



## Review Article

# 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 worldwide. However, the mortality of patients admitted to the intensive care unit (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 ICU admissions, either through discharge from the ICU or death. The definition thus did not include 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 (95%CI) was 41.6% (34.0–49.7%),  $I^2 = 93.2\%$ . Sub-group analysis by continent showed that mortality is broadly consistent across the globe. As the pandemic has progressed, the reported mortality rates have fallen 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 had a great impact on international health and healthcare delivery [1]. The rapid spread of the virus, the high caseload and the high proportion of patients requiring respiratory support have placed unprecedented demand on intensive care unit (ICU) services, necessitating rapid expansion of ICU infrastructure, capacity and staffing in many countries [2].

There is a 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 studies. Further, 'headline' survival rates are inconsistently reported due to variable follow-up periods, and many publications are complicated by the fact that some included patients are still receiving ICU support at the point of publication. In this

paper we aim to establish the mortality occurring within ICUs among patients admitted with COVID-19. Our main objective is to perform 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 Ethics Committee 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 (see online Supplementary Information Table S1). Manual searching was used to identify additional reports. 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) 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 both ICU and high dependency units (HDUs) were included. Studies were excluded if: the primary outcome was not reported; all patients were under 18 years old; or the report was of a single case.

Screening of titles and abstracts was performed in Microsoft Excel. All articles were screened independently by two authors (RA, AK) to identify studies potentially meeting the inclusion criteria. The full text of potentially eligible studies was independently assessed for eligibility, with disagreements resolved by discussion with the third reviewer. 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 (see online Supplementary Information Table S2). The Newcastle-Ottawa Scale is an eight-point scale that assesses patient selection (three points), comparability of cohorts (two points) and the ascertainment of outcomes (three points) [4]. Funnel plot asymmetry was used to assess heterogeneity and the 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 proportions 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 sub-group analyses based on study characteristics (single- or multicentre; 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 smaller studies were excluded to avoid data duplication with later publications [8–10]. One study reported both adult and paediatric populations: only data from 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, Fig. 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 (Fig. 2). There were reports of patients from China (eight studies); the USA (six studies); France (two studies); Canada, Denmark, the Netherlands, Hong Kong, Italy, Singapore, Spain and the UK (one study each). Reported ICU mortality rates ranged from 0%, in small case series, to 84.6% (Table 1).

The proportion of included patients who had completed their ICU stay (being dead or discharged) at the point the data were 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, see online Supplementary Information

