Do Mechanically Ventilated COVID-19 Patients Present a Higher Case-Fatality Rate Compared With Other Infectious Respiratory Pandemics? A Systematic Review and Meta-Analysis

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Background: Early reports on COVID-19 patient outcomes showed a marked fatality rate among patients requiring invasive mechanical ventilation (IMV).

Objective: Our aim was to compare case fatality rate (CFR) outcomes for patients requiring IMV due to severe acute respiratory syndrome (SARS)-associated coronavirus 2 (COVID-19), SARS-associated coronavirus 1, Middle East respiratory syndrome (MERS), and influenza (H1N1).

Materials and Methods: We searched PubMed, EMBASE, MEDLINE, Google Scholar, and Cochrane Library for relevant studies published between December 2019 and April 2021 for COVID-19, between January 2002 and December 2008 for SARS, between January 2012 and December 2019 for MERS, and between January 2009 and December 2016 for influenza (H1N1).

Results: Overall, this study included 81 peer-reviewed studies, pertaining to 65,058 patients requiring IMV: 61 studies including 62,809 COVID-19 patients, 4 studies including 148 SARS patients, 9 studies including 875 MERS patients, and 7 studies including 1226 influenza (H1N1) patients. The CFR for COVID-19 patients requiring IMV was not significantly different from the CFR for SARS and influenza (H1N1) patients (45.5% [95% confidence interval (CI), 38.5%–52.8%] vs. 48.1% [95% CI, 39.2%–57.2%] and 39.7% [95% CI, 29.3%–51.3%], respectively). However, CFR for COVID-19 patients was significantly lower compared with that for MERS patients (CFR, 70.6%; 95% CI, 60.9%–78.8%).

Conclusions: COVID-19 patients requiring IMV show a similar CFR compared with SARS and H1N1 influenza patients but a lower CFR compared with MERS patients. To improve survival in future pandemics, we recommend examining the pros and cons of the liberal use of endotracheal intubation and considering drafting guidelines for the selection of patients to intubate and the timing of intubation.

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O.B. searched the literature, collected the data, reviewed the published studies, and wrote the initial draft. S.F. revised and adjusted the second draft, A.M. reviewed the published studies, and Y.H. performed the statistical analysis. I.C. searched the literature and assisted in reviewing the published studies, Y.N. revised the article, and L.K.B. contributed to the critical revision of the first draft. All authors agreed to be accountable for all aspects of the work.

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Low respiratory tract infections are the most fatal communicable diseases globally, causing millions of deaths per year.[1] Four viral pandemics associated with acute hypoxemic respiratory failure (AHRF) have occurred during the last 2 decades. The first was the severe acute respiratory syndrome coronavirus 1 pandemic in 2002, caused by a coronavirus, infecting 8098 people globally, with a case fatality rate (CFR) of approximately 10.5%.[2] Second, the influenza virus (H1N1) pandemic took place in 2009, with a CFR of 0.2%.[3] The third pandemic, the Middle East respiratory syndrome (MERS-CoV), caused by a different coronavirus, occurred in 2012 with a total of 2519 laboratory-confirmed cases and a CFR of 34.4%.[4] The fourth pandemic, starting in December 2019 and still ongoing, is caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) that led to AHRF known as the coronavirus disease 2019 (COVID-19). The number of persons infected by SARS-CoV-2 continues to increase globally, with 160,686,749 confirmed cases and 3,335,948 deaths reported as of May 14, 2021.[5]

Genetic sequencing of the SARS-CoV-2 virus suggests that it is a beta-coronavirus closely linked to the severe acute respiratory syndrome (SARS) virus.[6] The novel virus shares 88% of its genetic sequence with 2 coronaviruses found in bats, namely, bat SLCoVZC45 and bat-SL-covVZXC21; 79% of its sequence is identical to the SARS coronavirus, and nearly half of its genetic sequence is identical to the MERS coronavirus.[7] The overall mortality due to COVID-19 ranges between 3% and 4% among identified cases according to the World Health Organization's reports.[8] Some patients (5%–10%) require admission to an intensive care unit (ICU).[9] In the absence of guidelines, there was difficulty to distinguish between critically ill patients requiring mechanical ventilation and those who could be managed with noninvasive respiratory support. Several studies conducted early in the pandemic concluded that noninvasive options (continuous positive airway pressure/bilevel positive airway pressure and or high-flow nasal cannula) were of questionable value and that they could cause aerosolization of the virus under positive pressure. Thus, intubation is preferred. Furthermore, delaying intubation would cause a more severe form of acute respiratory distress syndrome (ARDS).[10,11] Yang et al[10] reported that 56% of COVID-19 patients who were critically ill required invasive mechanical ventilation (IMV), whereas Richardson et al[12] claimed that as much as 89.9% required IMV. Several experts have shown in their studies that each day of mechanical ventilation exposes patients to complications. In addition, several studies reported places that experienced insufficient supply of ventilators (some authorities recommend connecting 4 patients to a single ventilator).[11] Taken these facts together had raised concerns that survival among those receiving mechanical ventilation would be poor.[13–16] Available recommendations on the type of first-line therapy of acute respiratory failure in pulmonary infections, especially in pandemics, when there is lack of knowledge about the virus and its clinical manifestation, are based mostly on published studies and experience from other pandemics: SARS epidemic in 2003, MERS epidemic in 2012, and influenza epidemic in 2009.

To address the question of whether COVID-19 patients requiring IMV present a high CFR, we decided to compare CFR of COVID-19 patients with CFR of patients with other coronaviruses (SARS, MERS) and with those with H1N1 influenza infection, during the pandemic stages of these diseases using systematic review and meta-analysis. Systematic reviews can be very useful decision-making tools for physicians. They objectively summarize large amounts of information, identifying gaps in medical research, and point out beneficial or harmful interventions that may be useful for clinicians, researchers, and even the public and policymakers.

Addressing this knowledge gap will assist in intensive care resource allocation and public health strategies, as the COVID-19 pandemic is still current and active.

MATERIALS AND METHODS

This study-level systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17]

Search Strategy

PubMed, EMBASE, MEDLINE, Google Scholar, and Cochrane Library were searched for relevant published literature on COVID-19, severe acute respiratory syndrome coronavirus 1, MERS-CoV, and influenza (H1N1). Studies in English, which included data concerning mortality among critically ill patients requiring IMV, were identified. Articles published between December 2019 and May 1, 2021, on COVID-19, between January 2002 and December 2008 on SARS, between January 2012 and December 2019 on MERS, and between January 2009 and December 2016 on influenza (H1N1) were considered.

Two authors reviewed the titles and abstracts identified for the search with the intent to select studies that met the following inclusion criteria: (1) the study was peer reviewed, (2) the study related to laboratory-confirmed COVID-19/SARS/MERS/influenza (H1N1) infections, (3) the study included IMV and patients' survival/mortality/death data, (4) the study participants were composed of adults 18 years and older, and (5) for influenza (H1N1), only cohorts based on patients who were given a diagnosis of the disease between years 2009 and 2010—the pandemic era.

