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Intensive Care and Organ Support Related Mortality in Patients With COVID-19: A Systematic Review and Meta-Analysis

Abhimanyu Chandel, MD[1]
Sahar Leazer, MD[2,3]
Karl C. Alcover, PhD[2]
Josiah Farley, BS[2]
Joshua Berk, BA[2]
Christopher Jayne, BS[2]
Ryan Mcnutt, BS[2]
Meredith Olsen, MD[1]
Rhonda Allard, MLIS[2]
Jiahong Yang, BS[2]
Caitlyn Johnson, BS[2]
Ananya Tripathi, BS[2]
Maria Rechtin, MD[1]
Mathew Leon, MMSc[2]
Mathias Williams, MD[1]
Phorum Sheth, MS[2]
Kyle Messer, DO[1]
Kevin K. Chung, MD[2]
Jacob Collen, MD[1,2]

OBJECTIVES: To perform a systematic review and meta-analysis to generate estimates of mortality in patients with COVID-19 that required hospitalization, ICU admission, and organ support.

DATA SOURCES: A systematic search of PubMed, Embase, and the Cochrane databases was conducted up to December 31, 2021.

STUDY SELECTION: Previously peer-reviewed observational studies that reported ICU, mechanical ventilation (MV), renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO)-related mortality among greater than or equal to 100 individual patients.

DATA EXTRACTION: Random-effects meta-analysis was used to generate pooled estimates of case fatality rates (CFRs) for in-hospital, ICU, MV, RRT, and ECMO-related mortality. ICU-related mortality was additionally analyzed by the study country of origin. Sensitivity analyses of CFR were assessed based on completeness of follow-up data, by year, and when only studies judged to be of high quality were included.

DATA SYNTHESIS: One hundred fifty-seven studies evaluating 948,309 patients were included. The CFR for in-hospital mortality, ICU mortality, MV, RRT, and ECMO were 25.9% (95% CI: 24.0–27.8%), 37.3% (95% CI: 34.6–40.1%), 51.6% (95% CI: 46.1–57.0%), 66.1% (95% CI: 59.7–72.2%), and 58.0% (95% CI: 46.9–68.9%), respectively. MV (52.7%, 95% CI: 47.5–58.0% vs 31.3%, 95% CI: 16.1–48.9%; $p = 0.023$) and RRT-related mortality (66.7%, 95% CI: 60.1–73.0% vs 50.3%, 95% CI: 42.4–58.2%; $p = 0.003$) decreased from 2020 to 2021.

CONCLUSIONS: We present updated estimates of CFR for patients hospitalized and requiring intensive care for the management of COVID-19. Although mortality remain high and varies considerably worldwide, we found the CFR in patients supported with MV significantly improved since 2020.

KEY WORDS: COVID-19; mechanical ventilation; pneumonia; respiratory distress syndrome; respiratory insufficiency; viral

Over 6.5 million deaths related to COVID-19 have been reported worldwide since December 2019. The unprecedented spread of the virus and the high proportion of severely ill patients requiring intensive care and organ support have strained hospital systems around the world (1). The heavy human toll created widespread disarray and misinformation among communities. The medical community was faced with two challenges: overcome saturated capacity and strained resources on the one hand and provide accurate information to patients and families regarding the morbidity and prognosis of the disease on the other. For ICU providers, patients, and their families, there was an immediate need to understand what the mortality was for patients that

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KEY POINTS

Question: What is the overall mortality in patients that required hospitalization, ICU admission, and organ support related to COVID-19?

Findings: In this meta-analysis, including nearly 1 million patients with COVID-19, the case fatality rate for in-hospital mortality, ICU mortality, mechanical ventilation, renal replacement therapy, and extracorporeal membrane oxygenation were 25.9%, 37.3%, 51.6%, 66.1%, and 58.0%, respectively. Mechanical ventilation mortality has decreased significantly since the start of the pandemic.