**Table 1** Included studies arranged by publication date. Values in the final two columns are number (proportion).

Study	Centres	Country	Area	First admission	Last admission	Last follow-up	Publication date	Proportion of patients with ICU outcome	Patients who died in ICU
Huang et al. [12]	Single	China	Wuhan	16 Dec 2019	02 Jan 2020	02 Jan 2020	24 Jan 2020	12/13 (92%)	5/12 (42%)
Stoecklin et al. [13]	Multiple	France	-	10 Jan 2020	24 Jan 2020	12 Feb 2020	13 Feb 2020	1/1 (100%)	0/1
Young et al. [14]	Multiple	Singapore	-	23 Jan 2020	03 Feb 2020	25 Feb 2020	03 Mar 2020	2/2 (100%)	0/2
Zhou 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 (62%)	11/13 (85%)
Wang et al. [17]	Single	China	Zhengzhou	21 Jan 2020	05 Feb 2020	07 Feb 2020	26 Mar 2020	1/2 (50%)	0/1
Bhatraju et al. [18]	Multiple	USA	Seattle	24 Feb 2020	09 Mar 2020	23 Mar 2020	30 Mar 2020	21/24 (88%)	12/21 (57%)
Grasselli et al. [19]	Multiple	Italy	Lombardy	20 Feb 2020	18 Mar 2020	25 Mar 2020	06 Apr 2020	661/1591 (42%)	405/661 (61%)
Ling et al. [20]	Multiple	Hong Kong	-	22 Jan 2020	11 Feb 2020	09 Mar 2020	06 Apr 2020	8/8 (100%)	1/8 (13%)
Wang et al. [21]	Single	China	Tongji	25 Jan 2020	25 Feb 2020	28 days	08 Apr 2020	318/344 (92%)	133/318 (42%)
Barrasa et al. [22]	Multiple	Spain	Vitoria	04 Mar 2020	31 Mar 2020	31 Mar 2020	09 Apr 2020	27/48 (56%)	14/27 (52%)
Zhang et al. [23]	Single	China	Wuhan	02 Jan 2020	10 Feb 2020	15 Feb 2020	09 Apr 2020	32/44 (73%)	9/32 (28%)
Klok et al. [24]	Multiple	Netherlands	-	07 Mar 2020	05 Apr 2020	05 Apr 2020	10 Apr 2020	45/184 (25%)	23/45 (51%)
Zhang et al. [25]	Single	China	Tongji	16 Jan 2020	28 Feb 2020	NR	21 Apr 2020	19/19 (100%)	8/19 (42%)
Zhou et al. [26]	Single	China	Hubei	28 Jan 2020	02 Mar 2020	NR	21 Apr 2020	16/21 (76%)	3/16 (19%)
Llitjos et al. [27]	Multiple	France	-	19 Mar 2020	11 Apr 2020	NR	22 Apr 2020	19/26 (73%)	3/19 (16%)
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%)
Pedersen et al. [28]	Single	Denmark	Roskilde	11 Mar 2020	12 Mar 2020	16 Apr 2020	27 Apr 2020	11/17 (65%)	7/11 (64%)
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%)
Zheng et al. [30]	Single	China	Hangzhou	22 Jan 2020	05 Mar 2020	05 Mar 2020	20 May 2020	20/34 (59%)	0/20
Auld et al. [31]	Multiple	USA	Atlanta	06 Mar 2020	17 Apr 2020	07 May 2020	26 May 2020	209/217 (96%)	62/209 (30%)
Maatman et al. [32]	Multiple	USA	Indianapolis	12 Mar 2020	31 Mar 2020	06 May 2020	27 May 2020	106/109 (97%)	27/106 (26%)
Mitra et al. [33]	Single	Canada	Vancouver	21 Feb 2020	14 Apr 2020	05 May 2020	27 May 2020	105/117 (90%)	18/105 (17%)
ICNARC [34]	Multiple	UK	England, Wales and Northern Ireland	01 Mar 2020	28 May 2020	28 May 2020	29 May 2020	8062/9347 (86%)	3483/8062 (43%)

NR, not reported.

Figure S1). All studies were observational cohort series with varying durations of patient follow-up. The median quality score for risk of bias was 5/8, while only two studies scored 4 and none below 4 (see online Supplementary Information Table S3). Details of ICU treatments were variably reported, making further analysis of the impact of treatment (other than mechanical ventilation) impractical (see online Supplementary Information Table S4).

The ICU mortality rate (95%CI) across all studies included in the quantitative analysis was 41.6 (34.0–49.7)%,  $I^2 = 93.2\%$ ; Fig. 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 (95%CI) or heterogeneity ( $I^2$ ), the values being 40.2 (30.4–50.9)% and 92.5% respectively. Egger's test for funnel plot asymmetry was negative (0.08,  $p = 0.92$ ; Fig. 4).