The 2 authors (O.B. and I.C.) who independently conducted the literature search uploaded their findings in an online file storage service (Google Drive) to cross-check them. Full-text screening was performed independently by the same authors, and any disagreement was resolved through discussion or involving a third reviewer (A.M.). The final choice of articles and the included references were based on the reviewers' judgment regarding their relevance to this subject. Figure 1 shows the article selection process for each disease.

We used the key phrases for COVID-19: (COVID-19 OR 2019nCoV OR SARS-CoV-2) AND ("critically ill" OR "ventilated patients" OR "mechanical ventilation" OR "invasive mechanical ventilation") AND ("mortality" OR "fatality" OR "outcomes" OR "survival" OR "death"). The key phrases for SARS were SARS-CoV-1 OR SARS OR severe acute respiratory syndrome, and for MERS, these were MERS-CoV OR MERS OR Middle East respiratory syndrome.

Data Extraction

Study characteristics, treatment (IMV), and clinical outcome were extracted from the identified studies. Data on clinical outcome included mortality and hospital/ICU data. Patients who were intubated early or late were considered as patients requiring IMV; all causes of mortality of patients requiring IMV and all durations of ventilation were included in the meta-analysis.

STATISTICAL ANALYSIS

This meta-analysis was performed using RStudio version 3.6.1, "meta" and "forestplot" packages, based on data extracted from peer-reviewed studies retrieved from the PubMed, EMBASE, and Cochrane Library databases. Categorical variables were described as counts and percentages. Case fatality rate was calculated by dividing the number of deaths of confirmed cases requiring IMV by the total number of confirmed cases that required IMV. The resulting ratio was then multiplied by 100 expressed as a percentage (Supplementary Tables 1–4, available at http://links.lww.com/IDCP/A45, http://links.lww.com/IDCP/A46, http://links.lww.com/IDCP/A47, and http://links.lww.com/IDCP/A48, respectively). Summary CFR's estimates and the corresponding 95% confidence intervals (CIs) were obtained through meta-analyses using inverse variance method and generalized linear mixed model for pooling.[18,19]

Forest plots were used to evaluate the pooled estimates of CFRs and corresponding 95% CIs for each study. The I^2 statistical test was performed to assess heterogeneity in this meta-analysis. A random-effects model was chosen where I^2 statistical tests (heterogeneity) were greater than 50%, and fixed-effects model was chosen where I^2 statistical tests were less than 50%.[20]

Ethics committee approval was waived because of study type (meta-analysis). This study was registered in PROSPERO (International Prospective Register of Systematic Reviews) and received a registration number (CRD 42021237186).

RESULTS

Overall, 1931 records were identified during the search conducted on the PubMed, EMBASE, MEDLINE, Google Scholar, and Cochrane Library databases. Of these identified records, 1332 were excluded based on title and abstract screening, 122 were excluded because they were reviews/systematic reviews/meta-analyses, 181 were excluded for duplication of the remaining 296 records, and 215 were excluded through full-text evaluation, because they did not meet the inclusion criteria. A total of 81 peer-reviewed studies were included in the final analysis.

COVID-19

Overall, 1541 records were identified from the search conducted on the 5 databases, of which 1290 were excluded based on title and abstract screening, duplications, or systematic reviews/meta-analyses. Of the remaining 251 records, 190 were excluded through full-text evaluation. Finally, a total of 61 peer-reviewed studies were included in the final analysis (Fig. 1A).[10,12,13,21–78] Of these final 61 studies, 11 studies were conducted in China, 3 were conducted in America (2 studies from South America and 1 study from Central America), 17 involved centers in the United States, 16 involved centers in Europe, 3 involved centers in Canada, 9 involved centers in Asia, and 2 were based on multinational collaborations (one was between the United Kingdom and Ireland, and the second was between the United States, Europe, Canada, and Japan). Of the 61 studies, 51 were retrospective cohorts, 9 were prospective cohorts, and 1 cross-sectional.

The 61 studies were conducted between December 2019 and September 2020: 15 were conducted up to March 2020, 19 were

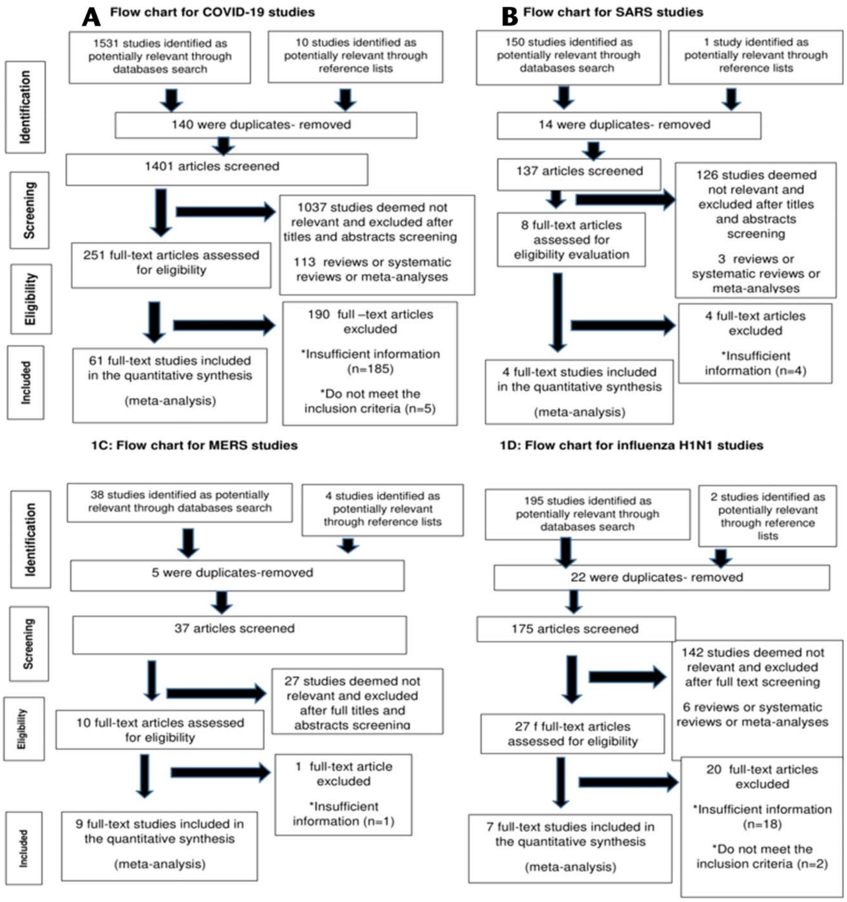

FIGURE 1. Flowchart of the study selection.

conducted between March and April 2020, and 27 were conducted between March and September 2020. The number of patients requiring IMV ranged between 2 and 45,205 (Supplemental Table 1, http://links.lww.com/IDCP/A45). The reported CFR across these studies was calculated at 45.5% (95% CI, 38.5%–52.8%). High heterogeneity was observed across all studies (I^2 = 99%). The reported CFRs varied between 0% (95% CI, 0%–4.3%) and 100% (95% CI, 54.1%–100%) among different studies (Fig. 2).

