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- Drabinski T *et al.* 2020 (evidence-based health economic model)[1]
- Trentino KM *et al.* 2020 (retrospective cohort study)[2]
- Wan S *et al.* 2020 (retrospective cohort study)[3]
- Kaserer A *et al.* 2019 (retrospective cohort study)[4]

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ECDC, European Centre for Disease Prevention and Control; PBM, patient blood management; RBC, red blood cell; WHO, World Health Organization. **References: 1.** Drabinski T *et al. Adv Ther.* 2020;37:3515–36. **2.** Trentino KM *et al. Anaesthesia.* 2021;76(3):357–65. **3.** Wan S *et al. J Arthroplasty.* 2020;35:3084–88. **4.** Kaserer A *et al. Anaesthesia.* 2019;74(12):1534–41. **5.** Shander A *et al. Anesth Analg.* 2020;131(1):75–85. **6.** WHO interim guidance: Maintaining a safe and adequate blood supply during the pandemic outbreak of coronavirus disease (COVID-19), March 2020. **7.** ECDC rapid risk assessment: Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – sixth update, March 2020. **8.** Leahy MF *et al. Transfusion.* 2017;57(6):1347–58. **9.** Keding V *et al. World J Surg Oncol.* 2018;16:159. **10.** Khalafallah AA *et al. Lancet Haematol.* 2016;3(9):e415–25. **11.** Deppe AC *et al. J Surg Res.* 2016;203(2):424–33. **12.** Althoff FC *et al. Ann Surg.* 2019;269(5):794–804. **13.** Gani F *et al. Ann Surg.* 2019;269(6):1073–79. **14.** Spahn DR *et al. Lancet.* 2019;393(10187):2201–12. **15.** Froessler B *et al. Ann Surg.* 2016;264(1):41–6. HQ-FCM-2100014 February 2021

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Review Article

Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies

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Summary

The COVID-19 pandemic continues to cause critical illness and deaths internationally. Up to 31 May 2020, mortality in patients admitted to intensive care units (ICU) with COVID-19 was 41.6%. Since then, changes in therapeutics and management may have improved outcomes. Also, data from countries affected later in the pandemic are now available. We searched MEDLINE, Embase, PubMed and Cochrane databases up to 30 September 2020 for studies reporting ICU mortality among adult patients with COVID-19 and present an updated systematic review and meta-analysis. The primary outcome measure was death in intensive care as a proportion of completed ICU admissions, either through discharge from intensive care or death. We identified 52 observational studies including 43,128 patients, and first reports from the Middle East, South Asia and Australasia, as well as four national or regional registries. Reported mortality was lower in registries compared with other reports. In two regions, mortality differed significantly from all others, being higher in the Middle East and lower in a single registry study from Australasia. Although ICU mortality (95%CI) was lower than reported in June (35.5% (31.3–39.9%) vs. 41.6% (34.0–49.7%)), the absence of patient-level data prevents a definitive evaluation. A lack of standardisation of reporting prevents comparison of cohorts in terms of underlying risk, severity of illness or outcomes. We found that the decrease in ICU mortality from COVID-19 has reduced or plateaued since May 2020 and note the possibility of some geographical variation. More standardisation in reporting would improve the ability to compare outcomes from different reports.

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Introduction

The global COVID-19 pandemic continues to impact international health and healthcare delivery [1]. To date, the World Health Organization has recorded more than 96 million cases worldwide, with the real number likely many-fold higher, and more than 2 million confirmed deaths [2]. Intensive care units (ICU) have an important role in managing the sickest of these patients, but mortality is high in this group. We conducted an initial systematic review and meta-analysis of 24 observational studies published by 31 May 2020, which included 10,150 patients, finding that mortality was 41.6%, with evidence that this was decreasing as the pandemic progressed [3, 4].

In the last few months, several studies have clarified which treatments do and do not provide benefit in the ICU management of COVID-19. Steroids (particularly dexamethasone) were shown in early June to improve survival in patients who are oxygen-dependent or receiving mechanical respiratory support [5, 6], while other drugs including chloroquine, azithromycin, lopinavir/ritonavir and remdesivir have been shown to have no clear mortality benefit [7–9]. Management of COVID-19 has also likely evolved over the year with changes in approaches to oxygen therapy, fluids and anticoagulation management [10, 11]. Since our first meta-analysis, the pandemic has spread further into the southern hemisphere and there has been time for studies from more countries to be reported.

Given these developments, mortality from COVID-19 in patients admitted to the ICU may have altered further. Here, we update the previous systematic review and meta-analysis to include studies published up to 30 September 2020.

Methods

The review, including our intention to update the analyses and outputs as new data came to light, was prospectively registered with PROSPERO and conducted according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [12]. The search strategy up to 31 May 2020 has been previously described [3]. We repeated the search of MEDLINE, Embase, PubMed and the Cochrane Library up until 30 September 2020 using the search terms "coronavirus", "covid19", "sars-cov-2" or "2019-ncov"; and "intensive care", "mortality" or "disease course". The exact terms used were adapted to each database (online Supporting Information, Table S1). Manual searching was used to identify additional results. We also contacted intensive care registries run by national societies (online Supporting Information, Table S2) to locate published data not indexed by the libraries above. Preprints and articles that were not published in journals were not included.

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 ICU and high dependency units were included. Studies were excluded if the primary outcome was not reported, all patients were < 18 years old, or the report was a single case. We analysed studies by geographical region using the World Bank classification of regions [13] as used in other analyses [14], but included Australia and New Zealand (Australasia) as an independent region from others in the East Asia and Pacific grouping as they are geopolitically discrete and experienced a later first surge.