Meaning: These updated and robust estimates of case fatality rates for critically ill patients with COVID-19 can be applied to guide patient counseling and further clinical research regarding the management of this disease.

were admitted to the ICU and required organ support modalities, in particular, mechanical ventilation (MV). Strikingly in modern medicine, we were faced with the reality of potentially needing to ration ICU care. If the mortality for a patient undergoing intubation and MV was upwards of 75%, it would be reasonable to consider not providing a precious, limited resource to that patient, and instead allot it to a younger patient with a better overall prognosis. Therefore, mortality estimates in this pandemic had an immediacy to direct patient care.

Clinical outcomes in a pandemic are affected by variables beyond pathogenicity, patient risk and illness severity. Patients treated in the first wave of a pandemic may have worse outcomes due to supply-demand mismatch for intensive care (2). The current pandemic has exposed limitations of critical care disaster management at large tertiary care centers in first-world nations (3). Comparing critical care outcomes between illnesses occurring in usual care settings and pandemics or other disasters may fail to account for these factors (4).

Mortality estimates among patients with COVID-19 that require intensive care, MV, and organ support have varied substantially over the course of the ongoing pandemic (5). Accurate estimation of these mortality rates have been challenged by considerations including the rapid emergence of this new pathogen, surges in cases resulting in breakdowns in care delivery models, staffing shortages, resource limitations, and the struggle to identify optimal ICU management of this new viral pathogen (5). Further, many prior estimates of mortality in the ICU were based on emerging data that had yet to undergo peer review and included patients with variable and incomplete follow-up periods (6, 7). Given these constraints, outcome estimates often were made including patients still receiving ICU support at the time of data reporting.

To ensure accurate information to facilitate expectation management, resource allocation, and patient counseling, it is critical to update prior estimates of ICU-related outcomes. We conducted a systematic review and meta-analysis to generate estimates of mortality in patients with COVID-19 that required hospitalization and ICU care. We further examined mortality based on specific organ support required, geographic region, and based on the availability of complete follow-up data.

MATERIALS AND METHODS

Our systematic review and meta-analysis were conducted in accordance with the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. This review was not prospectively registered.

Eligibility Criteria

Previously peer-reviewed and published English language observational studies that met the population, intervention, comparison, outcome, and study design criteria were eligible for inclusion in this systematic review. Studies were included if they reported ICU, MV, renal replacement therapy (RRT), or extracorporeal membrane oxygenation (ECMO)-related mortality of patients with COVID-19 and were published between December 1, 2019, and December 31, 2021. To maximize the quality of the analyzed data, we excluded reports of less than 100 patients, articles not presenting original data, studies with pediatric populations, and preprints. The search was conducted through February 2022 by a professional medical librarian (R.A.). We carried out electronic searches of PubMed, Embase, and the Cochrane databases using the following search terms: COVID-19, novel coronavirus 2019 and MV, intubation, pneumonia, ICU, critical care, critically ill patients, severely ill patients, clinical characteristics, mortality, and outcomes.

Study Selection

After search results were obtained, two of the authors (S.L., J.C.) independently screened and selected articles by title and abstract and cross-matched selections with the other. Full-text articles were then reviewed by the same method. The following study authors (A.C., S.L., J.F., J.B., C.J., R.M., M.O., J.Y., A.T., M.R., M.L., M.W., P.S., K.M.) extracted data in pairs from each article and resolved disagreement by consensus. The data extracted included the following variables: date of publication, authors, geographic region, study design, country of origin, age, gender, number of patients admitted to the ICU, number of patients supported with MV, RRT, and ECMO, ICU mortality, and mortality associated with organ support (MV, RRT, and ECMO). Complete study follow-up was defined as studies where all included patients had either recovered and been discharged or had died. In these instances, reported outcomes did not include patients where final disposition remained uncertain at the time of data reporting.

Quality Assessment

All included studies were retrospective cohort studies. The quality of the included studies was assessed independently by two researchers based on the Newcastle-Ottawa Scale (NOS) (8). Using this tool, each study was judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Stars are awarded such that the highest quality studies are awarded up to eight stars.