Severe Acute Respiratory Syndrome

Overall, 151 records were identified from the search conducted on the 5 databases, of which 143 were excluded based on title and abstract screening, duplications, or systematic reviews/meta-analyses. Of the remaining 8 records, 4 were excluded after full-text evaluation. Finally, a total of 4 peer-reviewed studies were included in the final analysis (Fig. 1B).[79–82] Three of these studies were conducted in Asian countries, whereas 1 study involved centers in Canada. Of the 4 studies, 3 were retrospective cohorts and 1 was a prospective cohort. All studies were conducted during 2003. The number of patients requiring IMV ranged from 27 to 46 (Supplemental Table 2, http://links.lww.com/IDCP/A46). The reported CFR across these studies was calculated at 48.1% (95% CI, 40.1%–56.2%). Low heterogeneity was observed across all studies (I^2 = 19%). The reported CFRs varied between 37% (95% CI, 23.2%–52.5%) and 56.5% (95% CI, 41.8%–71.1%) among different studies (Fig. 3).

Middle East Respiratory Syndrome

Overall, 42 records were identified from the search conducted on the 5 databases, of which 32 were excluded based on title and abstract screening or duplications. Of the remaining 10 studies, 1 was excluded after full-text evaluation. Finally, a total of 9 peer-reviewed studies were included in the final analysis (Fig. 1C).[83–91] Eight studies were conducted in Saudi Arabia, and 1 involved a center in Jordan. Of the 9 studies, 8 were retrospective cohorts and 1 was a prospective cohort. Eight studies were conducted between 2012 and 2015, 1 study was carried out between 2012 and 2018, and 1 study was conducted in 2019. The number of patients requiring IMV ranged between 3 and 297 (Supplemental Table 3, http://links.lww.com/IDCP/A47). The reported CFR across these studies was calculated at 70.6% (95% CI, 60.9%–78.8%). High heterogeneity was observed across all studies (I^2 = 77%). The reported CFRs varied between 30.8% (95% CI, 14.3%–51.8%) and 100% (95% CI, 29.2%–100%) among different studies (Fig. 4).

Influenza (H1N1)

Overall, 197 studies were identified from the 3 databases, of which 170 were excluded based on title and abstract screening (only studies who were based on cohorts between years 2009 and 2010 were included), duplications, or systematic reviews/meta-analyses. Of the remaining 27 records, 20 were excluded after full-text evaluation. Eventually, 7 peer-reviewed studies were included in the final analysis (Fig. 1D).[92–98] Of these, 1 study was conducted in North America and 6 were carried out in Europe. Of the 7 studies, 4 were retrospective cohorts and 3 were

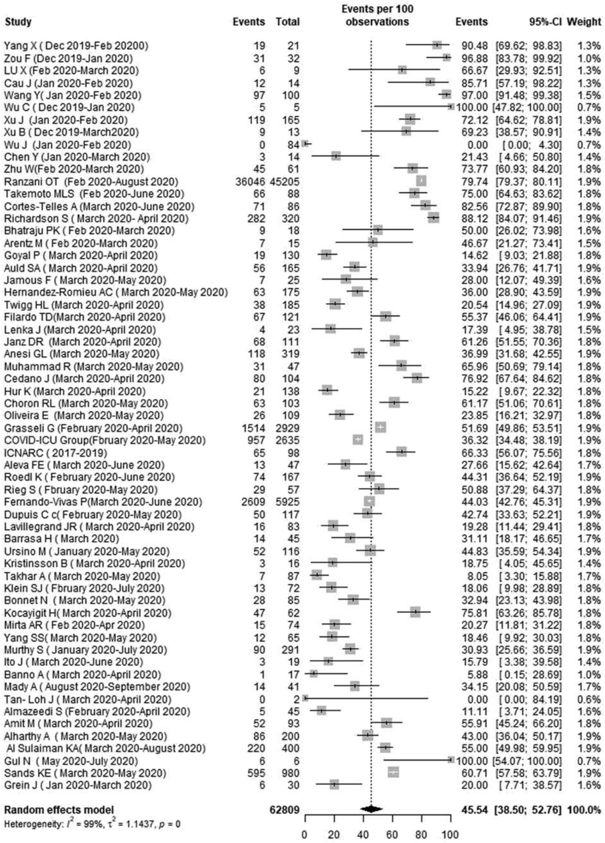

FIGURE 2. Study analysis of the case fatality rate (CFR) of COVID-19 patients requiring invasive mechanical ventilation. Diamond indicates overall estimates from the meta-analysis, squares indicate point estimates of the result of each study, and horizontal lines represent 95% confidence interval (CI) of CFR.

prospective cohorts. All 7 studies were conducted between 2009 and 2010, when influenza (H1N1) was considered a pandemic. The number of patients requiring IMV ranged between 6 and 233 (Supplemental Table 4, http://links.lww.com/IDCP/A48). The reported CFR across these studies was calculated at 39.7% (95% CI, 29.3%–51.0%). High heterogeneity was observed across all studies (I^2 = 87%). The reported CFRs varied between 22.9% (95% CI, 13.7%–34.5%) and 80% (95% CI, 44.4%–97.5%) among different studies (Fig. 5).

Summary of Main Results

The CFR of patients requiring IMV was highest among MERS patients (70.6% [95% CI, 60.9%–78.8%]), followed by SARS patients (48.1% [95% CI, 39.2%–57.2%]) and COVID-19 patients (45.5% [95% CI, 38.5%–52.8%]). Lowest CFR was observed for influenza H1N1 patients (39.7% [95% CI, 29.3%–51.0%]).

The CFR of COVID-19 patients requiring IMV was not significantly different from that of SARS and influenza (H1N1) patients requiring IMV (according to 95% CIs) but was significantly lower than that of MERS patients requiring IMV.

DISCUSSION

This systematic review and meta-analysis, which included 62,809 critically ill, mechanically ventilated COVID-19 patients, 148 ventilated SARS patients, 875 MERS patients, and 1226 influenza (H1N1) patients, indicates that the CFR of invasively mechanically ventilated patients was highest among MERS patients, followed by SARS patients and COVID-19 patients, and lowest for intubated influenza (H1N1) patients. Although the CFR of invasively mechanically ventilated COVID-19 patients was not significantly different from that of invasively mechanically ventilated SARS and influenza (H1N1) patients, it was significantly lower than the rate observed for intubated MERS patients.

