
| Arentz et al., [16] | Single | USA | Washington State | 20 Feb 2020 | 05 Mar 2020 | 17 Mar 2020 | 19 Mar 2020 | 13/21 (61.9) | 11/13 (84.6) |
| Wang, L et al., [17] | Single | China | Zhengzhou | 21 Jan 2020 | 05 Feb 2020 | 07 Feb 2020 | 26 Mar 2020 | 1/2 (50) | 0/1 (0) |
| Bhatraju et al., [18] | Multiple | USA | Seattle | 24 Feb 2020 | 09 Mar 2020 | 23 Mar 2020 | 30 Mar 2020 | 21/24 (87.5) | 12/21 (57.1) |
| Grasselli et al., [19] | Multiple | Italy | Lombardy | 20 Feb 2020 | 18 Mar 2020 | 25 Mar 2020 | 06 Apr 2020 | 661/1591 (41.5) | 405/661 (61.3) |
| Ling et al., [20] | Multiple | Hong Kong | - | 22 Jan 2020 | 11 Feb 2020 | 09 Mar 2020 | 06 Apr 2020 | 8/8 (100) | 1/8 (12.5) |
| Wang, Y et al., [21] | Single | China | Tongji | 25 Jan 2020 | 25 Feb 2020 | 28 days | 08 Apr 2020 | 318/344 (92.4) | 133/318 (41.8) |
| Barrasa et al., [22] | Multiple | Spain | Vitoria | 04 Mar 2020 | 31 Mar 2020 | 31 Mar 2020 | 09 Apr 2020 | 27/48 (56.2) | 14/27 (51.9) |
| Zhang, G et al., [23] | Single | China | Wuhan | 02 Jan 2020 | 10 Feb 2020 | 15 Feb 2020 | 09 Apr 2020 | 32/44 (72.7) | 9/32 (28.1) |
| Klok et al., [24] | Multiple | The Netherlands | - | 07 Mar 2020 | 05 Apr 2020 | 05 Apr 2020 | 10 Apr 2020 | 45/184 (24.5) | 23/45 (51.1) |
| Zhang, J et al., [25] | Single | China | Tongji | 16 Jan 2020 | 28 Feb 2020 | NR | 21 Apr 2020 | 19/19 (100) | 8/19 (42.1) |
| Zhou, Y et al., [26] | Single | China | Hubei | 28 Jan 2020 | 02 Mar 2020 | NR | 21 Apr 2020 | 16/21 (76.2) | 3/16 (18.8) |
| Llitjos et al., [27] | Multiple | France | - | 19 Mar 2020 | 11 Apr 2020 | NR | 22 Apr 2020 | 19/26 (73.1) | 3/19 (15.8) |
| Richardson et al., [11] | Multiple | USA | New York | 01 Mar 2020 | 04 Apr 2020 | 04 Apr 2020 | 22 Apr 2020 | 371/371 (100) | 291/371 (78.4) |
| Pedersen et al., [28] | Single | Denmark | Roskilde | 11 Mar 2020 | 12 Mar 2020 | 16 Apr 2020 | 27 Apr 2020 | 11/17 (64.7) | 7/11 (63.6) |
| Ferguson et al., [29] | Multiple | USA | San Francisco | 13 Mar 2020 | 11 Apr 2020 | 02 May 2020 | 14 May 2020 | 21/21 (100) | 3/21 (14.3) |
| Zheng et al., [30] | Single | China | Hangzhou | 22 Jan 2020 | 05 Mar 2020 | 05 Mar 2020 | 20 May 2020 | 20/34 (58.8) | 0/20 (0) |
| Auld et al., [31] | Multiple | USA | Atlanta | 06 Mar 2020 | 17 Apr 2020 | 07 May 2020 | 26 May 2020 | 209/217 (96.3) | 62/209 (29.7) |
| Maatman et al., [32] | Multiple | USA | Indianapolis | 12 Mar 2020 | 31 Mar 2020 | 06 May 2020 | 27 May 2020 | 106/109 (97.2) | 27/106 (25.5) |

Commented [A14]: These need renumbering now

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mitra et al., [33] | Single | Canada | Vancouver | 21 Feb 2020 | 14 Apr 2020 | 05 May 2020 | 27 May 2020 | 105/117 (89.7) | 18/105 (17.1) |
| ICNARC [34] | Multiple | UK | England, Wales and Northern Ireland | 01 Mar 2020 | 28 May 2020 | 28 May 2020 | 29 May 2020 | 8062/9347 (86.3) | 3483/8062 (43.2) |

**Captions for Figures**

**Figure 1** PRISMA flowchart

**Figure 2** Indicative summary of study recruitment, follow-up and reporting. Data represent study admission dates (filled bar), length of final patient follow-up (solid line) and publication date (diamond) for all studies, grouped by continent (represented by colour).

**Figure 3** Meta-analysis of mortality of patients admitted to ICU with COVID-19 infection. Data represent deaths per 100 completed intensive care admissions, grouped by continent (Asia, Europe, North America), and combined. Each individual study is represented by a square with outcome estimate in the centre and 95% confidence interval (95% CI) as horizontal line either side. The size of the square reflects the study weight based on random effects. The diamonds represent meta-analysis results with outcome estimate in the centre and left and right sides corresponding to lower and upper confidence limits

**Figure 4** Funnel plot of number of patients with ICU outcomes against reported ICU mortality rate (%) for 24 included studies. The dotted lines represent 3 standard deviations.