Screening of titles and abstracts was performed in Microsoft Excel (Microsoft, Inc., Redmond, CA, USA). All articles were screened independently by two authors (two of RA, AK, EK, FO) to identify studies potentially meeting inclusion criteria. The full texts of potentially eligible studies were independently assessed for eligibility with disagreements resolved by discussion with a third reviewer (TC). The pre-specified primary outcome was the mortality rate in patients with completed ICU admission. Data were only included when this outcome was reported clearly. 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. We used a modified version of the Newcastle-Ottawa Scale (online Supporting Information, Table S3) to assess the quality of included studies, as previously described, and funnel plot asymmetry to assess heterogeneity and risk of publication bias [3, 15].

Meta-analysis was conducted using the 'meta' package (Version 4.15-1, 2020) in R (The R Foundation for Statistical Computing; Version 4.0.3, 2020). An inverse-variance random-effects model was used for all analyses. Between-study heterogeneity was assessed using the I^2 test. A funnel plot was produced using the Public Health England tool [15]. 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 (both region and World Bank income region [13]). We also conducted a sensitivity analysis excluding all national registries. Meta-regression was used to explore the effects of patient characteristics and treatments (proportion ventilated; average age; proportion of male sex); geographical location; publication date; and proportion of patients with outcomes reported.

Results

The updated search found an additional 7341 articles available since our previous analysis [3], including 1359 duplicates, leaving 5982 to be screened. After exclusion by title or abstract of 5787 articles, 195 full-text articles were reviewed, of which 28 reported the primary outcome of interest. One of these was an updated report from Lombardy [16]. Three studies from Wuhan, China were excluded to avoid data duplication due to the overlap of both the data collection period and hospital location [17–19]. A report from the European Risk Stratification in COVID-19 patients in the ICU (RISC-19-ICU) cohort was

included as it was not possible to determine whether patients were duplicated in other series [20]. Manual searching and direct contact yielded five additional regional or national registries, including an updated report from the UK's Intensive Care National Audit and Research Centre (ICNARC). To avoid duplication of cases, two earlier reports from the Netherlands [21, 22] and one from Germany [23] were excluded. A total of 52 reports were included in the analysis [16, 20, 24–73], comprising the 31 new reports and 21 of the 24 reports from our earlier review (removing the previous reports from ICNARC, Grasselli et al. and Klok et al. [21, 74, 75]; Table 1, Fig. 1).

These studies reported ICU outcome data for 43,128 patients admitted to ICU with a COVID-19 diagnosis. Median (IQR [range]) number of patients in each study was 44 (20–140 [1–19,229]) patients; the smallest series were from reports of larger cohorts that included non-ICU patients. Recruitment in these 52 studies was from 16 December 2019 to 27 October 2020 with publication dates from 24 January 2020 to 27 October 2020 (Fig. 2). The median (IQR [range]) interval from recruitment of the last patient to publication was 50 (26–82 [0–170]) days, but this was longer after 31 May 2020 than before this (40 (21–50 [9–76]) days vs. 84 (45—117 [0–170]) days, p = 0.002). [Correction added on 9 February 2021, after first online publication: In the preceding sentence, the median: (404 (21–50 [9–76]) was changed to (40 (21–50 [9–76])]. Studies reported on patients from China (n = 10) [24, 27, 29, 32, 34–36, 42, 62, 63]; USA (n = 8) [28, 30, 38, 40, 43, 44, 60, 61]; France (n = 4) [25, 37, 46, 48]; Spain (n = 4) [33, 47, 53, 58]; Switzerland (n = 3) [41, 54, 57]; Canada (n = 2) [45, 66]; Denmark (n = 2) [39, 65]; Australia [71]; Belgium [69]; Europe [20]; Germany [72]; Greece [55]; Hong Kong [31]; Iceland [59]; India [50]; Iran [49]; Israel [56]; Italy [16]; Kuwait [51]; Netherlands [73]; Poland [68]; Scotland [52]; Singapore [26]; Sweden [64]; UK [70]; and Yemen [67] (n = 1 each). Reported ICU mortality rates ranged from 0% to 84.6%, with values at both extremes arising from small case series.

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: 16 studies reported outcome data for all participants and in the remaining 36 studies the percentage varied from 42.2% to 98.8% (Table 1, online Supporting Information, Figure S1). All studies were observational cohort studies with varying durations of patient follow-up. The median (IQR [range]) quality score for risk of bias was 6 (5–7 [3–8]) out of 8, indicating a low risk of bias. Only four studies were rated 8/8, with one scoring 3/8 and six scoring 4/8 (online Supporting Information, Table S4). Details of ICU treatments were variably reported making further analysis of the impact of treatment on the outcome, other than invasive mechanical ventilation, impractical (online Supporting Information, Table S5).

The ICU mortality rate (95%CI) across all studies included in the quantitative analysis was 35.5% (31.3–39.9%), I^2 = 97.6% (Fig. 3). The largest patient cohorts were from national registries of Germany (19,229 patients [72]) and the UK (11,480 [70]). A sensitivity analysis removing all national and regional registries [52, 70–73] did not significantly affect the mortality rate or heterogeneity (36.8% (31.6–42.4%), I^2 = 91.8%) and Egger's test of funnel plot asymmetry was negative (t = 0.89, p = 0.38; Fig. 4).