Although COVID-19 characteristics are similar to previous historical coronavirus infections (SARS/MERS), with a relatively stable transmission rate and a deceptively slow incubation time, significant differences in CFR were found between COVID-19 patients requiring IMV and MERS patients requiring IMV. It may be explained by the fact that COVID-19 is less pathogenic than MERS-CoV (≈40%).[99] Middle East respiratory syndrome causes a more severe clinical composite than seen among COVID-19 and SARS patients, requiring hospitalization more frequently.[100] The study by Al-Hameed et al[87] showed that AHRF developed in up to 70% of hospitalized patients with MERS and was associated with high mortality. Most patients with MERS arrived to the hospital late in the manifestation of the disease and in clinically critical conditions. This delay in treatment may be due to the lack of clinically informative global data and the lack of public press that we are witnessing in the current COVID-19 pandemic.

Other studies showed that patients with COVID-19 pneumonia and respiratory distress share many clinical similarities with patients having other types of severe viral pneumonia and often meet the Berlin definition of ARDS; accumulating clinical evidence suggests that there are important phenotypic differences in their manifestation.[101]

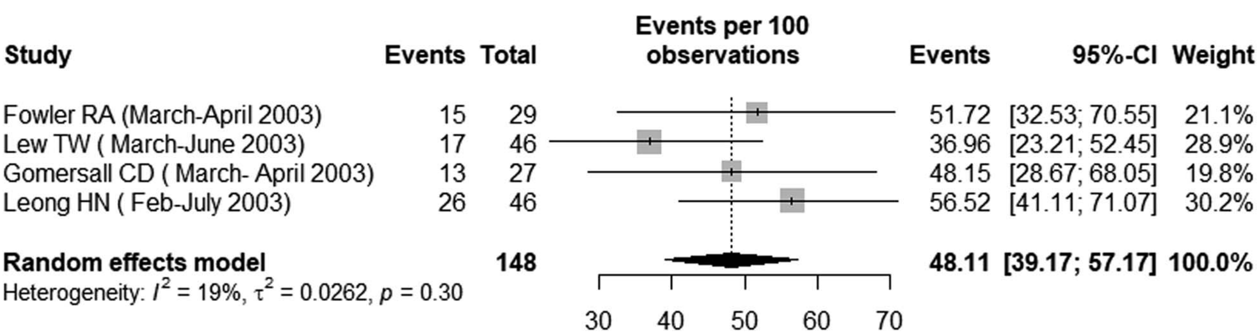

FIGURE 3. Study analysis of the case fatality rate (CFR) of severe acute respiratory syndrome patients requiring invasive mechanical ventilation. Diamond indicates overall estimates from the meta-analysis, squares indicate point estimates of the result of each study, and horizontal lines represent 95% confidence interval (CI) of CFR.

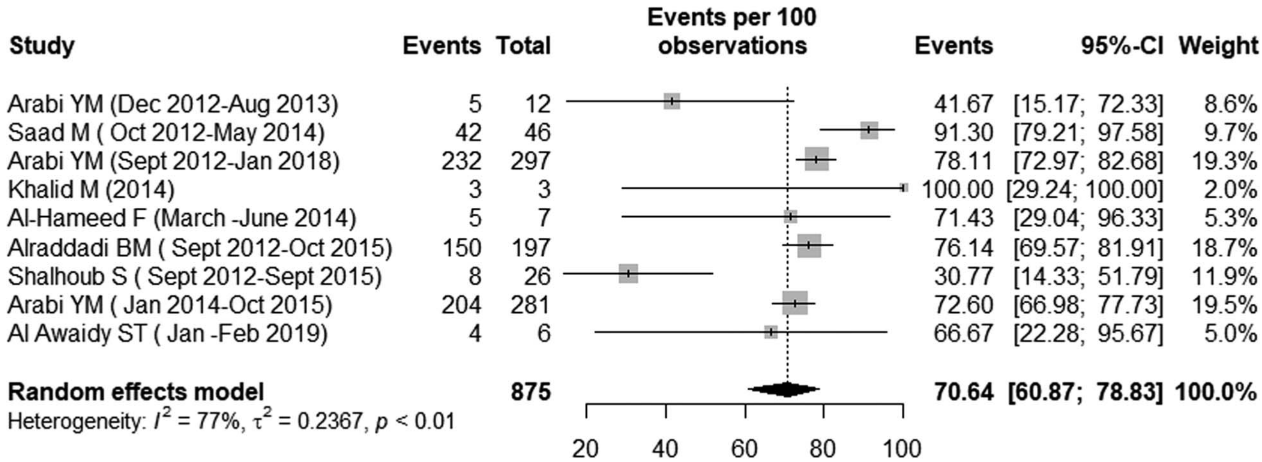

FIGURE 4. Study analysis of the case fatality rate (CFR) of Middle East respiratory syndrome patients requiring invasive mechanical ventilation. Diamond indicates overall estimates from the meta-analysis, squares indicate point estimates of the result of each study, and horizontal lines represent 95% confidence interval (CI) of CFR.

The study by Cobb et al[102] compared critically ill patients with COVID-19 and patients with influenza. They found that, whereas among patients with influenza, the cause of ICU admission may have been more responsive to antibiotic treatment, patients with COVID-19 not only had higher rates of ARDS but also had a different trajectory of respiratory failure with longer durations of mechanical ventilation. Ackermann et al[103] described certain histologic features, including alveolar microthrombi and vascular angiogenesis, that may be more common among patients with COVID-19 than in patients with ARDS secondary to influenza. These histologic features could explain higher mortality rates among COVID-19 patients requiring IMV compared with influenza (H1N1) patients. It should be noted that Cobb et al's study was based on a very small sample of patients and not during the disease pandemic era.

Another study from Tang et al[104] was aiming to explore the different clinical presentations between COVID-19 and influenza (H1N1) pneumonia in patients with ARDS. This group found a higher mortality rate in those with H1N1-induced ARDS than in COVID-19–induced ARDS (34.7% vs. 28.8%). However, in this study, approximately 36% of patients with COVID-19 remained hospitalized at the end of the study, a finding that could change the outcomes, had it included outcomes only upon conclusion of all COVID-19 patients' final course.

Contrary to our study, a study by Lim et al[105] reported that the CFR of COVID-19 patients requiring IMV was higher than that of H1N1 influenza patients (45% [95% CI, 39%–52% vs. 24.2%–26.5%, respectively]) and the CFRs of SARS and MERS patients receiving IMV were similar to those of COVID-19 outbreak patients (45%–48% and 60%–74%, respectively). However, they based their results on a very small number of studies and did not compare 95% CI to find whether these results are significantly different.

