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Global Impact of Coronavirus Disease 2019 Infection Requiring Admission to the ICU
A Systematic Review and Meta-analysis

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BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has placed unprecedented burden on the delivery of intensive care services worldwide.

RESEARCH QUESTION: What is the global point estimate of deaths and risk factors for patients who are admitted to ICUs with severe COVID-19?

STUDY DESIGN AND METHODS: In this systematic review and meta-analysis Medline, Embase, and the Cochrane library were searched up to August 1, 2020. Pooled prevalence of participant characteristics, clinical features, and outcome data was calculated with the use of random effects models. Subgroup analyses were based on geographic distribution, study type, quality assessment, sample size, end date, and patient disposition. Studies that reported in-hospital mortality rate of adult patients (age > 18 years) with confirmed COVID-19 admitted to an ICU met study eligibility criteria. Critical evaluation was performed with the Newcastle Ottawa Scale for nonrandomized studies.

RESULTS: Forty-five studies with 16,561 patients from 17 countries across four continents were included. Patients with COVID-19 who were admitted to ICUs had a mean age of 62.6 years (95% CI, 60.4-64.7). Common comorbidities included hypertension (49.5%; 95% CI, 44.9-54.0) and diabetes mellitus (26.6%; 95% CI, 22.7-30.8). More than three-quarters of cases experienced the development of ARDS (76.1%; 95% CI, 65.7-85.2). Invasive mechanical ventilation was required in 67.7% (95% CI, 59.1-75.7) of case, vasopressor support in 65.9% (95% CI, 52.4-78.4) of cases, renal replacement therapy in 16.9% (95% CI, 12.1-22.2) of cases, and extracorporeal membrane oxygenation in 6.4% (95% CI, 4.1-9.1) of cases. The duration of ICU and hospital admission was 10.8 days (95% CI, 9.3-18.4) and 19.1 days (95% CI, 16.3-21.9), respectively, with in-hospital mortality rate of 28.1% (95% CI, 23.4-33.0; $I^2 = 96\%$). No significant subgroup effect was observed.

INTERPRETATION: Critically ill patients with COVID-19 who are admitted to the ICU require substantial organ support and prolonged ICU and hospital level care. The pooled estimate of global death from severe COVID-19 is <1 in 3.

KEY WORDS: coronavirus; critical illness; intensive care; respiratory medicine; SARS-CoV-2

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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Since emerging in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has placed an unprecedented burden on ICUs around the world. SARS-CoV-2 is a highly transmissible upper respiratory tract virus that causes coronavirus disease 2019 (COVID-19). A striking feature of COVID-19 is rapidly progressive respiratory failure, which develops in approximately 5% of infected adults.

At the time of writing (August 28, 2020), there have been >24 million confirmed cases of COVID-19 and more than three-quarters of a million deaths worldwide. In early case series, mortality rates for critically ill patients with COVID-19 were between 40% and 61%, despite advanced ICU supports. This mortality rate is substantially greater than in previous viral pneumonitis pandemics, such as the 2009 H1N1 influenza pandemic with mortality rates between 10% and 30%. Usual provision of ICU level support has also been strained during the current pandemic by the natural history of severe COVID-19 with reports of protracted ICU lengths of stay.

Although COVID-19 is a global pandemic, the burden of disease has not been homogenous, and a number of regions that experienced earlier, rapid community spread reported strained or resource limited health care systems, which may have contributed to the high mortality rates. More recent ICU series from regions with lesser COVID-19 population prevalence have reported lower ICU mortality rates of approximately 15%. Although there is a need to measure the international burden of critical illness, there is limited understanding of the global impact and outcomes of COVID-19 infection requiring ICU admission.

The objective of this systematic review and meta-analysis was to provide a contemporary and global assessment of the point estimate of death and risk factors for severe disease in patients admitted to an ICU with COVID-19.

Methods

Search Strategy and Selection Criteria

This review was performed in accordance with the Meta-analysis of Observational studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines (e-Appendix 1).

Three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) were searched from inception to August 1, 2020. Key search terms included “coronavirus,” “COVID-19,” “SARS-CoV-2” or “severe acute respiratory syndrome,” “intensive care,” “critically ill,” “critical care,” “severe.” Exact terms used are presented in e-Appendix 2. In addition, reference lists of relevant studies and review articles were searched manually for potentially eligible studies not captured in the primary search. Corresponding authors were contacted for additional data necessary for a meta-analysis. Two reviewers (E. T., J. S.) independently screened titles and abstracts of all identified studies for eligibility. Any discrepancies were resolved by consensus after discussion with a third reviewer (M. P. P.).