In a sub-group analysis, the mortality reported in the registries was significantly lower than in other reports (25.7% (18.4–34.7%), I^2 = 99.6% vs. 36.8% (31.6–42.4%), I^2 = 96.8%, p = 0.04). Sub-group analysis by geographical location demonstrated higher mortality in studies from the Middle East (61.9% (52.5–70.5%), I^2 = 30%) and lower mortality in the single registry from Australia (10.6% (8.7–12.9%)) [71], with similar rates elsewhere (between-group differences p < 0.001). Mortality was higher in the one low-income country [67] but similar in other income groups (between-group differences p < 0.001). Sub-group analysis by month of publication demonstrated higher mortality in the earliest reported series (between-group differences p < 0.05) (Table 2). Sub-group analyses based on study characteristics (single or multiple centres; sample size; complete outcome reporting) showed no significant between-group differences or substantial reductions in heterogeneity (online Supporting Information, Table S6).

Multivariate meta-regressions based on patient characteristics and treatments (age; male sex; proportion of invasively ventilated patients) and proportion of patient outcomes reported (i.e. the proportion of patients in each study with a completed ICU stay) were not significant. Univariate meta-regression by month of publication; month of last admission; and month of last patient follow-up, all showed apparent reductions in mortality over time (treatment effect (logit transformed proportion) -0.13 per 1-month increment in publication date, p = 0.002; -0.12 per 1-month increment in last admission date, p = 0.004; -0.16 per 1-month increment in last patient follow-up date, p = 0.001). In multivariate meta-regression adjusting for patient and treatment characteristics, the proportion of outcomes reported, geographical location and income