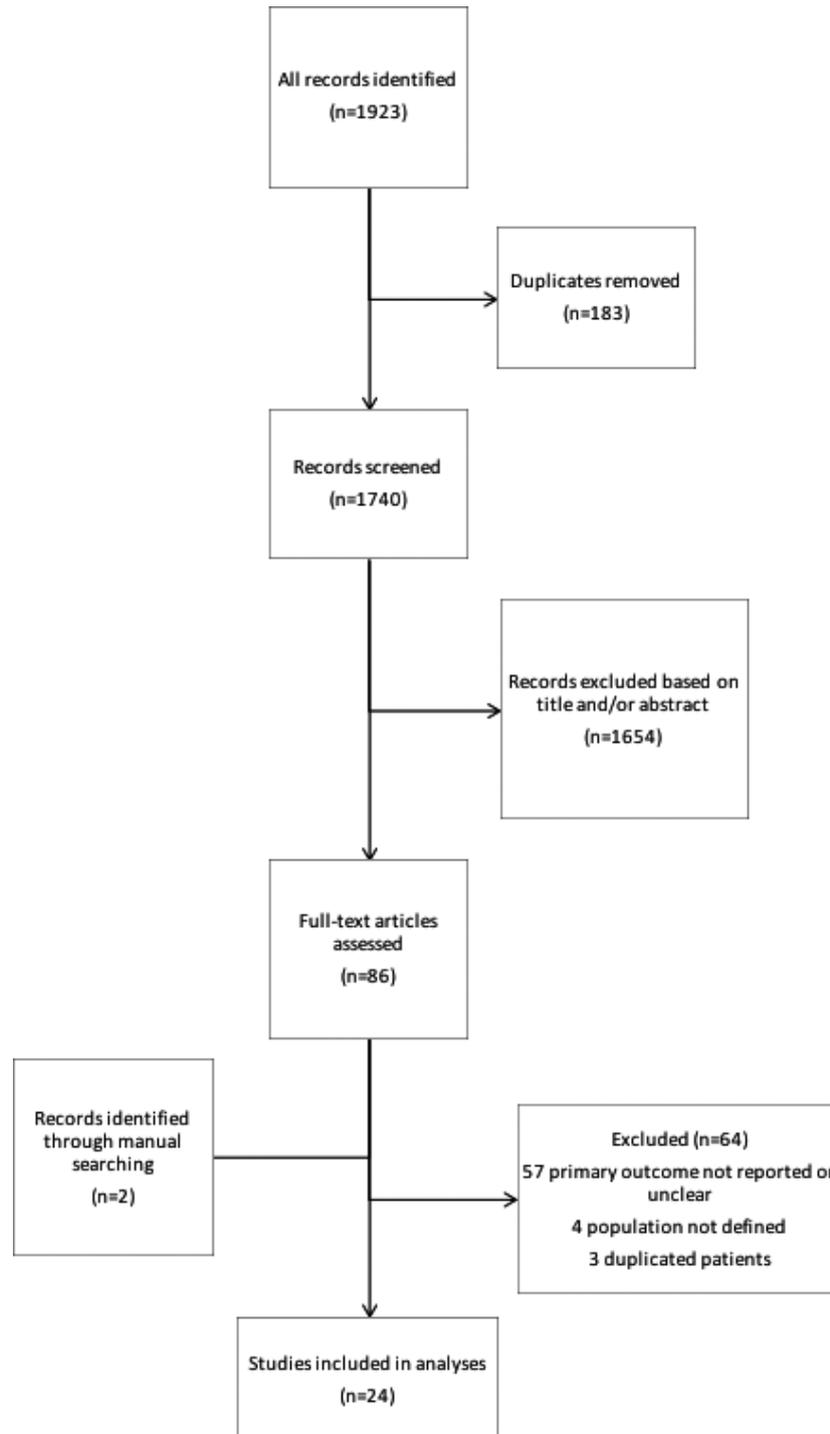
Sub-group analyses by geographical location and study characteristics (single or multiple centres; sample size; complete outcome reporting) showed no significant between-group differences or substantial reduction in

heterogeneity (see online Supplementary Information Table S5).

Meta-regressions based on patient characteristics (age, proportion of invasively ventilated patients) and proportion of patient outcomes reported, were not significant (see online Supplementary Information 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,  $p = 0.02$ ; see online Supplementary Information 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,  $p = 0.01$ ) (see online Supplementary Information 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 including 10,150 patients demonstrate an ICU mortality rate (95%CI) in those with a completed ICU



**Figure 1** PRISMA flowchart of included and excluded studies.

stay of 41.6 (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 for other viral pneumonias. Further, the

overall mortality from completed episodes of ICU differs considerably from the crude mortality rates in some early reports.