The inclusion criteria for studies were (1) design that included randomized controlled trials, nonrandomized controlled trials (case control or controlled cohort), observational studies and case series, (2) study population that included adult patients (≥18 years old) admitted to an ICU or high dependency unit, which included studies that compared ICU and non-ICU cohorts, (3) disease that confirmed COVID-19 or SARS-CoV-2, and (4) outcome that reported in-hospital mortality rates. Exclusion criteria were (1) review articles, opinion articles, case reports, (2) studies that did not define COVID-19 severity or did not include baseline physiologic data, (3) retracted studies, (4) studies that reported probable COVID-19 only, (5) duplicate patient data (from the same source and capture period) with preference given to sample size and quality for inclusion (e-Appendix 3), and (6) studies published in a language other than English.

Data Analysis

Two authors (E. T., J. S.) independently extracted predefined data. Data estimated values of the mean and SD were derived by formulas designed by Wan et al. Extracted information included study characteristics (author, geographic location, design, sample size, and start and end date), participant characteristics (age, sex, smoking status, BMI, comorbidities), presenting symptoms, admission pathologic data, and pulmonary radiologic findings (radiographic and CT imaging, organ system dysfunction, complications, severity of illness scores, treatment and ICU supports, and outcome data (ICU and hospital length of stay and in-hospital mortality rate).

The methodologic quality of included studies was assessed according to the modified versions of the Newcastle-Ottawa scale or the Quality and Synthesis of Case Series and Case Reports Protocol, as appropriate. Two reviewers independently assessed each study. Any discrepancies were discussed and resolved by consensus.

The criterion to undertake modelling in the outcome of interest was a minimum of three studies reporting relevant data. The random-effects model (DerSimonian and Laird method) was applied to estimate the pooled prevalence and 95% CIs. To account for extreme prevalence data, prevalence estimates were transformed with the use of the double arc sine method then back-transformed for ease of interpretation. Publication bias was assessed with the use of the funnel plot with asymmetry ascribed to an LFX index greater than ±1. Statistically significant heterogeneity was assessed as a Cochrane’s Q test (P < .10) and I^2 > 75%. Heterogeneity was further explored through subgroup analyses with the use of the following categoric study characteristics: (1) geographic distribution (North America vs Asia vs Europe vs Middle East), (2) quality assessment - risk of bias (high vs low), (3) sample size (>150 vs ≤150 patients), (4) center type (multicenter vs single center), (5) study type (case series vs retrospective cohort vs case control vs prospective cohort vs prospective cross-sectional vs chart review and national audit), (6) study end date (before April 2020 vs after April), and (7) patient disposition-proportion censored at study end date (<20% in-hospital at time of...
publication vs ≥20% in-hospital). Statistical analyses for pooled prevalence were performed with MetaXL (version 5.3; EpiGear International Pty Ltd). For categoric variables (mortality rate by sex), pooled ORs and associated 95% CIs were calculated with the use of a Mantel-Haenszel model; for continuous variables (length of stay), mean differences and associated 95% CIs were calculated with an inverse-variance with the use of Review Manager (RevMan; version 5.3; The Cochrane Collaboration).

**Results**

A total of 3,873 articles were retrieved with the use of the search strategy. After screening was performed by abstract and title, 191 articles were selected for full-text assessment. Forty-five studies met the inclusion criteria and were included in this review and meta-analysis (Fig 1).

The 45 studies included 16,561 patients from 17 countries from December 29, 2019, to July 30, 2020. There were 16 studies from Europe (n = 13,485),20-36 15 studies from China (n = 1,385),37-51 11 studies from North America (n = 1,469),52-62 and three studies from Middle East (n = 222).63-65 There were 18 case series,22,24,25,29,31-33,36,38,41,44-50,52,55,60,62,65 nine retrospective cohort studies,21,23,35,40,45,53,59,61,63 nine case-control studies,30,37,39,42-44,46,51,58 five prospective cohort studies,20,26,34,54,55 two chart reviews,57,64 one cross-sectional study,47 and one national audit.27 The main characteristics of the included studies are shown in Table 1 and e-Appendix 4. Sixty variables were analyzed for this meta-analysis (Table 2).