Statistical Analysis

Each outcome variable was analyzed separately. For each outcome, a case fatality rate (CFR) was estimated by the meta-analytic summary estimate obtained from conducting meta-analysis of study-specific proportions of death. In each study, CFR was calculated by taking the number of deaths and dividing it by the total number of confirmed cases (i.e., hospital patients with confirmed cases of COVID-19). CFR includes only the confirmed cases (denominator) as opposed to the total number in the at-risk population, which is the denominator in calculating mortality rate (not analyzed).

The meta-analysis employed a random-effects model with DerSimonian and Laird estimator and estimated heterogeneity using the inverse-variance fixed-effect model. For studies with the proportions equal to (or close to) 0 or 1, the variance estimates were stabilized using the Freeman-Tukey double arcsine transformation of the data. The pooled estimate of the rate was then back transformed and presented, along with their Wald 95% CI estimated using the Score method. Heterogeneity between studies was estimated using the I^2 statistic and its p value. In this study, we used the pooled estimates obtained from the meta-analysis to report the fatality rates, which are often different from the rates obtained by manually combining all the number of deaths and cases from individual studies. Publication bias was assessed by examining visually the funnel plots and performing Egger tests. We also explored subgroup variations based on the analysis of complete cases only, stratified by date of last admission (ending on or before December 31, 2020), and when only studies rated as "Good" quality by NOS were included. Finally, as an exploratory analysis of how outcome varies based on geographic region, outcomes were stratified by primary country of data collection. All statistical analyses were conducted in Stata statistical software Version 17 (StataCorp LLC, College Station, TX). The meta-analysis of proportions used the *metaprop* command in Stata.

RESULTS

Study Selection and Characteristics

The complete literature-search process is displayed in **Figure 1**. A total of 11,442 abstracts were retrieved. After screening by abstract and title, 571 articles were selected for full-text assessment. In total, 157 studies evaluating 948,309 patients were included in the meta-analysis (9–159). The characteristics of all the included studies are shown in **Table S1** (http://links.lww.com/CCX/B152). Of the included patients, 54.2% were male and the median age of the cohorts ranged from 34 to 73 years old.

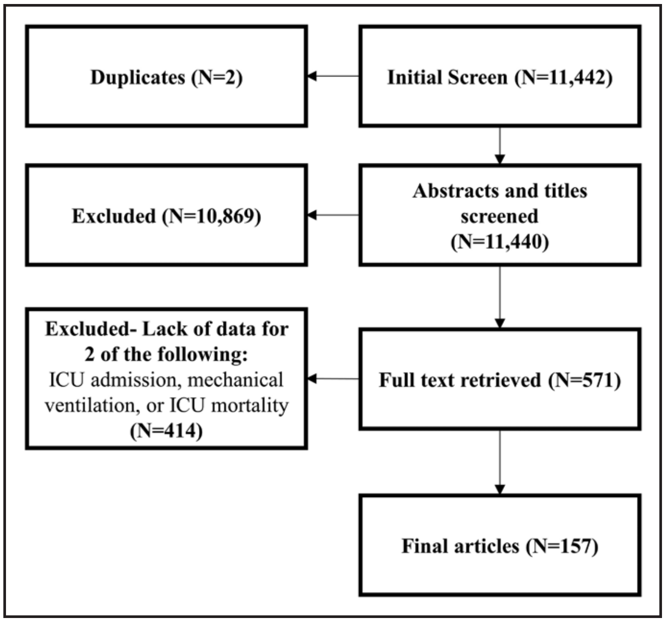

Figure 1. Preferred Reporting Items for Systematic Reviews flowchart of included and excluded studies.