Studies based on nonpandemic diseases showed that mortality for pneumonia requiring IMV was between 34.2% and 44.2%.[106] Máca et al[107] found in a systematic review on ARDS mortality rate that rates of in-hospital, ICU, and 28/30- and 60-day mortality were 45%, 38%, 30%, and 32%, respectively. Other studies found that, frequently in a lifesaving intervention, patients requiring IMV have hospital mortality exceeding 35%,[108–112] pertaining to severity of the underlying condition. In this regard, we cannot conclude that during a pandemic of an infectious disease–induced AHRF/ARDS/pneumonia (COVID-19/SARS/influenza [H1N1]), CFRs of patients requiring IMV are comparable with those during

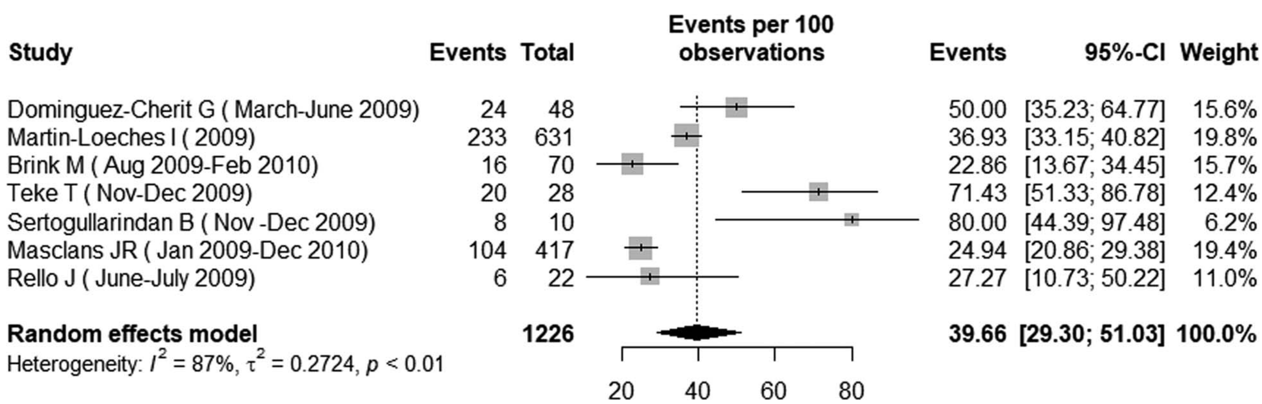

FIGURE 5. Study analysis of the case fatality rate (CFR) of influenza (H1N1) patients requiring invasive mechanical ventilation. Diamond indicates overall estimates from the meta-analysis, squares indicate point estimates of the result of each study, and horizontal lines represent 95% confidence interval (CI) of CFR.

a nonpandemic era of infectious diseases because CIs were not introduced in the previously mentioned studies.

The wide range of CFRs among COVID-19 patients requiring IMV in different countries could be multifactorial. Among the studies published in the beginning of the outbreak, we found a higher CFR among patients requiring IMV. Studies from China with the highest mortality outcomes 28 days after hospital and ICU admission started recruiting patients in December 2019 up to February 2020.[10,21,23–26,28] Thus, they reported CFRs among patients receiving IMV at earlier stages during the pandemic, compared with the studies from France,[57,63] the United States,[37–39,41] Spain,[58] and Netherlands,[52] which started recruiting patients in March 2020 and reported lower mortality rates at the same lengths of follow-up.

At the beginning of the outbreak, healthcare systems were overwhelmed and sometimes over their maximal capacities.[53] Specifically, critical care departments experienced insufficiently staffed settings and shortage of ventilators. As time went on, countries whose peak COVID-19 pandemic outbreak occurred later (March 2020 and onwards) already managed to obtain sufficient equipment, including mechanical ventilators, and to have proper staffing and processes of care.[48]

Another possible cause for the disparity is that most mortality cases, especially at the beginning, occurred among patients older than 60 years. It could be explained by less physiologic reserve and additional comorbidities. For example, Richardson et al[12] reported that 97.2% of patients were older than 65 years, and similarly in other studies, a mean age of 70 years was evident.[21,113] The population in China has 10% of its total population (1,440,661,405) older than 60 years and 7% older than 65 years.[114] The number of people older than 65 years amounts to 3,214,000 in New York and 1,460,000 in Georgia.[115] The difference in the total number of patients who would potentially require IMV and possibly die explains the significant regional and national variance in mortality rate.

The third possible factor is that high-income countries compared with mid- and low-income countries had the means to obtain ventilators, protective equipment, and medicines earlier and to affect CFR as such.[116] For example, as personal protective equipment was scarce during the preliminary phases of the pandemic, early intubation preference for AHRF patients was in place, in an attempt to protect staff and other patients from possible cross-contamination using noninvasive ventilation strategies. Yet, another possible factor is that different countries started the pandemic with different healthcare system capacities and different strategies to contain the pandemic in their respective country. Several used “mitigation” strategy, and some used “containment” strategy, which led to varying depletion of hospital resources and surge of patients in hospitals.[117] A fifth possible explanation is changes in practices and guidelines, such as clustered nursing care, changes in sedation practices, and environmental services that may have affected care and patient outcomes compared with the beginning of the outbreak. As time passed and more evidence emerged regarding the appropriate treatment strategies, clinicians conducted the care of critically ill patients differently. For example, anticoagulation and dexamethasone-treated mechanically ventilated patients have improved mortality rates.[118] All these facts could also potentially explain the higher mortality rates evidenced earlier in the pandemic. Data from the Intensive Care National Audit and Research Center in the United Kingdom show that ICU mortality in all ages except those older than 80 years old has declined significantly from April to May/June and points to better outcomes in patients with longer stays in the ICU.[119]

Globalization increases the likelihood that infectious diseases appearing in one country will spread rapidly to another and cause a pandemic and a surge of people who require IMV, as respiratory support with IMV remains a cornerstone of critical care medicine.[106] To mitigate CFRs among patients requiring IMV earlier during a possible future pandemic outbreak, several steps should be observed: First, governments should impose travel restrictions, once the World Health Organization warns against another pandemic outbreak. This will delay the spread of the pathogen and diminish the number of infected people who will require healthcare. Second, at the outbreak of a pandemic, vulnerable individuals, such as people with comorbidities and those of advanced age, should be protected by the use of social distancing. Third, national healthcare systems should empirically prepare sufficiently and systematically for the occurrence of the next pandemic, by allocation of sufficient means, equipment, and training for such contingencies. These funds are substantial and require proper planning, as one can view for example that, during a nonpandemic era, patients requiring IMV represent 2.8% of hospital admissions, but that translates to 12% of all hospital costs at $27 billion per year in the United States.[113]

As we view it, this study’s results can assist clinicians in reaching appropriate decisions while approaching future pandemic viral diseases at their early stages. The evolution of knowledge pertaining to appropriate treatment modalities usually lags the rapidity of spread and accumulation of patients. The understanding of the varied nature of these outbreaks, as well as their possible evolution over time, and the impact of ventilation of severely ill patients on their projected outcomes can be useful tools in the general approach of clinicians.