Critically ill patients with COVID-19 had a mean age of 62.6 years (95% CI, 60.4-64.7), a mean BMI of 30.1 kg/m² (95% CI, 28.7-31.4) and more than two-thirds were male (65.6%; 95% CI, 62.7-68.5). Mortality rates did not differ between sex (OR [men vs women], 1.20; 95% CI, 0.93-1.55; \( P = .16 \)) (Table 2; e-Appendices 5, 6). Common comorbidities included hypertension (49.5%;

![Figure 1 - Preferred reporting items for systematic reviews and meta-analysis study flow diagram. COVID-19 = coronavirus disease 2019; MERS = Middle East respiratory syndrome; SARS-CoV = severe acute respiratory syndrome coronavirus.](image-url)
### Characteristics of Included Studies

| Study                  | Country    | Study Design                  | Sample Size | Dates                  | Quality |
|------------------------|------------|-------------------------------|-------------|------------------------|---------|
| Almazeedi et al (2020) | Kuwait     | Retrospective cohort          | 42          | 24/02-20/4/2020        | Good    |
| Amit et al (2020)      | Israel     | Chart review                  | 156         | 05/03-27/04/2020       | Good    |
| Arentz et al (2020)    | United States | Case series               | 21          | 20/02-05/03/2020      | Fair    |
| Auld et al (2020)      | United States | Retrospective cohort      | 217         | 06/03-17/04/2020      | Poor    |
| Barrasa et al (2020)   | Spain      | Prospective cohort           | 48          | 04/03-24/03/2020      | Poor    |
| Bhatla et al (2020)    | United States | Retrospective cohort   | 79          | 06/03-19/05/2020     | Good    |
| Bhatraju et al (2020)  | United States | Case series              | 24          | 24/02-09/03/2020     | Fair    |
| Borobia et al (2020)   | Spain      | Retrospective cohort         | 75          | 25/02-19/04/2020      | Good    |
| Cardoso et al (2020)   | Portugal   | Case series                  | 20          | 10/03/2020            | Poor    |
| Chen et al (2020)      | China      | Retrospective case control subject | 51    | 22/01-25/03/2020      | Poor    |
| Cui et al (2020)       | China      | Case series                  | 81          | 30/01-22/03/2020      | Poor    |
| Cummings et al (2020)  | United States | Prospective cohort     | 257         | 02/03-01/04/2020      | Good    |
| Ferguson et al (2020)  | United States | Chart review              | 21          | 13/03-11/04/2020     | Poor    |
| Grasselli et al (2020) | Italy      | Retrospective cohort        | 1715        | 20/02-22/04/2020     | Poor    |
| Halasz et al (2020)    | Italy      | Case series                  | 242         | 02-04/2020            | Fair    |
| Halvatsiotis et al (2020) | Greece    | Case series                  | 90          | 10/03-13/04/2020      | Fair    |
| Helms et al (2020)     | France     | Prospective cohort          | 150         | 03/03-31/03/2020      | Good    |
| Hur et al (2020)       | United States | Retrospective case control subject | 138    | 01/03-08/04/2020     | Good    |
| ICNARC et al (2020)    | England    | National clinical audit      | 10624       | 01/03-30/07/2020     | …       |
| Khamis et al (2020)    | Oman       | Case series                  | 24          | 24/02-24/04/2020      | Poor    |
| Klok et al (2020)      | Netherlands | Case series                | 184         | 07/03-05/04/2020      | Poor    |
| Li J et al (2020)      | China      | Retrospective case control subject | 74     | 25/01-26/02/2020     | Poor    |
| Ling et al (2020)      | China      | Retrospective cohort        | 8           | 22/01-11/02/2020      | Poor    |
| Liltjos et al (2020)   | France     | Retrospective case control subject | 26     | 19/03-11/04/2020     | Poor    |
| Longchamp et al (2020) | Switzerland | Case series                | 25          | 08/03-04/04/2020      | Poor    |
| Maatman et al (2020)   | United States | Retrospective cohort   | 109         | 12/03-31/03/2020      | Poor    |
| Mitra et al (2020)     | Canada     | Case series                  | 117         | 21/02-14/04/2020      | Fair    |

(Continued)
95% CI, 44.9-54.0), diabetes mellitus (26.6%; 95% CI, 22.7-30.8), and cardiovascular disease (22.2%; 95% CI, 13.9-31.8). Nearly one-fifth of patients were current smokers (17.4%; 95% CI, 11.8-23.8). The most frequent symptoms on presentation were fever (78.9%), dyspnea (70.0%), cough (68.1%), and anorexia (46.8%). The median time from onset of symptoms to ICU admission was 9.0 days (95% CI, 7.9-10.0) (Table 2; e-Appendix 7).