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	Patients with ICU outcome	Patients who died in ICU
Huang et al. [24]	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. [25]	Multi	France	–	10 Jan 2020	24 Jan 2020	12 Feb 2020	13 Feb 2020	1/1 (100%)	0/1 (0%)
Young et al. [26]	Multi	Singapore	–	23 Jan 2020	03 Feb 2020	25 Feb 2020	03 Mar 2020	2/2 (100%)	0/2 (0%)
Zhou et al. [27]	Multi	China	Wuhan	29 Dec 2019	31 Jan 2020	31 Jan 2020	09 Mar 2020	50/50 (100%)	39/50 (78%)
Arentz et al. [28]	Single	USA	Washington	20 Feb 2020	05 Mar 2020	17 Mar 2020	19 Mar 2020	13/21 (61.9%)	11/13 (84.6%)
Wang et al. [29]	Single	China	Zhengzhou	21 Jan 2020	05 Feb 2020	07 Feb 2020	26 Mar 2020	1/2 (50%)	0/1 (0%)
Bhatraju et al. [30]	Multi	USA	Seattle	24 Feb 2020	09 Mar 2020	23 Mar 2020	30 Mar 2020	21/24 (87.5%)	12/21 (57.1%)
Ling et al. [31]	Multi	Hong Kong	–	22 Jan 2020	11 Feb 2020	09 Mar 2020	06 Apr 2020	8/8 (100%)	1/8 (12.5%)
Wang et al. [32]	Single	China	Tongji	25 Jan 2020	25 Feb 2020	24 Mar 2020	08 Apr 2020	318/344 (92.4%)	133/318 (41.8%)
Barrasa et al. [33]	Multi	Spain	Vitoria	04 Mar 2020	31 Mar 2020	31 Mar 2020	09 Apr 2020	27/48 (56.2%)	14/27 (51.9%)
Zhang et al. [34]	Single	China	Wuhan	02 Jan 2020	10 Feb 2020	15 Feb 2020	09 Apr 2020	32/44 (72.7%)	9/32 (28.1%)
Zhang et al. [35]	Single	China	Tongji	16 Jan 2020	28 Feb 2020	NR	21 Apr 2020	19/19 (100%)	8/19 (42.1%)
Zhou et al. [36]	Single	China	Hubei	28 Jan 2020	02 Mar 2020	NR	21 Apr 2020	16/21 (76.2%)	3/16 (18.8%)
Llitjos et al. [37]	Multi	France	–	19 Mar 2020	11 Apr 2020	NR	22 Apr 2020	19/26 (73.1%)	3/19 (15.8%)
Richardson et al. [38]	Multi	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. [39]	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. [40]	Multi	USA	San Francisco	13 Mar 2020	11 Apr 2020	02 May 2020	14 May 2020	21/21 (100%)	3/21 (14.3%)
Longchamp et al. [41]	Single	Switzerland	Sion	08 Mar 2020	04 Apr 2020	09 May 2020	14 May 2020	23/25 (92%)	5/23 (21.7%)
Zheng et al. [42]	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. [43]	Multi	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. [44]	Multi	USA	Indianapolis	12 Mar 2020	31 Mar 2020	06 May 2020	27 May 2020	106/109 (97.2%)	27/106 (25.5%)
Mitra et al. [45]	Single	Canada	Vancouver	21 Feb 2020	14 Apr 2020	05 May 2020	27 May 2020	105/117 (89.7%)	18/105 (17.1%)
Fraissé et al. [46]	Single	France	Argenteuil	06 Mar 2020	22 Apr 2020	06 May 2020	02 Jun 2020	66/92 (71.7%)	38/66 (57.6%)
Borobia et al. [47]	Single	Spain	Madrid	25 Feb 2020	19 Apr 2020	19 Apr 2020	04 Jun 2020	121/237 (51.1%)	55/121 (45.5%)
Rubin et al. [48]	Single	France	Bordeaux	03 Mar 2020	14 Apr 2020	14 Apr 2020	06 Jun 2020	42/71 (59.2%)	4/42 (9.5%)
Shahriarirad et al. [49]	Multi	Iran	Fars Province	20 Feb 2020	20 Mar 2020	NR	18 Jun 2020	9/11 (81.8%)	5/9 (55.6%)
Shukla et al. [50]	Single	India	Maharashtra	01 Apr 2020	17 May 2020	17 May 2020	01 Jul 2020	24/24 (100%)	4/24 (16.7%)
Almazeedi et al. [51]	Single	Kuwait	South Surra	24 Feb 2020	20 Apr 2020	20 Apr 2020	04 Jul 2020	23/42 (54.8%)	17/23 (73.9%)
Wendel Garcia et al. [20]	Multi	Europe	RISC-19-ICU registry (Switzerland, Spain, Italy, France, Germany, Others)	13 Mar 2020	22 Apr 2020	22 Apr 2020	06 Jul 2020	398/639 (62.3%)	97/398 (24.4%)
SICSAG [52]	Multi	Scotland	–	01 Mar 2020	20 Jun 2020	20 Jun 2020	08 Jul 2020	509/521 (97.7%)	193/509 (37.9%)
Giesen et al. [53]	Single	Spain	Madrid	27 Feb 2020	30 Jun 2020	29 Jun 2020	11 Jul 2020	99/103 (96.1%)	36/99 (36.4%)
Pellaud et al. [54]	Single	Switzerland	Fribourg	01 Mar 2020	12 Apr 2020	10 May 2020	14 Jul 2020	43/49 (87.8%)	11/43 (25.6%)
Grasselli et al. [16]	Multi	Italy	Lombardy	20 Feb 2020	22 Apr 2020	30 May 2020	15 Jul 2020	3818/3988 (95.7%)	1769/3818 (46.3%)
Halvatsiotis et al. [55]	Multi	Greece	–	10 Mar 2020	13 Apr 2020	13 Apr 2020	17 Jul 2020	38/90 (42.2%)	26/38 (68.4%)
Amit et al. [56]	Multi	Israel	–	05 Mar 2020	27 Apr 2020	08 May 2020	18 Jul 2020	156/156 (100%)	87/156 (55.8%)
Primmaz et al. [57]	Single	Switzerland	Geneva	09 Mar 2020	19 May 2020	19 May 2020	29 Jul 2020	129/129 (100%)	24/129 (18.6%)
Muñoz et al. [58]	Single	Spain	Madrid	01 Mar 2020	11 Mar 2020	NR	30 Jul 2020	10/13 (76.9%)	5/10 (50%)
Kristinsson et al. [59]	Multi	Iceland	–	14 Mar 2020	13 Apr 2020	05 May 2020	11 Aug 2020	27/27 (100%)	3/27 (11.1%)
Miller et al. [60]	Single	USA	New York	01 Apr 2020	23 Apr 2020	NR	18 Aug 2020	19/19 (100%)	5/19 (26.3%)
Mukherjee et al. [61]	Single	USA	New York	10 Mar 2020	07 Apr 2020	18 May 2020	19 Aug 2020	135/137 (98.5%)	82/135 (60.7%)
Zhou et al. [62]	Single	China	Hunan	01 Jan 2020	28 Apr 2020	28 Apr 2020	21 Aug 2020	45/45 (100%)	2/45 (4.4%)
Hu et al. [63]	Single	China	Wuhan	08 Jan 2020	12 Mar 2020	12 Mar 2020	29 Aug 2020	55/55 (100%)	16/55 (29.1%)
Larsson et al. [64]	Single	Sweden	Stockholm	09 Mar 2020	20 Apr 2020	30 Apr 2020	06 Sep 2020	198/260 (76.2%)	60/198 (30.3%)
Haase et al. [65]	Multi	Denmark	–	10 Mar 2020	19 May 2020	16 Jun 2020	15 Sep 2020	319/323 (98.8%)	108/319 (33.9%)
Cavayas et al. [66]	Single	Canada	Montreal	20 Mar 2020	13 May 2020	27 Jul 2020	15 Sep 2020	75/75 (100%)	17/75 (22.7%)
Lee et al. [67]	Single	Yemen	–	NR	NR	NR	23 Sep 2020	47/47 (100%)	32/47 (68.1%)
Kokoszka-Bargieł et al. [68]	Single	Poland	Silesian	10 Mar 2020	10 Jun 2020	10 Jun 2020	26 Sep 2020	27/32 (84.4%)	18/27 (66.7%)
Van Aerde et al. [69]	Single	Belgium	Leuven	13 Mar 2020	08 Jun 2020	NR	28 Sep 2020	111/114 (97.4%)	11/111 (9.9%)

(continued)

Table 1 (*continued*)

Study	Centres	Country	Area	First admission	Last admission	Last follow-up	Publication date	Patients with ICU outcome	Patients who died in ICU
ICNARC [70]	Multi	UK	England, Wales and Northern Ireland	01 Mar 2020	15 Oct 2020	28 May 2020	16 Oct 2020	11,480/12,133 (94.6%)	4457/11,480 (38.8%)
ANZICS (Victoria) [71]	Multi	Australia	Victoria	01 Jan 2020	30 Sep 2020	30 Sep 2020	22 Oct 2020	819/883 (92.8%)	87/819 (10.6%)
Germany registry [72]	Multi	Germany	–	01 Jan 2020	22 Oct 2020	22 Oct 2020	22 Oct 2020	19,229/20,259 (94.9%)	4443/19,229 (23.1%)
Netherlands registry [73]	Multi	Netherlands	–	01 Mar 2020	27 Oct 2020	27 Oct 2020	27 Oct 2020	3652/4161 (87.8%)	942/3652 (25.8%)

NR, not reported; SICSAG, Scottish Intensive Care Society Audit Group; ICNARC, Intensive Care National Audit and Research Centre; ANZICS, Australia and New Zealand Intensive Care Society.

region, the reduction in mortality over time remained significant for last patient follow-up date (-0.30 per 1-month increment in last patient follow-up date, p = 0.02), but not publication or last admission date (online Supporting Information, Table S7).