In-Hospital Case Fatality Rate

A total of 157 studies were included that reported death in patients admitted to the hospital with COVID-19. The total number of in-hospital deaths observed was 290,996 resulting in an overall estimated in-hospital CFR of 25.9% (95% CI: 24.0–27.8%; I^2 = 99.6%) (**Table 1**). The in-hospital CFR was significantly higher (p = 0.018) in studies with complete follow-up (27.9%, 95% CI: 24.4–31.6%; I^2 = 99.6%) compared with studies without follow-up data (22.8%, 95% CI: 20.5–25.2%; I^2 = 99.4%) (**Table S2**, http://links.lww.com/CCX/B152). Estimated in-hospital CFR was numerically higher when compared based on year of the pandemic (2020 vs 2021; p = 0.102) (25.3%, 95% CI: 23.4–27.3%; I^2 = 99.6% vs 31.4%, 95% CI: 24.5–38.6%; I^2 = 99.6%) (**Table S3**, http://links.lww.com/CCX/B152).

TABLE 1.
Overall Results of the Meta-Analysis

Hospital and Organ Support Related Mortality	Meta-Analysis Summary	
	Rate (%)	95% CI (%)
In-hospital	25.9	24.0–27.8
ICU	37.3	34.6–40.1
Mechanical ventilation	51.6	46.1–57.0
Renal replacement therapy	66.1	59.7–72.2
Extracorporeal membrane oxygenation	58.0	46.9–68.9

ICU Case Fatality Rate

Of the included studies, 155 reported deaths in the ICU (**Fig. S1**, http://links.lww.com/CCX/B152). The total number of deaths in the ICU was 175,115 with an overall estimated ICU CFR of 37.3% (95% CI: 34.6–40.1%; I^2 = 99.6%) (Table 1). The ICU CFR in studies with complete follow-up (41.2%, 95% CI: 37.2–45.2%; I^2 = 99.3%) was higher compared with studies that reported estimates including patients with incomplete follow-up data (32.3%, 95% CI: 27.3–37.2%) and this difference was statistically significant (p = 0.006) (**Fig. 2*A***). Estimated ICU CFR was similar when compared based on year of the pandemic (2020 vs 2021) (37.4%, 95% CI: 34.3–40.5% vs 36.6%, 95% CI: 29.8–43.7%; p = 0.839) (**Fig. 2*B***) and when estimates were made restricting included studies to those rated as having good overall quality (39.5%, 95% CI: 36.4–42.5%) (**Table S4**, http://links.lww.com/CCX/B152).

MV Case Fatality Rate

A total of 118,862 deaths in patients that received MV were reported in 77 studies (**Fig. S2**, http://links.lww.com/CCX/B152). The overall MV CFR across all studies was 51.6% (95% CI: 46.1–57.0%; I^2 = 99.7%). The MV CFR in studies with complete follow-up (56.8%, 95% CI: 49.8–63.8%; I^2 = 99.6%) was higher compared with studies including patients with incomplete follow-up data (44.0%, 95% CI: 31.6–56.7%; I^2 = 99.7%), although this difference was not statistically significant (p = 0.082). Interestingly, MV CFR significantly decreased (p = 0.023) from 2020 to 2021 (52.7%, 95% CI: 47.5–58.0%; I^2 = 99.6% vs 31.3%, 95% CI: 16.1–48.9%; I^2 = 99.5%). Estimated MV CFR remained similar when analysis was restricted to only good quality studies (54.1%, 95% CI: 47.6–60.5%; I^2 = 99.7%).

RRT Case Fatality Rate

A total of 1,286 deaths in patients that received RRT across the studies (of 2,047 patients that received RRT) and the overall CFR of RRT was 66.1% (95% CI: 59.7–72.2%; I^2 = 84.3%). The RRT CFR in studies with complete follow-up (69.8%, 95% CI: 61.8–77.2%; I^2 =