On admission, inflammatory markers were elevated: C-reactive protein 170.0 mg/L (95% CI, 113.6-226.3), ferritin 1968.3 μg/mL (95% CI, 660.4-3276.1), procalcitonin 1.5 ng/L (95% CI, 1.0-2.0), and D-Dimer 3.1 mg/L (95% CI, 2.0-4.1). Lactate 1.3 mmol/L (95% CI, 1.1-1.6) was not raised markedly. In ten studies that reported chest radiography findings, bilateral infiltrates were seen in 72% (95% CI, 48.1-90.7) of patients.40,41,43,48,52,55,57,61,63,65 In five studies that reported CT findings, ground glass opacities were reported in 66% (95% CI, 23.7-97.7) of patients.39,41,42,52,63 (Table 2; e-Appendix 8).

More than three-quarters of patients were diagnosed with ARDS during their ICU admission (76.1%; 95% CI, 65.7-85.2) (Fig 2). Approximately one-quarter of patients were reported to have acute kidney injury (27.1%; 95% CI, 20.6-34.2), shock (25.3%; 95% CI, 16.7-35.0), acute cardiac injury (24.2%; 95% CI, 13.5-36.7),

| Study | Country | Study Design | Sample Size | Dates | Quality |
|-------|---------|--------------|-------------|-------|---------|
| Myers et al61 (2020) | United States | Retrospective cohort | 113 | 01/03-31/03/2020 | Poor |
| Pavoni et al32 (2020) | Italy | Case series | 40 | 28/02-10/04/2020 | Fair |
| Pedersen et al33 (2020) | Denmark | Case series | 16 | 11/03-01/04/2020 | Poor |
| Richardson et al32 (2020) | United States | Case series | 373 | 01/03-04/04/2020 | Fair |
| Rodriguez et al34 (2020) | Spain | Prospective cohort | 43 | 14/03-16/04/2020 | Poor |
| Simonnet et al35 (2020) | France | Retrospective cohort | 124 | 27/02-05/04/2020 | Good |
| Thomas et al36 (2020) | United Kingdom | Case series | 63 | 15/03-14/04/2020 | Poor |
| Wang Y et al31 (2020) | China | Case series | 344 | 25/01-25/02/2020 | Good |
| Wei et al42 (2020) | China | Retrospective case control subject | 14 | 27/01-11/03/2020 | Poor |
| Wu et al43 (2020) | China | Retrospective case control subject | 83 | 20/01-19/02/2020 | Good |
| Xu B et al44 (2020) | China | Retrospective case control subject | 107 | 26/12-01/03/2020 | Good |
| Xu J et al45 (2020) | China | Retrospective cohort | 239 | 12/01-03/02/2020 | Good |
| Yang L et al46 (2020) | China | Retrospective case control subject | 29 | 30/01-08/02/2020 | Good |
| Yu et al47 (2020) | China | Prospective cross-sectional | 226 | 26/02-26/02/2020 | Poor |
| Zhang G et al48 (2020) | China | Case series | 55 | 02/01-10/02/2020 | Fair |
| Zhang J et al49 (2020) | China | Case series | 19 | 16/01-20/02/2020 | Poor |
| Zheng et al50 (2020) | China | Case series | 34 | 22/01-05/03/2020 | Fair |
| Zhou Y et al51 (2020) | China | Retrospective case control subject | 21 | 28/01-02/03/2020 | Poor |
### TABLE 2  Pooled Prevalence of Patient Characteristics, Presenting Symptoms, Interventions, Treatment, and Disposition