Discussion

In this updated systematic review and meta-analysis of 52 studies involving 43,128 patients admitted to ICU with COVID-19, we found an ICU mortality rate (95%CI) in those with a completed ICU stay of 35.5% (31.3–39.9%). Relative

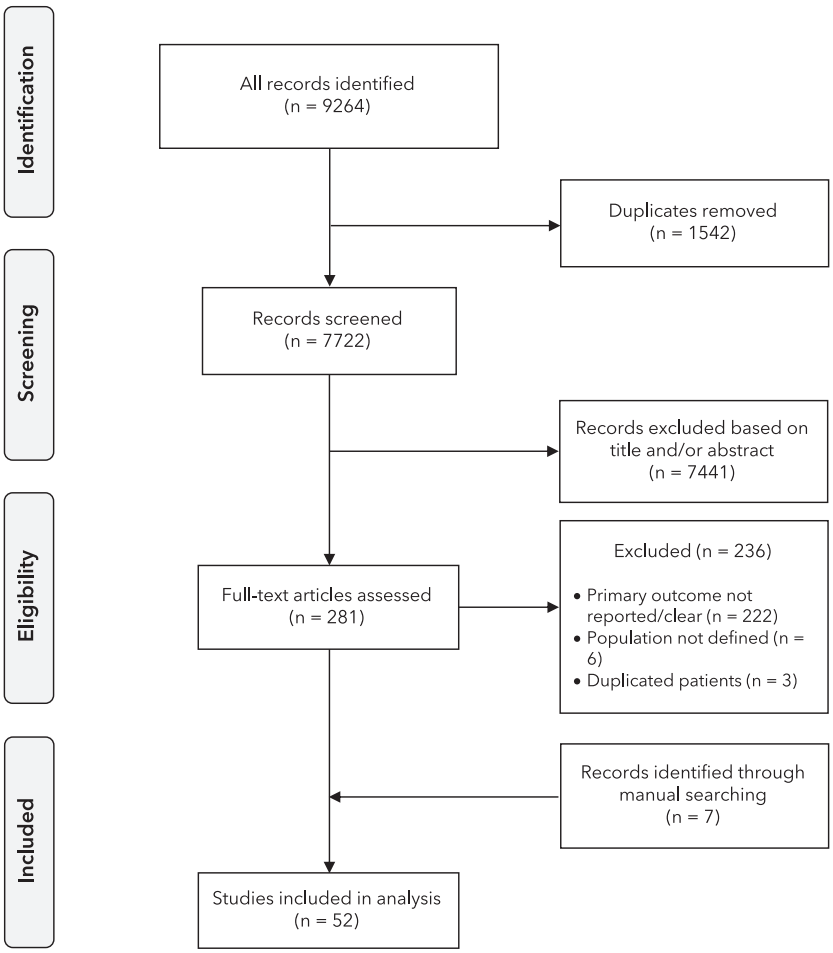

Figure 1 Flowchart of study inclusion.