Limitations of the Study

First, we observed substantial differences of mortality reports. Several studies report on cohorts with incomplete outcomes for large proportions of the patients, pertaining to the time of submission. This prevents an accurate estimate of mortality. Second, there were differences of triage and care systems. For example, when ventilators were depleted, like in some regions in Italy during the earlier phases of the COVID-19 pandemic, prioritization systems and strict selection criteria were advocated by local medical societies, to benefit those more likely to survive. Another factor to be considered is inconsistencies in data collection of the various studies. Fifth in the different pandemics, different drugs were administered at different stages of the disease. For instance, oseltamivir was administered at the beginning of the H1N1 pandemic, whereas steroids were proven to reduce mortality a few months into the COVID-19 pandemic. We cannot rule out the effect this had on the difference in mortality among 4 viruses. Sixth and finally, studies were based on data acquired from different waves of the disease, which had a very different impact on health systems.

In conclusion, COVID-19 patients requiring IMV showed similar CFRs when compared with influenza (H1N1) patients requiring IMV, during its pandemic phase, and with SARS patients requiring IMV. It did show lower CFRs for COVID-19 patients compared with MERS patients. To improve survival in future pandemics, we recommend examining the pros and cons of the liberal use of endotracheal intubation and considering drafting guidelines for the selection of patients to intubate and the timing of intubation.

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REFERENCES

1. Forum of International Respiratory Societies (FIRS). *The Global Impact of Respiratory Disease*. 2nd ed. Sheffield, UK: European Respiratory

Society; 2017. Available at: https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease.pdf. Accessed February 12, 2022.

2. WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Updated recommendations October 2004. *World Health Organization Guidelines for the Global Surveillance of Severe Acute Respiratory 361 Syndrome (SARS)*. Geneva, Switzerland: World Health Organization; 2004. Available at: https://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1.pdf. Accessed March 15, 2020.
3. Hayward AC, Fragaszy EB, Bermingham A, et al, Flu Watch Group. Comparative community burden and severity of seasonal and pandemic influenza: results of the flu watch cohort study. *Lancet Respir Med*. 2014; 2:445–454.
4. World Health Organization (WHO). Epidemic and pandemic-prone diseases. MERS situation update, January 2020. *Regional Office for Eastern Mediterranean: MERS Situation 364 Update*. Geneva, Switzerland: World Health Organization; 2020. Available at: http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-january-2020.html. Accessed March 15, 2020.
5. World Health Organization. Coronavirus disease (COVID-19) outbreak. 2020. Available at: https://covid19.who.int/. Accessed May 14, 2021.
6. World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected Interim guidance. 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf. Accessed February 12, 2022.
7. Chen J, Hu C, Chen L, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. *Engineering (Beijing)*. 2020;6:1153–1161.
8. *Coronavirus Disease 2019 (COVID-2019): Situation Report–54*. Geneva, Switzerland: World Health Organization; 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/331478/nCoVsitrep14Mar2020-eng.pdf?sequence=1&isAllowed=y. Accessed March 15, 2020.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–1069.
10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020; 8(5):475–481.
11. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. *Ann Intensive Care*. 2020;10(1):78.
12. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323(20):2052–2059.
13. Hernandez-Romieu AC, Adelman MW, Hockstein MA, et al. Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. *Crit Care Med*. 2020;48(11): e1045–e1053.
14. Wunsch H. Mechanical ventilation in COVID-19: interpreting the current epidemiology. *Am J Respir Crit Care Med*. 2020;202:1–4.
15. Gattinoni L, Coppola S, Cressoni M, et al. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;201:1299–1300. Available at: https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0817LE18.
16. Wang K, Zhao W, Li J, et al. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. *Ann Intensive Care*. 2020;10:37.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009; 6(7):e1000100.
18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000; 283(15):2008–2012.
19. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3):1–48.
20. O'Connor AM, Sargeant JM, Wang C. Conducting systematic reviews of intervention questions III: synthesizing data from intervention studies using meta-analysis. *Zoonoses Public Health*. 2014;61(suppl 1):52–63.
21. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
22. Lu X, Zhang M, Qian A, et al. Lungultrasound score in establishing the timing of intubation in COVID-19 interstitial pneumonia: a preliminary retrospective observational study. *PLoS One*. 2020;15(9):e0238679.
23. Cao J, Tu WJ, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;71(15):748–755.
24. Wang Y, Lu X, Li Y, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am J Respir Crit Care Med*. 2020;201: 1430–1434.
25. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934–943.
26. Xu J, Yang X, Yang L, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. *Crit Care*. 2020;24(1):394.
27. Xu B, Fan CY, Wang AL, et al. Suppressed T cell-mediated immunity in patients with COVID-19: a clinical retrospective study in Wuhan, China. *J Infect*. 2020;81(1):e51–e60.
28. Wu J, Li W, Shi X, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). *J Intern Med*. 2020;288(1):128–138.
29. Chen Y, Zhang K, Zhu G, et al. Clinical characteristics and treatment of critically ill patients with COVID-19 in Hebei. *Ann Palliat Med*. 2020; 9(4):2118–2130.
30. Zhu W, Zhang H, Li Y, et al. Optimizing management to reduce the mortality of COVID-19: experience from a designated hospital for severely and critically ill patients in China. *Front Med (Lausanne)*. 2021;8:582764.
31. Ranzani OT, Bastos LSL, Gelli JGM, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med*. 2021;9(4):407–418.
32. Takemoto M, Menezes MO, Andreucci CB, et al. Clinical characteristics and risk factors for mortality in obstetric patients with severe COVID-19 in Brazil: a surveillance database analysis. *BJOG*. 2020;127(13): 1618–1626.
33. Cortés-Tellés A, López-Romero S, Mancilla-Ceballos R, et al. Risk factors for mortality in hospitalized patients with COVID-19: an overview in a mexican population. *Tuberc Respir Dis (Seoul)*. 2020;83(suppl 1): S46–S54.
34. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region—case series. *N Engl J Med*. 2020;382(21): 2012–2022.
35. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020; 323(16):1612–1614.
36. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of covid-19 in New York city. *N Engl J Med*. 2020;382(24):2372–2374.
37. Auld SC, Caridi-Scheible M, Blum JM, et al, Emory COVID-19 Quality and Clinical Research Collaborative. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. *Crit Care Med*. 2020; 48(9):e799–e804.