| Variable                        | Studies | Total Sample Size | Patients | Crude Prevalence (%) | Pooled Prevalence (%), or Pooled Mean, Unit | 95% CI (Upper-Lower) | Heterogeneity | I² (%) | P Value |
|--------------------------------|---------|------------------|----------|----------------------|---------------------------------------------|----------------------|--------------|--------|---------|
| **Demographics**               |         |                  |          |                      |                                             |                      |              |        |         |
| Age                            | 38      | 15,654           |          | ...                  | 62.6 y                                      | (60.4-64.7)          | 98           | <.01   |         |
| BMI                            | 12      | 1,391            |          | ...                  | 30.1 kg/m²                                  | (28.7-31.4)          | 93           | <.01   |         |
| Male                           | 41      | 14,431           | 9,925    | 68.8%                | 65.6%                                       | (62.7-68.5)          | 80           | <.01   |         |
| Current smoker                 | 19      | 1,321            | 218      | 16.5%                | 17.4%                                       | (11.8-23.8)          | 87           | <.01   |         |
| **Comorbidities**              |         |                  |          |                      |                                             |                      |              |        |         |
| Hypertension                   | 34      | 3,283            | 1,631    | 49.7%                | 49.5%                                       | (44.9-54.0)          | 84           | <.01   |         |
| Diabetes mellitus              | 35      | 3,345            | 907      | 27.1%                | 26.6%                                       | (22.7-30.8)          | 84           | <.01   |         |
| Cardiovascular disease         | 31      | 13,604           | 766      | 5.6%                 | 22.2%                                       | (13.9-31.8)          | 98           | <.01   |         |
| OSA                            | 5       | 287              | 54       | 18.8%                | 20.0%                                       | (12.0-29.5)          | 64           | .03    |         |
| Chronic kidney disease         | 25      | 12,786           | 431      | 3.4%                 | 10.0%                                       | (6.2-14.6)           | 95           | <.01   |         |
| COPD                           | 21      | 2,053            | 183      | 8.9%                 | 9.4%                                        | (7.3-11.8)           | 59           | <.01   |         |
| Asthma                         | 11      | 985              | 89       | 9.0%                 | 9.2%                                        | (7.0-11.6)           | 27           | .18    |         |
| Malignancy                     | 21      | 1,925            | 125      | 6.5%                 | 6.5%                                        | (5.0-8.1)            | 42           | .02    |         |
| Chronic liver disease          | 17      | 1,744            | 78       | 4.5%                 | 4.7%                                        | (2.9-6.8)            | 69           | <.01   |         |
| Organ transplantation          | 4       | 499              | 21       | 4.2%                 | 4.4%                                        | (2.7-6.3)            | 0            | .51    |         |
| Immunosuppressed               | 10      | 11,437           | 402      | 3.5%                 | 4.1%                                        | (2.5-6.0)            | 60           | <.01   |         |
| **Presenting symptoms**        |         |                  |          |                      |                                             |                      |              |        |         |
| Fever                          | 17      | 1,377            | 1,071    | 77.8%                | 78.9%                                       | (68.6-87.6)          | 94           | <.01   |         |
| Dyspnea                        | 19      | 1,386            | 935      | 67.5%                | 70.0%                                       | (59.7-79.4)          | 93           | <.01   |         |
| Cough                          | 20      | 1,503            | 1,001    | 66.6%                | 68.1%                                       | (58.5-77.0)          | 93           | <.01   |         |
| Anorexia                       | 3       | 473              | 166      | 35.1%                | 46.8%                                       | (21.7-72.8)          | 95           | <.01   |         |
| Fatigue                        | 10      | 794              | 364      | 45.8%                | 37.6%                                       | (24.3-51.8)          | 92           | <.01   |         |
| Sputum                         | 10      | 633              | 221      | 34.9%                | 34.2%                                       | (24.9-44.1)          | 77           | <.01   |         |
| Myalgia                        | 12      | 781              | 192      | 24.6%                | 23.2%                                       | (14.4-33.4)          | 87           | <.01   |         |
| Diarrhea                       | 15      | 1,278            | 236      | 18.5%                | 15.5%                                       | (10.9-20.7)          | 79           | <.01   |         |
| Rhinorrhea                     | 5       | 393              | 38       | 9.7%                 | 11.2%                                       | (6.3-17.1)           | 42           | .14    |         |
| Sore throat                    | 11      | 701              | 71       | 10.1%                | 10.9%                                       | (5.5-17.7)           | 82           | <.01   |         |
| Nausea                         | 8       | 455              | 42       | 9.2%                 | 9.5%                                        | (6.1-13.6)           | 35           | .16    |         |
| Chest pain                     | 3       | 211              | 19       | 9.0%                 | 9.3%                                        | (5.7-13.6)           | 0            | .70    |         |
| Headache                       | 12      | 663              | 38       | 5.7%                 | 6.5%                                        | (4.2-9.1)            | 24           | .21    |         |
| Hemoptysis                     | 4       | 151              | 8        | 5.3%                 | 4.5%                                        | (0.6-11.2)           | 49           | .12    |         |
| Symptoms onset to ICU admission| 8       | 2,030            |          | ...                  | 9.0 d                                       | (7.9-10.0)           | 91           | <.01   |         |
| **Laboratory results on ICU admission** | | | | | | | | | | |
| C-Reactive Protein             | 7       | 732              |          | ...                  | 170.0 mg/L                                   | (113.6-226.3)        | 99           | <.01   |         |
| D-Dimer                        | 8       | 929              |          | ...                  | 3.1 mg/L                                     | (2.0-4.1)            | 95           | <.01   |         |
| Ferritin                       | 2       | 37               |          | ...                  | 1,968.3 μg/mL                                | (660.4-3276.1)       | 91           | .02    |         |
| Lactate                        | 4       | 377              |          | ...                  | 1.3 mmol/L                                   | (1.1-1.6)            | 88           | <.01   |         |
| Lymphocyte count               | 9       | 745              |          | ...                  | 0.8 × 10⁹/L                                  | (0.8-0.9)            | 54           | .03    |         |
| Procalcitonin                  | 3       | 448              |          | ...                  | 1.5 ng/L                                     | (1.0-2.0)            | 72           | .03    |         |