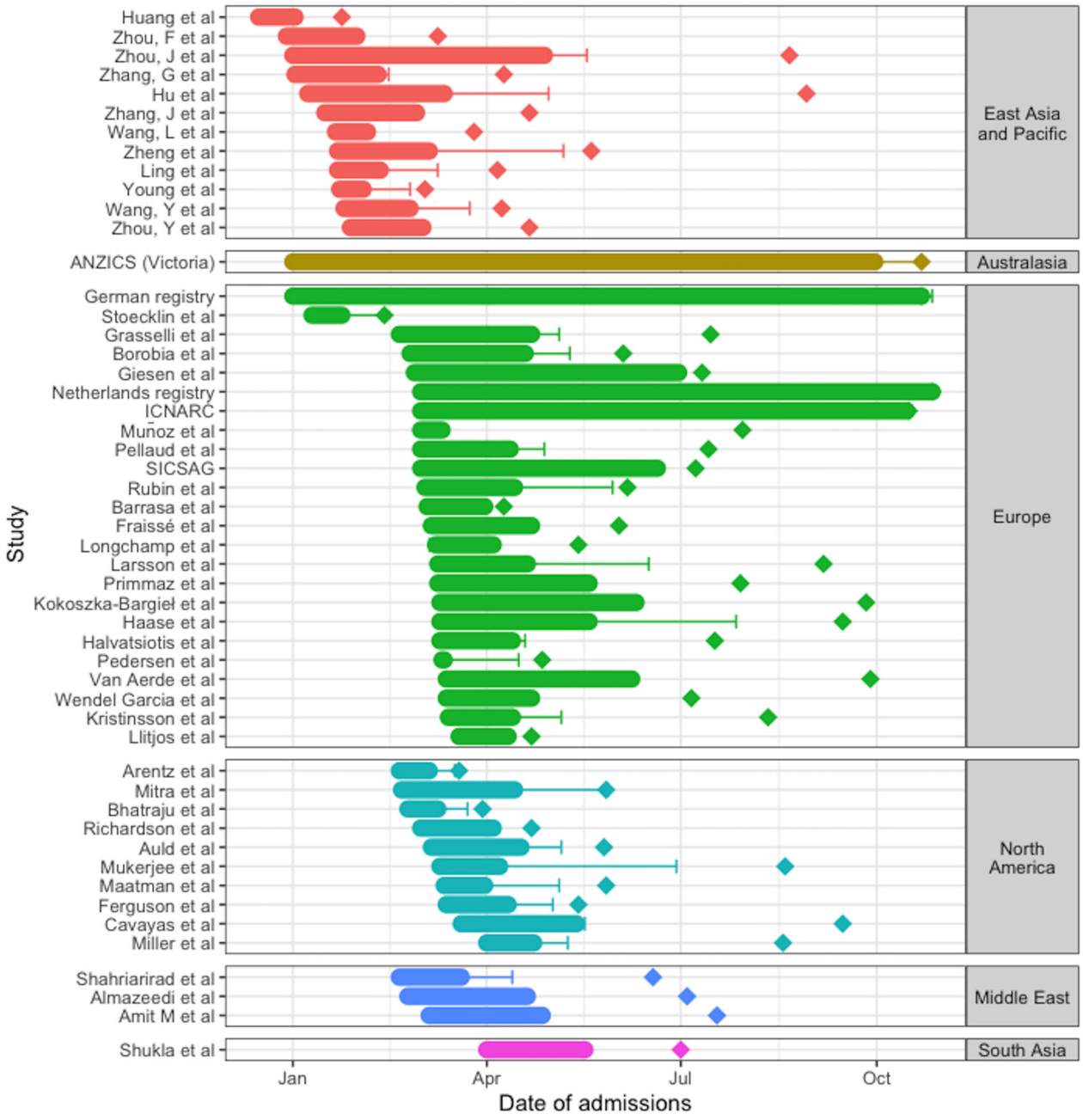

Figure 2 Indicative summary of study recruitment, follow-up and reporting. Data represent study admission dates (filled bar), length of final patient follow-up (solid line) and publication date (diamond) for all studies, grouped by continent (represented by colour). ICNARC, Intensive Care National Audit and Research Centre; SICSAG, Scottish Intensive Care Society Audit Group; ANZICS, Australia and New Zealand Intensive Care Society. [Correction added on 9 February 2021, after first online publication: Fig. 2 was updated to reflect correct analysis of data].

to other geographical regions, the mortality rate was higher in the Middle East and lower in a single study from Australasia. The previously identified reduction in mortality over time has become less pronounced between May and September 2020.

This updated analysis included 31 new studies and two updates of earlier reports [16, 70], with outcome data for an additional 32,978 patients. The updated search found reports from several countries and regions not represented in the previous review (Australia; Belgium; Germany; Greece; Iceland; India; Israel; Kuwait; Poland; Scotland; Sweden; Switzerland; Yemen) and several national and regional registries which had reported outcomes in the intervening months.