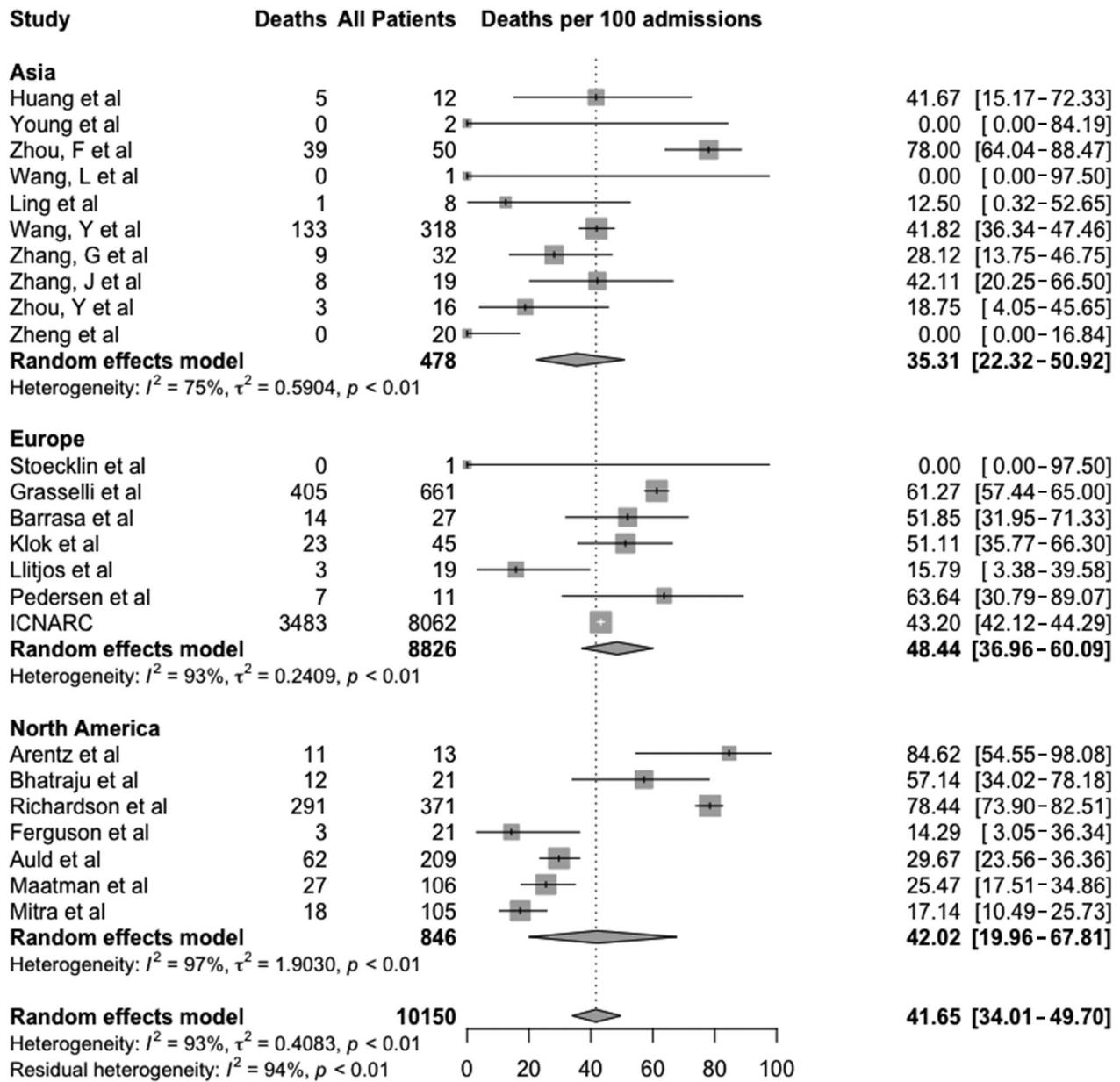
The pandemic of COVID-19 disease has been challenging, not least because of the large number of patients who have required advanced respiratory support,



**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).

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 ICU 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 ICU services there has been widespread use of advanced respiratory support (non-invasive ventilation or high flow nasal oxygen) outside ICUs, and this may have meant that patients actually admitted to ICU are disproportionately sicker. The observed ICU mortality rate is notably lower than crude mortality rates in some reports early in the pandemic, which exceeded 90%