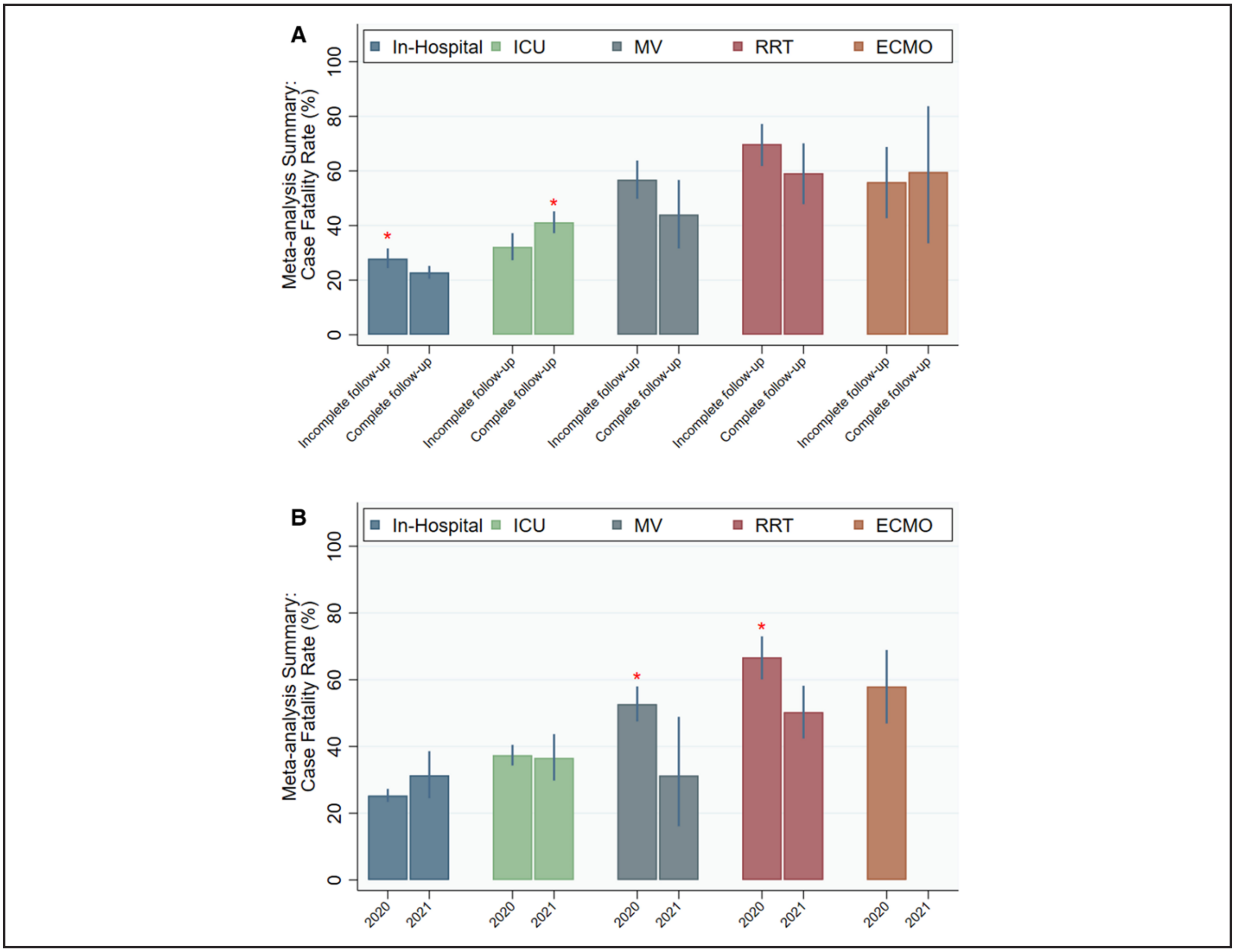

Figure 2. Intensive care unit case fatality rate. **A**, Case fatality rates stratified by complete versus incomplete follow-up data. **B**, Case fatality rates stratified by year of the end of study enrollment. ECMO = extracorporeal membrane oxygenation, MV = mechanical ventilation, RRT = renal replacement therapy.