(Continued)
TABLE 2  (Continued)

| Variable | Studies | Total Sample Size | Patients | Crude Prevalence (%) | Pooled Prevalence (%), or Pooled Mean, Unit | 95% CI (Upper-Lower) | Heterogeneity |
|----------|---------|-------------------|----------|----------------------|---------------------------------------------|----------------------|--------------|
| **Imaging** |         |                   |          |                      |                                             |                      |              |
| Chest radiography: bilateral chest infiltrates | 10 | 735 | 381 | 51.8% | 71.7% | (48.1-90.7) | 97 | <.01 |
| CT chest: ground glass opacity | 5 | 495 | 267 | 53.9% | 65.5% | (23.7-97.7) | 98 | <.01 |
| **Disease severity on ICU admission** |         |                   |          |                      |                                             |                      |              |
| Sequential Organ Failure Assessment score | 12 | 1,391 | ... | ... | 6.3% | (5.1-7.6) | 99 | <.01 |
| Acute Physiology and Chronic Health Evaluation II score | 7 | 11,099 | ... | ... | 16.8% | (14.9-18.8) | 98 | <.01 |
| **Organ dysfunction** |         |                   |          |                      |                                             |                      |              |
| ARDS | 13 | 1,260 | 819 | 65.0% | 76.1% | (65.7-85.2) | 93 | <.01 |
| Acute kidney injury | 13 | 1,287 | 380 | 30.2% | 27.1% | (20.6-34.2) | 84 | <.01 |
| Acute liver injury | 6 | 715 | 270 | 37.8% | 25.8% | (1.3-61.6) | 98 | <.01 |
| Shock | 7 | 895 | 230 | 25.7% | 25.3% | (16.7-35.0) | 88 | <.01 |
| Acute cardiac injury | 11 | 1,326 | 357 | 26.9% | 24.2% | (13.5-36.7) | 95 | <.01 |
| Arrhythmia | 3 | 302 | 49 | 16.2% | 22.7% | (3.1-50.5) | 93 | <.01 |
| Thrombotic event | 7 | 852 | 195 | 22.9% | 22.6% | (16.3-29.5) | 76 | <.01 |
| Secondary infection | 9 | 873 | 159 | 18.2% | 18.4% | (14.0-23.2) | 60 | <.01 |
| **Interventions** |         |                   |          |                      |                                             |                      |              |
| Invasive mechanical ventilation | 28 | 13,543 | 9,247 | 68.3% | 67.7% | (59.1-75.7) | 98 | <.01 |
| Vasopressors | 12 | 1,052 | 581 | 55.2% | 65.9% | (52.4-78.4) | 94 | <.01 |
| Renal replacement therapy | 18 | 12,276 | 3,017 | 24.6% | 16.9% | (12.1-22.2) | 92 | <.01 |
| Noninvasive mechanical ventilation | 15 | 1,519 | 276 | 18.2% | 16.6% | (9.4-25.3) | 93 | <.01 |
| Extracorporeal membrane oxygenation | 18 | 1,828 | 103 | 5.6% | 6.4% | (4.1-9.1) | 76 | <.01 |
| **Treatment** |         |                   |          |                      |                                             |                      |              |
| Antimicrobial therapy | 18 | 1,677 | 1,526 | 91.0% | 94.6% | (90.6-97.6) | 88 | <.01 |
| Antiviral therapy | 18 | 1,580 | 791 | 50.1% | 74.3% | (51.9-91.9) | 99 | <.01 |
| Intravenous immunoglobulin | 8 | 917 | 365 | 39.8% | 50.1% | (17.8-82.3) | 99 | <.01 |
| Glucocorticoid | 17 | 1,617 | 704 | 43.5% | 43.2% | (24.8-62.5) | 98 | <.01 |
| **Disposition** |         |                   |          |                      |                                             |                      |              |
| ICU length of stay | 11 | 2,484 | ... | ... | 10.8 d | (9.3-18.4) | 94 | <.01 |
| Hospital length of stay | 10 | 2,518 | ... | ... | 19.1 d | (16.3-21.9) | 95 | <.01 |
| In-hospital deaths | 45 | 16,561 | 6,783 | 41.0% | 28.1% | (23.4-33.0) | 96 | <.01 |
| Remain in hospital | 32 | 15,842 | 1,590 | 10.0% | 22.6% | (16.8-28.9) | 98 | <.01 |
| Discharged from hospital | 33 | 15,896 | 7,689 | 48.4% | 43.9% | (38.9-48.9) | 95 | <.01 |