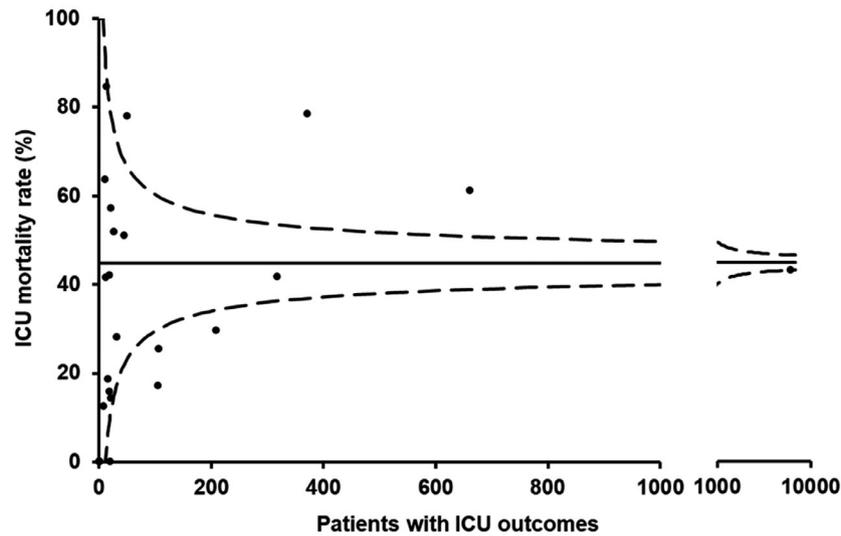


**Figure 3** Forest plot of ICU COVID-19 deaths per 100 completed intensive care admissions, grouped by continent (Asia, Europe, North America), and combined. Values are proportions (95% CI).

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 also 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, where 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, defined either as 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 the proportion of patients with outcome data reported, did not reveal significant differences in mortality rates. Conversely, a proportion of patients



**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.

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 all 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 10 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 the rapid learning that has taken place on a global scale due to the prompt publication of clinical reports early in the pandemic. It may also be that ICU admission criteria have changed over time, for example, with more non-invasive ventilatory management outside ICU. It is also likely to

reflect the fact that long ICU stays, for example, due to prolonged respiratory weaning, take time to be reflected in the data. Critical illness associated with COVID-19 is protracted, 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 well into the course of the disease. There is a possibility too that early studies, which were smaller, were prone to overestimating mortality. Funnel plot analysis does not strongly support this notion, as there was no significant asymmetry and smaller studies appeared to report lower death rates. 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, the relative proportions of patients receiving non-invasive and invasive respiratory support varied, with more non-invasive ventilation in reports from Asia. Similarly, antiviral drugs, 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 suggesting that no specific therapy reduces ICU mortality. Mortality from COVID-19 is highly age-dependent, and variations in population age, or in the age of admitted patients are likely to have a significant

influence on mortality [34]. Similar arguments may apply for comorbidities. Further, there seems to be a relationship between 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 origin, may contribute to the outcomes [34, 39–41]. As we had 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. Whereas 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 datasets, several have small numbers of patients. In the random effects model used here, the relatively large number of small studies, which inherently show greater dispersion of results, may contribute towards the (predictable) high degree of heterogeneity. To characterise this further, we assessed the variation in ICU mortality by patients in each study by funnel plot analysis (Fig. 4). Seventeen of the 24 studies fell within the 3 SD confidence interval limits of the funnel plot. There were three studies with higher than expected mortality (>3 SD above the 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 US, at points where local health systems may have been stretched [11, 15, 19]. Indeed it is known that in Lombardy there were high rates of non-invasive ventilation in patients outside ICU due to severe demand for critical care beds [43]. Patients admitted to ICU were more likely to undergo invasive mechanical ventilation and more likely to die. Intensive care provision and admission criteria likely differ across global healthcare systems, and so the definition of 'intensive care' is unlikely to be consistent in all studies. This may also go some way towards explaining 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 boundaries, we suggest that 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], is rapidly updated, and is an exemplar of good practice that would be of benefit in other countries. Whereas this study accounts for most cases in this analysis, a sensitivity analysis which removed ICNARC data did not affect the 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, severity of illness, admission criteria and interventions undertaken. It is therefore possible that there is publication bias towards worse outcomes being reported. Further case series and collections of registry data may be in preparation and/or currently undergoing peer review.

Elements of our final analysis varied from the pre-specified plan we 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 (> 18 years). We were not able to distinguish reliably between HDU and ICU settings of care, and so could not separate the data for these two different levels of care. 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.

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, supplemented by clear definitions of 'intensive care' and including the admission criteria applied, 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.

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## Supporting Information

Additional supporting information may be found online via the journal website.

**Figure S1.** Proportion of included patients with outcome reported and not reported for each study, grouped by continent.

**Figure S2.** Bubble plot with regression line showing the relationship between month of publication and reported mortality.

**Table S1.** Search strategy.

**Table S2.** Modified Newcastle-Ottawa Scale.

**Table S3.** Study quality and risk of bias assessment.

**Table S4.** Reported clinical features, rates of organ support and pharmacotherapy.

**Table S5.** Sensitivity and sub-group analyses.

**Table S6.** Results of meta-regression analyses.