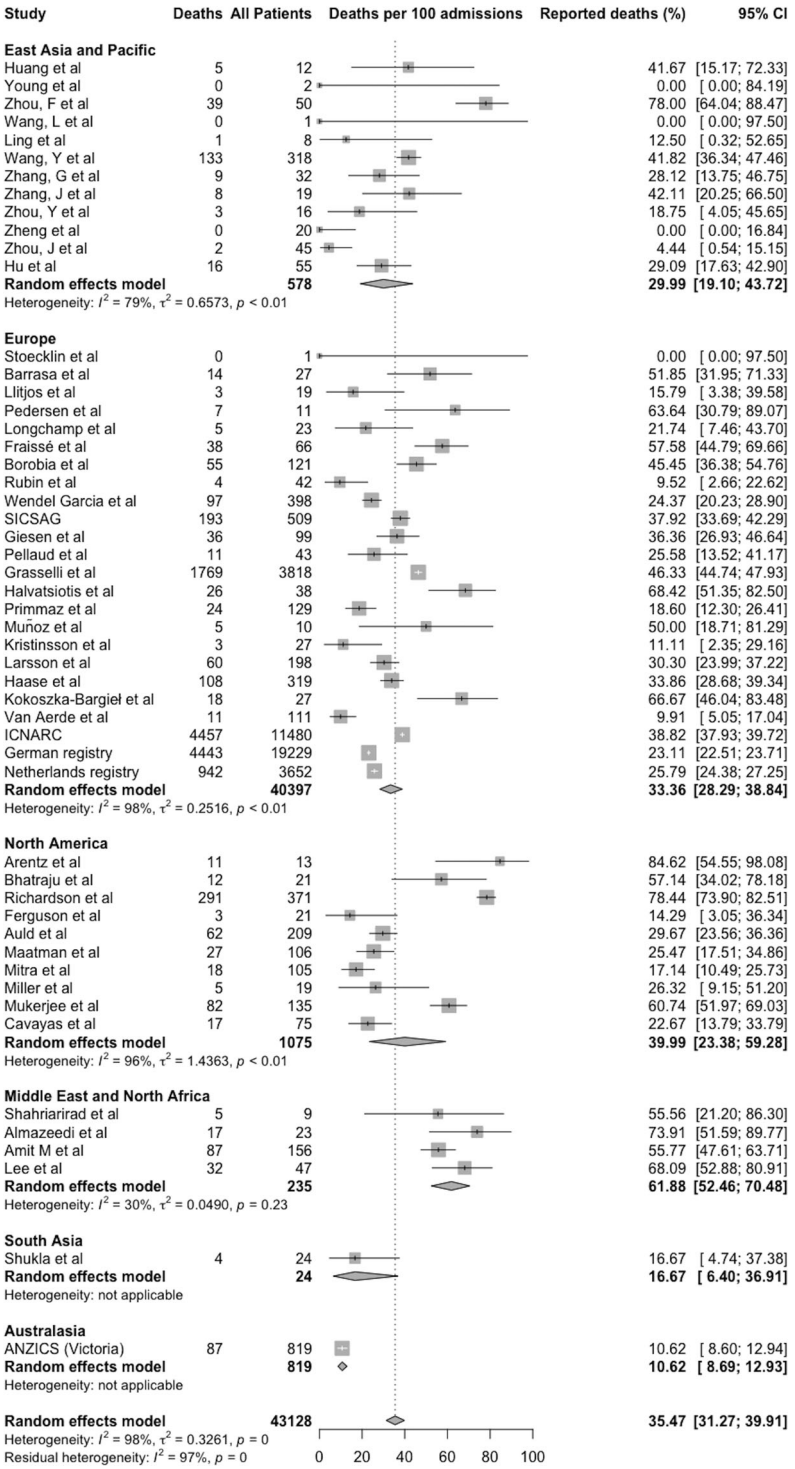

Figure 3 Meta-analysis of mortality of patients admitted to ICU with COVID-19 infection. Data represent deaths per 100 completed intensive care admissions, grouped by geography and combined. Each study is represented by a square with outcome estimate in the centre and 95%CI as a horizontal line either 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. ICNARC, Intensive Care National Audit and Research Centre; SICSAG, Scottish Intensive Care Society Audit Group; ANZICS, Australia and New Zealand Intensive Care Society. [Correction added on 9 February 2021, after first online publication: Fig. 3 was updated to reflect correct analysis of data].

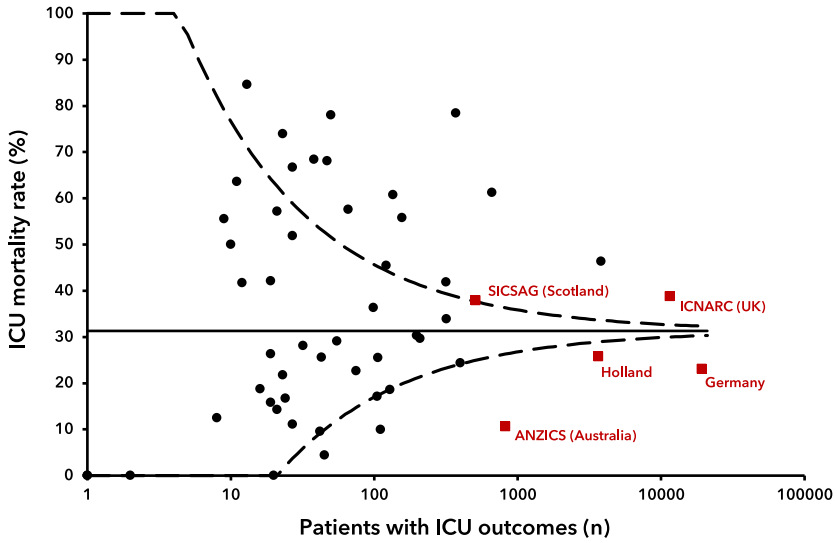

Figure 4 Funnel plot of the number of patients with ICU outcomes against reported ICU mortality rate (%) for 52 included studies. The solid line represents the average reported mortality. The dotted lines represent three standard deviations. [Correction added on 9 February 2021, after first online publication: The solid line representation has now been explained]

Overall mortality in all studies is lower to the end of September (35.5%) than when we reported this to the end of May (41.6%), and this is with the inclusion of more studies from more countries and a wider geographical area, over a longer time period, such that we now have a more complete picture of the first months of the pandemic. Before May 2020, there was a clear reduction in mortality over time. An analysis of mortality based on dates of last patient follow-up finds mortality continues to fall, but this is complicated by the observation that the interval between data collection

Table 2 Statistically significant sub-group analyses showing variation in survival of intensive care unit admission after admission with COVID-19 between registry and non-registry reports, geographical region and month of publication.

	Studies	Mortality % (95%CI)	I^2 (%)	p value
Registries				
Registry reports	5	25.7% (18.4–34.7%)	99.6%	0.037
Other studies	47	36.8% (31.6–42.4%)	91.8%	
Geographical region				
East Asia and Pacific	12	30.0% (19.1–43.7%)	79.4%	< 0.001
Europe	24	33.4% (28.3–38.8%)	98.4%	
North America	10	40.0% (23.4–59.3%)	96.3%	
Middle East and North Africa	4	61.9% (52.5–70.5%)	30.0%	
South Asia	1	16.7% (6.4–36.9%)	–	
Oceania	1	10.6% (8.7–12.9%)	–	
World Bank income region				
High-income	39	35.1% (30.4–40.0%)	98.1%	< 0.001
Upper-middle income	11	33.7% (22.1–47.8%)	80.6%	
Lower-middle income	1	16.7% (6.4–36.9%)	–	
Low income	1	68.1% (53.6–79.8%)	–	
Month of publication				
Jan–Mar	7	59.5% (39.8–76.5%)	54.1%	0.034
Apr–Jun	19	32.6% (22.9–44.0%)	93.0%	
Jul–Oct	26	33.1% (28.1–38.4%)	98.5%	

and publication has progressively increased (Fig. 2). Additionally, this single time-point is only a proxy for the timeline of admissions in each study, which cannot be evaluated further due to a lack of patient-level data. Meta-regression also did not show clear temporal improvements within individual regions, when adjusted for other variables. Thus, the clear fall in mortality over time observed between January and May is now less evident, and while over time mortality has undoubtedly fallen, it is likely that the improvement has reduced or plateaued. We are not able to comment on whether mortality has reduced at specific time points, such as since the randomised evaluation of COVID-19 therapy (RECOVERY) study reported reduced mortality with the use of dexamethasone [5], as this would likely require individual patient-level data and separation of cohorts into those admitted before and after the relevant time-point, which is not currently available.