Arrhythmia (22.7%; 95% CI, 3.1-50.5), and/or a thrombotic event (22.6%; 95% CI, 16.3-29.5). The pooled initial Sequential Organ Failure Assessment (SOFA) score was 6.3 (95% CI, 5.1-7.6) and Acute Physiology and Chronic Health Evaluation (APACHE) II score was 16.8 (95% CI, 14.9-18.8) (Table 2; e-Appendix 9). Invasive
mechanical ventilation was required in 67.7% (95% CI, 59.1-75.7) of patients; 65.9% (95% CI, 52.4-78.2) of patients required vasopressor support; 16.9% (95% CI, 12.1-22.2) of patients received renal replacement therapy; 16.6% (95% CI, 9.4-25.3) of patients received noninvasive ventilation, and 6.4% (95% CI, 4.1-9.1) of patients received extracorporeal membrane oxygenation (Table 2, e-Appendix 10).

Antimicrobial therapy was administered to 94.6% (95% CI, 90.6-97.6) of patients with severe-to-critical COVID-19 infection. Antiviral therapy use was reported in 18 studies, with a pooled prevalence of 74.3% (95% CI, 51.9-91.9). Ten studies reported using lopinavir/ritonavir, and five studies reported using remdesivir (Table 2, e-Appendix 10). Glucocorticoid was prescribed to 43.2% (95% CI, 24.8-62.5) of patients.

The pooled mean duration of ICU admission was 10.8 days (95% CI, 9.3-18.4), and the pooled mean hospital duration of admission was 19.1 days (95% CI, 16.3-21.9). The pooled estimate for patients who remained in hospital with uncertain outcomes at the study end point was 22.6% (95% CI, 16.8-28.9). The pooled estimate for in-hospital mortality rate was 28.1% (95% CI, 23.4-33.0) (Fig 3), and discharge from hospital alive was 43.9% (95% CI, 38.9-48.9), albeit with considerable statistical heterogeneity (I² 96%, P < .01; I² 95%, P < .01, respectively). The funnel plot of all 45 studies was asymmetric, which suggests possible publication bias (Table 2; e-Appendixes 11-13).

Subgroup analyses revealed that mortality rate did not differ by geographic distribution, study type or quality, sample size, center type, end of study date, or patient disposition. There is no evidence of substantial difference in the mortality rates across the prespecified subgroups. (e-Appendix 14).