83.7%) was higher compared with studies including patients with incomplete follow-up data (59.2%, 95% CI: 47.8–70.1%; I^2 = 82.5%), although this difference was not statistically significant (p = 0.087). Like the MV CFR, the RRT CFR significantly decreased (p = 0.003) from 2020 to 2021 (66.7%, 95% CI: 60.1–73.0%; I^2 = 83.9% vs 50.3%, 95% CI: 42.4–58.2%; I^2 = not available). Estimated RRT CFR remained similar when analysis was restricted to only good quality studies (65.4%, 95% CI: 58.2–72.3%; I^2 = 65.4%).

ECMO Case Fatality Rate

A total of 275 ECMO-related deaths were reported across the studies (of 482 patients that were supported with ECMO). The overall ECMO CFR across these studies was 58.0% (95% CI: 46.9–68.9%; I^2 = 71.2%). The ECMO CFR in studies with complete follow-up (55.9%, 95% CI: 42.7–68.8%; I^2 = 66.3%) was similar compared with studies including patients with incomplete follow-up data (59.6%, 95% CI: 33.5–83.7%; I^2 = 76.5%). Insufficient data were available to compare how outcomes differed from 2020 to 2021.

ICU Case Fatality Rate by Country

Studies included represented data reported from a total of 42 countries (**Table S5**, http://links.lww.com/CCX/B152). Most studies were from the United States (n = 22), the United Kingdom (n = 11), and China (n = 16). The ICU CFR varied widely across

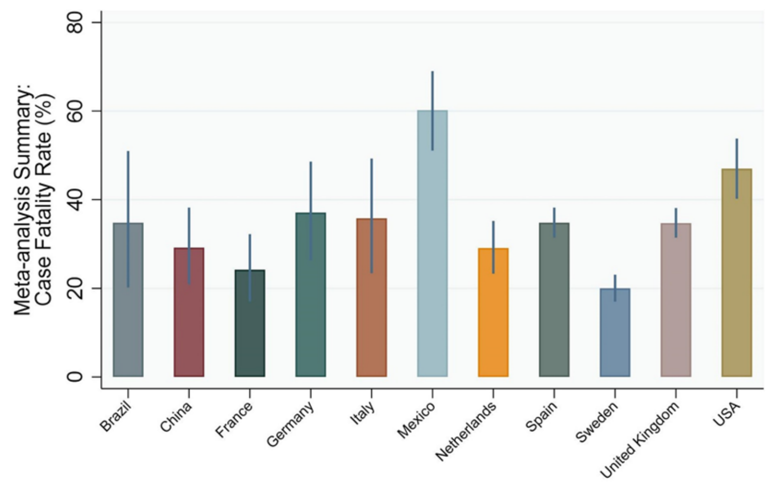

Figure 3. ICU case fatality rate for countries with available data encompassing more than 5,000 total patients.

the included countries ranging from as low as less than 15% (Australia, Iceland, Qatar, and the United Arab Emirates) to has high as 84% (Nepal). ICU CFR for countries with available data encompassing more than 5,000 total patients is included in **Figure 3**. Notably, among these countries, ICU CFR was lowest in France (24.2%; I^2 = 93.8%) and Sweden (20%; I^2 = 90.7%) while substantially higher in the United States (47.0%; I^2 = 95.0%) and Mexico (60.2%; I^2 = 94.4%).

Risk of Bias Assessment

Risk of bias was assessed through funnel plots of the estimates versus the estimate precisions and are displayed in **Figures S3–S7** (http://links.lww.com/CCX/B152). The Eggers test demonstrated evidence suggestive of "small-study effects" ($p < 0.05$) for the outcomes of ICU and MV-related mortality. Additionally, visual inspection of the funnel plots for all in-hospital, ICU, and MV revealed asymmetry, which suggests publication bias or other relevant bias may be present.