In most geographical regions, the mortality rate is 30–40%. Two geographical regions fall outside these limits and are statistically significantly different from other geographical regions. A single registry report from Victoria State in Australia reports very low mortality of 10.6%. Conversely in the Middle East, mortality is high at 61.9%. These studies are variable in terms of the country of origin (two from high-income countries [51, 56]; one upper-middle [49]; and one low-income [67]); quality (two were at high risk of bias); and one is from a critical care unit in an area of humanitarian crisis – despite this, the studies showed similar mortality rates and considerable homogeneity (I^2 = 30%). There are several potential explanations for this finding, including the fact that studies from the Middle East included patients early in the pandemic when mortality was higher and those included in Australia arose later in the pandemic when mortality was lower. It is possible that variations in healthcare resource, variation in admission criteria and clinical and statistical uncertainty associated with single-centre and small reports could have also contributed. Which of these explanations holds sway is uncertain but the variation merits further exploration and further reports from these regions would be welcome.

There remain limited reports from the southern hemisphere, where the pandemic centred later than in the north. We were unable to include any reports from South America; we are aware of a large registry from Brazil but it could not be included as the primary outcome cannot be calculated from the data reported. The African COVID-19 Critical Care Outcomes Study (ACCCOS) has reported provisional outcomes in a pre-print paper from 38 hospitals in 6 countries, reporting relatively high mortality (95%CI) of 54.7% (51.9–57.6%) (Biccard et al., preprint, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3707415) and further data are being added to this study.

One notable finding is that mortality was lower in registry reports than in non-registry studies (absolute difference 11%; relative risk 0.70). Registry reports tended to have high proportions of completed episodes (mostly above 90%), included patient outcomes towards the latter stages of our data collection period and were all from high-income countries. These factors, allied with networks that underpin the registries, may all be factors in their lower reported mortality rates. In the UK, the ICNARC group has reported a fall in mortality in the periods before and after the peak of the first surge [76]. The report is notable because mortality increased during the peak period of the surge and the characteristics of admitted patients also varied during this period, with patients being younger and sicker. That paper hints at both improvements in outcomes over time and poorer outcomes when healthcare systems are stressed. The changes in outcomes during and after periods of health system stress has implications for defining adequate health resource provision and for comparing performance between locations with differing resource and degrees of healthcare stress.

There are several limitations to this study. There remains a lack of reports from many countries and a paucity of reports from the southern hemisphere, so we are not able to provide a genuinely global picture of regional variation in outcomes. There is, as previously described [3], a notable lack of consistency of reporting with no standardisation of what constitutes intensive care, entry criteria for patients, admitted patients' underlying health characteristics and severity of critical illness or reporting on the nature or intensity of treatments. This means that the included patients' underlying risk is unknown and outcomes between studies are not directly comparable. Additional factors such as critical care provision (e.g. ICU beds per capita) may also contribute to the differences observed, though we do not have up-to-date data on these metrics, particularly as it is likely this has changed considerably throughout the pandemic. Indeed, it is also likely that some of these factors may even have varied during the pandemic in individual series or registries (e.g. [76]). The RISC-19-ICU registry (https://www.risc-19-icu.net) provides one approach towards the creation of a standardised minimum dataset in this patient cohort. Its website currently lists 93 participating centres from 16 countries collecting standardised data. There is an argument that unaccounted-for differences in patient populations, definitions of ICU and marked heterogeneity of results mean the data should not be pooled, but we have decided there is value in presenting

pooled data while highlighting its limitations. This analysis, therefore, likely should be a starting point for further study and analysis rather than an end in itself. Next, the vast majority of included patients have been in ICU during the first global surge and we cannot comment on whether the mortality rate has changed in the second surge, when it is likely that there will be different pressures on many healthcare systems, including through the necessity to catch up on non-COVID-19 healthcare demands. Our geographical analysis separates countries by geography rather than other factors which might impact outcomes, such as average national income, average population age, access to general healthcare or number of critical care beds per capita. Analyses based on such factors would be of considerable interest but are beyond the remit of this study. Our analysis includes studies published only up to the end of September and registry data up to the end of October. Since then, several variant viruses have emerged and in some countries transformed the trajectory of the pandemic through December 2020 and into January 2021. This has increased the demand on ICU in those locations and will merit further analysis in due course. To counter this, vaccination is now available in many countries and we can hope that this too will, over several months, positively impact on the pandemic trajectory and demand on ICU care.

In conclusion, this expanded meta-analysis of survival of patients admitted to ICU with COVID-19 has shown that any fall in mortality rate between June and September appears to have flattened or plateaued. We have identified geographical regions of both low (Australasia) and high (Middle East) mortality that merit further exploration. Mortality rate is lower in reports from registries than from non-registry studies. Further analysis is hampered by a lack of definitions and standardisation of reporting. Standardisation of reporting would enable far more valuable comparisons of outcomes between locations and over time. Registries may be the best-placed organisations to act on this first. Despite these limitations, this analysis provides an overview of outcomes among patients admitted to ICU with COVID-19 in the first pandemic surge.

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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 (red) and not reported (blue) for each study, grouped by geographical region.

Table S1. Search strategy.

Table S2. Registries or societies contacted directly.

Table S3. Modified Newcastle-Ottawa Scale.

Table S4. Study quality and risk of bias assessment.

Table S5. Reported clinical features, rates of organ support and pharmacotherapy.

Table S6. Sensitivity and sub-group analyses.

Table S7. Results of meta-regression analyses.