Discussion

This systematic review and meta-analysis of 45 studies includes 16,561 patients from 17 countries across four continents. The main findings are that patients who were admitted to ICU with COVID-19 required considerable organ support, with point estimates that more than three-quarters were diagnosed with ARDS and one-quarter were recorded as having shock and/or acute kidney injury. Invasive mechanical ventilation and vasopressor support were required in more than two-thirds of patients; renal replacement therapy was required in one-fifth of patients, and more than one in 20 of the patients received extracorporeal membrane oxygenation. The in-hospital mortality rate was between 23.4% and 33.0%.

More than 80% of coronavirus cases experience mild-to-moderate symptoms; approximately 15% have severe disease that requires hospitalization, and around 5% require intensive care support. Previous meta-analyses have examined risk factors for mortality rates in COVID-19 infections; however, these studies included a majority of data within a certain region or included patients with COVID-19 infections but less severe
To address this limitation, the current systematic review and meta-analysis provides a comprehensive global overview of patient demographic, comorbidities, signs and symptoms, initial laboratory and imaging results, treatment, organ dysfunction, and outcomes in adults with severe and critical COVID-19. More than two-thirds of patients with severe COVID-19 were men, with a mean age of 62.6 years and a mean BMI of 30.1 kg/m², which confirms previous reports that there is a preponderance to severe disease with male sex, older age, and obesity. In keeping with an older overweight population, we describe a comorbid...
demographic that progress to severe COVID-19, with one-half of patients having arterial hypertension and approximately one-quarter having diabetes mellitus and cardiovascular disease.

This analysis confirms that, across the globe, once admitted to ICU with COVID-19 infection, the duration of admission to ICU and hospital is protracted. The mean ICU length of stay of 10.8 days was approximately double the duration of admission for severe community-acquired pneumonia and longer than observed with H1N1 influenza pneumonia. However, the upper 95% CI for in-hospital mortality rates was only 33.0%. Given that both the duration of admission and the intensity of ICU-level supports have led to enormous strain on critical care provision, particularly in geographic areas that experienced rapid community transmission, this may have contributed to the heterogeneity of mortality data.

These estimates of global death for severe COVID-19 (in-hospital mortality rate between 23.4% and 33.0%) may impact the interpretation of existing trial data. For example, data from the RECOVERY trial indicated that dexamethasone caused a marked reduction in deaths (in-hospital censored at day 28) in patients with COVID-19 whose condition required mechanical ventilation (dexamethasone 29.3% vs usual care 41.4%). However, the current meta-analysis of 16,561 patients with severe COVID-19 infection suggests that the magnitude of benefit observed with dexamethasone during the RECOVERY trial may not be reproducible across all settings.

Furthermore, given that global data suggest that less than one-third of patients die once admitted to ICU, the implication of this meta-analysis is that provision of sufficient ICU level service capacity is a global health priority to prevent inequalities in outcomes from this disease.

With 16,561 critically ill patients across 17 countries and four continents, this review is the largest and most granular assessment of outcomes of severe COVID-19 to date. Limitations of this systematic review include the presence of publication bias and that most included studies were case series and retrospective in design. There is a risk of survivor bias, with nearly one-quarter of patients remaining in hospital. The pooled prevalence for patients discharged alive was only 43.9% (95% CI, 38.9-48.9). Studies varied with the censor date for the identification of death. We specified the outcome measure as “death,” “remained in hospital,” and “discharged alive,” and it is possible that all-cause death that is censored at some later landmark (eg, day 90) may be greater than reported in this meta-analysis. There was considerable statistical heterogeneity found for many results. However, despite exploring the cause of heterogeneity through extensive subgroup analyses, there was no singular cause identified. Finally, studies were excluded that were not written in English. Although the risk of bias from excluding studies not published in English is considered low, it is uncertain how the additional patients would have affected the 95% CIs.

This systematic review provides the most expansive snapshot to date of the international experience of COVID-19 that requires critical care support. Advanced age, male sex, obesity, smoking, hypertension, diabetes mellitus, and cardiovascular disease are major risk factors for severe COVID-19. More than two-thirds of patients require invasive mechanical ventilation; approximately 20% of patients require renal replacement therapy, and the mean duration of ICU admission was 11 days. There was marked heterogeneity in mortality rate; however, the global mortality rate point estimate for patients with COVID-19 who are admitted to an ICU was 28%.
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