DISCUSSION

In our meta-analysis and systematic review including nearly 1 million patients with COVID-19, we found an overall ICU CFR of 37.3% and a MV CFR of 51.6%. Among studies including complete follow-up data, the ICU CFR was 41.2% and the MV CFR was 56.8%. The overall ICU CFR of patients with COVID-19 remained unchanged over the first 2 years of the pandemic; however, the overall CFR for patients that require MV decreased substantially from 2020 to 2021 (52.7–31.3%). The presented results are valuable given the size, temporal, and geographic diversity of the collated patients. Furthermore, the results are likely to be reliable given the inclusion of only studies reporting results from at least 100 patients and the inclusion of a sensitivity analysis confirming results are similar when only the highest quality studies were analyzed. Analysis of studies that report completed follow-up also strengthens the accuracy of our estimates. Our study provides the largest systematic analysis of COVID-19 ICU outcomes to date, with more reliable estimates of mortality rates that can assist clinicians who counsel patients about potential outcomes in the ICU while also demonstrating that these outcomes have improved over the course of the pandemic.

Mortality among patients with COVID-19 treated in the ICU and with MV has been estimated in smaller meta-analyses performed earlier in the pandemic. In a systematic review of studies published before May 1, 2020, including over 12,000 patients from 28 studies (including 11 studies that had not underwent peer-review), ICU mortality was estimated at 28.3%, while mortality of patients requiring MV was estimated at 43% (7). Relatedly, four other systematic reviews of studies published prior to September 30, 2020, found the ICU CFR to range between 34% and 42% (160–163). Similarly, a separate systematic review incorporating only data from 2020 (including 14 studies that were not peer-reviewed) estimated the MV CFR to be 45% (164). Whereas other reviews from 2020 found MV CFR to range considerably from 43% to 83% (7, 163, 165). A notable limitation of estimates of CFR related to the ongoing COVID-19 pandemic has been the rapid emergence of data and the related publication of data from cohorts where a sizable percentage of patients studied remained hospitalized related to COVID-19 and significant clinical, methodological, and statistical heterogeneity exits. As such, many of these prior systematic reviews provided estimates to consider best and worse-case scenarios estimates for CFR incorporating this incomplete data (7, 161, 164). These sensitivity analyses resulted in even further variability in CFR estimates and necessitated updated systematic review once additional data in patients with complete clinical follow-up have become available (162).

Our group previously reported a systematic review presenting data related to critical care outcomes in patients with COVID-19 (166). This review was limited by its inclusion of low-quality small sample studies and the restriction to studies published before the start of 2021. To ensure the availability of high-quality epidemiologic data that incorporates all published data to date, we chose to update this prior work. Compared with this prior systematic review, our current study incorporated data from nearly 15 times as many patients, allowing for more precise and robust estimates of CFR across outcomes. These updated estimates allow for more appropriate patient-physician counseling, resource management, and clinical trial planning.

In this current analysis, compared with 2020, patients critically ill with COVID-19 supported with organ support in 2021 had substantially lower observed CFRs related to MV and RRT. Interestingly, the ICU CFR did not change from 2020 to 2021. This discrepancy is challenging to reconcile and raises the possibility that changes in care strategies, such as more frequent and prolonged utilization of noninvasive respiratory support, application of noninvasive ventilation outside of ICU settings, and reluctance or shortages of resources to provide RRT may have resulted in the observed changes in organ-specific CFRs (167, 168).

The notion that resource constraints and case volume can have unpredictable effects on mortality has been discussed by other investigators. Kadri et al (169) demonstrated an increase in mortality linked to surges in cases and overall hospital loads between August 2020 and October 2020. Another study by Dale et al (2) found that there was a significant decrease in survival to hospital discharge in patients with COVID-19 when a higher percentage of the hospital census was occupied by patients with COVID-19. Outside of resource-limited environments and the current pandemic, the medical community has generally noted that concentrated caseloads lead to better outcomes due to the increased relative expertise of the treatment teams (170). However, during the COVID-19 pandemic, we were confronted with extreme limitations in staffing, standard critical care treatment modalities, hospital beds, and even personal protective equipment. The magnitude of these limitations and the climate that accompanied these challenges likely amplified the impact of resource constraints. Unfortunately, the studies we reviewed are inadequate for evaluating the impact of confounding factors such as nurse-to-patient ratios in the ICU, relative or absolute equipment shortages, physician-to-patient ratios, or numerous other factors that may lead to poorer patient outcomes. It is reasonable to infer that those facilities which experienced higher caseloads were at greater risk of becoming overwhelmed compared with facilities with smaller or more select caseloads. Relatedly, we observed a wide variation in CFR based on country of origin of the included studies. Likely, this observation reflects a combination of factors including reporting bias, medical infrastructure, severity and burden of viral outbreaks, and the influence, rapid uptake, and utilization of effective COVID-19 treatments. Although based on our current data, we can only speculate as to the cause of these discrepancies, the observed wide differences in CFR worldwide emphasizes the need for further study of these outcome inequities.

It is also worth noting that some studies found no difference in mortality among patients with COVID-19 during surge months or based on resource availability (171). However, it is possible that hospitals worldwide experienced a surge of patients with COVID-19 during different time frames based on spread of the culprit virus, and this variation in timing was a confounding factor in applied analyses. For example, one study found that there was no difference in mortality among different ICUs averaged over comparable time frames, but when the data was analyzed on individual ICU outcomes, it was apparent that individual ICUs did have substantially higher mortality during surge months (3). Clarifying the impact of resource constraints would require studies that have predefined endpoints looking at resource-related variables linked to outcomes.

Our review has several limitations that should be acknowledged. First, although our analysis encompasses the largest cohort of critically ill patients with COVID-19 to date, it is limited by the availability and heterogeneity of published data. The presented findings correspond to an update of existing data. Although this limits the novelty of the findings, it is valuable to continue to update the expected clinical outcomes of patients with COVID-19 as the pandemic continues to evolve. Several geographic regions are underrepresented by the currently available data, and it is critical that such data be gathered to improve public health understanding of the impact of the COVID-19 pandemic. As such, our results may not be generalizable to these underrepresented regions. Further, there is substantial heterogeneity regarding standardized data reporting, definitions of intensive care, and resource availability around the world. Relatedly, assessment of the risk of bias related to the publication demonstrated the potential for small-study effects and publication bias, which may impact the precision of our results. We choose to analyze CFR as a measure of the severity of disease outbreak as this index allows for the estimation of rate of death among confirmed cases which is essential to characterize a disease outbreak. Although suited for this goal, CFR has the potential to overestimate the outcome rate in regions where COVID-19 testing may be limited. Finally, although outcomes of patients supported with MV or RRT appear to have improved over the course of the COVID-19 pandemic, the cause of this observation could not be identified and likely reflects the convergence of multiple factors potentially including available treatments and immunizations, which may have reduced the severity of illness over the course of the pandemic. Due to the potential for substantial bias resulting from the retrospective analysis of these factors, which would make interpretation of these data challenging, the impact of these factors was not examined in this current work. Likewise, the emergence of viral variants has likely influenced ICU outcomes. However, as these variants have impacted geographic regions at varying paces, their impact on ICU and organ support outcomes could also not be assessed directly in this review.

In conclusion, in this large meta-analysis of studies reporting data representing at least 100 patients with COVID-19, we found the ICU and MV CFR to be 37.3% and 51.6%, respectively. Although the CFR related to MV appears to have improved considerably since 2020, ICU mortality remains high. The mortality is in line with the worst outcomes of other respiratory pandemics in recent history, only on a greater scale. Even with advances in care over the course of the pandemic, outcome improvements have been modest for those patients that are critically ill or require MV. These data are valuable to guide expectation management, resource allocation, and patient counseling.

1 Department of Pulmonary and Critical Care Medicine, Walter Reed National Medical Center, Bethesda, MD.

2 Department of Medicine, Uniformed Services University of Health Sciences, Bethesda, MD.

3 The Metis Foundation, San Antonio, TX.

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For information regarding this article, E-mail: Abhimanyu.chandel.mil@health.mil

All data used in the analysis is available upon reasonable request.

The views expressed in this article are those of the author and do not necessarily reflect the official policy of the Uniformed Services University of Health Sciences, the Department of Defense, or the U.S. Government.

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