38. Jamous F, Meyer N, Buus D, et al. Critical illness due to covid-19: a description of the surge in a single center in Sioux falls. *S D Med*. 2020; 73(7):312–317.
39. Twigg HL 3rd, Khan SH, Perkins AJ, et al. Mortality rates in a diverse cohort of mechanically ventilated patients with novel coronavirus in the urban Midwest. *Crit Care Explor*. 2020;2(8):e0187.
40. Filardo TD, Khan MR, Krawczyk N, et al. Comorbidity and clinical factors associated with COVID-19 critical illness and mortality at a large public hospital in New York City in the early phase of the pandemic (March-April 2020). *PLoS One*. 2020;15(11):e0242760.
41. Lenka J, Chhabria MS, Sharma N, et al. Clinical characteristics and outcomes of critically ill patients with COVID-19 in a tertiary community hospital in upstate New York. *J Community Hosp Intern Med Perspect*. 2020;10(6):491–500.
42. Janz DR, Mackey S, Patel N, et al. Critically ill adults with coronavirus disease 2019 in New Orleans and care with an evidence-based protocol. *Chest*. 2021;159(1):196–204.
43. Anesi GL, Jablonski J, Harhay MO, et al. Characteristics, outcomes, and trends of patients with COVID-19-related critical illness at a learning health system in the United States. *Ann Intern Med*. 2021;174(5):613–621.
44. Muhammad R, Ogunti R, Ahmed B, et al. Clinical characteristics and predictors of mortality in minority patients hospitalized with COVID-19 infection. *J Racial Ethn Health Disparities*. 2022;9(1):335–345.
45. Cedano J, Fabian Corona E, Gonzalez-Lara M, et al. Characteristics and outcomes of patients with COVID-19 in an intensive care unit of a community hospital; retrospective cohort study. *J Community Hosp Intern Med Perspect*. 2021;11(1):27–32.
46. Hur K, Price CPE, Gray EL, et al. Factors associated with intubation and prolonged intubation in hospitalized patients with COVID-19. *Otolaryngol Head Neck Surg*. 2020;163(1):170–178.
47. Choron RL, Butts CA, Bargoud C, et al. Fever in the ICU: a predictor of mortality in mechanically ventilated COVID-19 patients. *J Intensive Care Med*. 2021;36(4):484–493.
48. Oliveira E, Parikh A, Lopez-Ruiz A, et al. ICU outcomes and survival in patients with severe COVID-19 in the largest health care system in Central Florida. *PLoS One*. 2021;16(3):e0249038.
49. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180(10):1345–1355.
50. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med*. 2021;47(1):60–73.
51. ICNARC COVID-19 Study Case Mix Programme Database. ICNARC Report on COVID-19 in Critical Care. 2020.
52. Aleva FE, Van Mourik L, Broeders MEAC, et al. COVID-19 in critically ill patients in North Brabant, the Netherlands: patient characteristics and outcomes. *J Crit Care*. 2020;60:111–115.
53. Roedl K, Jarczak D, Thasler L, et al. Mechanical ventilation and mortality among 223 critically ill patients with coronavirus disease 2019: a multicentric study in Germany. *Aust Crit Care*. 2020;34(2):167–175.
54. Rieg S, von Cube M, Kalbhenn J, et al. COVID-19 in-hospital mortality and mode of death in a dynamic and non-restricted tertiary care model in Germany. *PLoS One*. 2020;15(11):e0242127.
55. Ferrando-Vivas P, Doidge J, Thomas K, et al. Prognostic factors for 30-day mortality in critically ill patients with coronavirus disease 2019: an observational cohort study. *Crit Care Med*. 2021;49(1):102–111.
56. Dupuis C, Bouadma L, de Montmollin E, et al. Association between early invasive mechanical ventilation and day-60 mortality in acute hypoxemic respiratory failure related to coronavirus disease-2019 pneumonia. *Crit Care Explor*. 2021;3(1):e0329.
57. Lavillegrand JR, Garnier M, Spaeth A, et al. Elevated plasma IL-6 and CRP levels are associated with adverse clinical outcomes and death in critically ill SARS-CoV-2 patients: inflammatory response of SARS-CoV-2 patients. *Ann Intensive Care*. 2021;11(1):9.
58. Barrasa H, Rello J, Tejada S, et al. SARS-CoV-2 in Spanish intensive care units: early experience with 15-day survival in Vitoria. *Anaesth Crit Care Pain Med*. 2020;39(5):553–561.
59. Ursino M, Dupuis C, Buetti N, et al. Multistate modeling of COVID-19 patients using a large multicentric prospective cohort of critically ill patients. *J Clin Med*. 2021;10(3):544.
60. Kristinsson B, Kristinsdottir LB, Blondal AT, et al. Nationwide incidence and outcomes of patients with coronavirus disease 2019 requiring intensive care in Iceland. *Crit Care Med*. 2020;48(11):e1102–e1105.
61. Takhar A, Surda P, Ahmad I, et al. Timing of tracheostomy for prolonged respiratory wean in critically ill coronavirus disease 2019 patients: a machine learning approach. *Crit Care Explor*. 2020;2(11):e0279.
62. Klein SJ, Bellmann R, Dejaco H, et al. Structured ICU resource management in a pandemic is associated with favorable outcome in critically ill COVID-19 patients. *Wien Klin Wochenschr*. 2020; 132(21–22):653–663.
63. Bonnet N, Martin O, Boubaya M, et al. High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study. *Ann Intensive Care*. 2021;11(1):37.
64. Kocayiğit H, Özmen Süner K, Tomak Y, et al. Characteristics and outcomes of critically ill patients with covid-19 in Sakarya, Turkey: a single centre cohort study. *Turk J Med Sci*. 2021;51(2):440–447.
65. Mitra AR, Fergusson NA, Lloyd-Smith E, et al. Baseline characteristics and outcomes of patients with COVID-19 admitted to intensive care units in Vancouver, Canada: a case series. *CMAJ*. 2020;192:E694–E701.
66. Yang SS, Lipes J, Dial S, et al. Outcomes and clinical practice in patients with COVID-19 admitted to the intensive care unit in Montreal, Canada: a descriptive analysis. *CMAJ Open*. 2020;8(4):E788–E795.
67. Murthy S, Archambault PM, Atique A, et al. Characteristics and outcomes of patients with COVID-19 admitted to hospital and intensive care in the first phase of the pandemic in Canada: a national cohort study. *CMAJ Open*. 2021;9(1):E181–E188.
68. Ito J, Seo R, Kawakami D, et al. Clinical characteristics and outcomes of critically ill patients with COVID-19 in Kobe, Japan: a single-center, retrospective, observational study. *J Anesth*. 2021;23:1–9.
69. Banno A, Hifumi T, Okamoto H, et al. Clinical characteristics and outcomes of critically ill COVID-19 patients in Tokyo: a single-center observational study from the first wave. *BMC Infect Dis*. 2021;21(1):163.
70. Mady A, Aletreby W, Abdulrahman B, et al. Tocilizumab in the treatment of rapidly evolving COVID-19 pneumonia and multifaceted critical illness: a retrospective case series. *Ann Med Surg (Lond)*. 2020;60:417–424.
71. Tan-Loh J, Cheong BMK. A descriptive analysis of clinical characteristics of COVID-19 among healthcare workers in a district specialist hospital. *Med J Malaysia*. 2021;76(1):24–28.
72. Almazeedi S, Al-Youha S, Jamal MH, et al. Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait. *EClinicalMedicine*. 2020;24:100448.
73. Amit M, Sorkin A, Chen J, et al. Clinical course and outcomes of severe Covid-19: a national scale study. *J Clin Med*. 2020;9(7):2282.
74. Alharthy A, Aletreby W, Faqihi F, et al. Clinical characteristics and predictors of 28-day mortality in 352 critically ill patients with COVID-19: a retrospective study. *J Epidemiol Glob Health*. 2021;11(1):98–104.
75. Al Sulaiman KA, Aljuhani O, Eljaaly K, et al. Clinical features and outcomes of critically ill patients with coronavirus disease 2019 (COVID-19): a multicenter cohort study. *Int J Infect Dis*. 2021;105:180–187.
76. Gul N, Usman U, Ahmed U, et al. Clinical characteristics and outcomes of patients with COVID-19 pneumonia admitted to an intensive care unit in Faisalabad, Pakistan. *Int J Clin Pract*. 2021;17:e14152.
77. Sands KE, Wenzel RP, McLean LE, et al. Patient characteristics and admitting vital signs associated with coronavirus disease 2019

(COVID-19)-related mortality among patients admitted with noncritical illness. *Infect Control Hosp Epidemiol*. 2021;42:399–405.

78. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382(24):2327–2336.
79. Fowler RA, Lapinsky SE, Hallett D, et al. Critically ill patients with severe acute respiratory syndrome. *JAMA*. 2003;290(3):367–373.
80. Lew TW, Kwek TK, Tai D, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA*. 2003;290:374–380.
81. Gomersall CD, Joynt GM, Lam P, et al. Short-term outcome of critically ill patients with severe acute respiratory syndrome. *Intensive Care Med*. 2004;30:381–387.
82. Leong HN, Earnest A, Lim HH, et al. SARS in Singapore—predictors of disease severity. *Ann Acad Med Singap*. 2006;35:326–331.
83. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med*. 2014;160:389–397.
84. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis*. 2014;29:301–306.
85. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis*. 2020;70:1837–1844.
86. Khalid M, Khan B, Al Rabiah F, et al. Middle Eastern respiratory syndrome corona virus (MERS CoV): case reports from a tertiary care hospital in Saudi Arabia. *Ann Saudi Med*. 2014;34:396–400.
87. Al-Hameed F, Wahla AS, Siddiqui S, et al. Characteristics and outcomes of Middle East respiratory syndrome coronavirus patients admitted to an intensive care unit in Jeddah, Saudi Arabia. *J Intensive Care Med*. 2016;31:344–348.
88. Alraddadi BM, Qushmaq I, Al-Hameed FM, et al. Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome. *Influenza Other Respi Viruses*. 2019;13:382–390.
89. Shalhoub S, Al-Hameed F, Mandourah Y, et al. Critically ill healthcare workers with the Middle East respiratory syndrome (MERS): a multicenter study. *PLoS One*. 2018;13:e0206831.
90. Arabi YM, Al-Omari A, Mandourah Y, et al. Critically ill patients with the Middle East respiratory syndrome: a multicenter retrospective cohort study. *Crit Care Med*. 2017;45:1683–1695.
91. Al Awaidy ST, Al Maqbali AA, Omer I, et al. The first clusters of Middle East respiratory syndrome coronavirus in Oman: time to act. *J Infect Public Health*. 2020;13(5):679–686.
92. Domínguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA*. 2009;302:1880–1887.
93. Martin-Loeches I, Díaz E, Vidaur L, et al. Pandemic and post-pandemic influenza A (H1N1) infection in critically ill patients. *Crit Care*. 2011;15:R286.
94. Brink M, Hagberg L, Larsson A, et al. Respiratory support during the influenza A (H1N1) pandemic flu in Sweden. *Acta Anaesthesiol Scand*. 2012;56:976–986.
95. Teke T, Coskun R, Sungur M, et al. 2009 H1N1 influenza and experience in three critical care units. *Int J Med Sci*. 2011;8:270–277.
96. Sertogullarindan B, Ozbay B, Gunini H, et al. Clinical and prognostic features of patients with pandemic 2009 influenza A (H1N1) virus in the intensive care unit. *Afr Health Sci*. 2011;11:163–170.
97. Masclans JR, Pérez M, Almirall J, et al. Early non-invasive ventilation treatment for severe influenza pneumonia. *Clin Microbiol Infect*. 2013;19:249–256.
98. Rello J, Rodríguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by influenza A (H1N1)v in Spain. *Crit Care*. 2009;13:R148.
99. Chen J. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. *Microbes Infect*. 2020;22:69–71.
100. Petrosillo N, Viceconte G, Ergonul O, et al. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect*. 2020;26(6):729–734.
101. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020;46:1099–1102.
102. Cobb NL, Sathe NA, Duan KI, et al. Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus influenza. *Ann Am Thorac Soc*. 2021;18(4):632–640.
103. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383:120–128.
104. Tang X, Du RH, Wang R, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. *Chest*. 2020;158:195–205.
105. Lim ZJ, Subramaniam A, Ponnapa Reddy MP, et al. Case fatality rates for patients with COVID-19 requiring invasive mechanical ventilation. A meta-analysis. *Am J Respir Crit Care Med*. 2021;203(1):54–66.
106. Mehta AB, Syeda SN, Wiener RS, et al. Epidemiological trends in invasive mechanical ventilation in the United States: a population-based study. *J Crit Care*. 2015;30(6):1217–1221.
107. Máca J, Jor O, Holub M, et al. Past and present ARDS mortality rates: a systematic review. *Respir Care*. 2017;62(1):113–122.
108. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA*. 2002;287:345–355.
109. Esteban A, Ferguson ND, Meade MO, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med*. 2008;177:170–177.
110. Luhr OR, Antonsen K, Karlsson M, et al. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF study group. *Am J Respir Crit Care Med*. 1999;159:1849–1861.
111. Vasilyev S, Schaap RN, Mortensen JD. Hospital survival rates of patients with acute respiratory failure in modern respiratory intensive care units. An international, multicenter, prospective survey. *Chest*. 1995;107:1083–1088.
112. Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. *Chest*. 2000;118:1100–1105.
113. Wunsch H, Linde-Zwirble WT, Angus DC, et al. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med*. 2010;(10):1947–1953.
114. Sun R, Cao H, Zhu X, et al. Current aging research in China. *Protein Cell*. 2015;6(5):314–321.
115. Himes CL. Elderly Americans. Population Bulletin 2002;56(4). Available at: https://www.prb.org/wp-content/uploads/2001/12/Population-Bulletin-2002-56-4-ACFD30.pdf. Accessed February 12, 2022.
116. Papoutsi E, Giannakoulis VG, Xourgia E, et al. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. *Crit Care*. 2021;25(1):121.
117. Chen YH, Fang CT. Mortality from COVID-19: a cross-country comparison of containment versus mitigation strategy. *J Formos Med Assoc*. 2020;119(11):1710–1712.
118. Vafea MT, Zhang R, Kalligeros M, et al. Mortality in mechanically ventilated patients with COVID-19: a systematic review. *Expert Rev Med Devices*. 2021;18(5):457–471.
119. Docherty AB, Mulholland RH, Lone NI, et al. Changes in in-hospital mortality in the first wave of COVID-19: a multicenter prospective observational cohort study using the WHO Clinical Characterisation Protocol, Sheffield, UK. *Lancet Respir Med*. 2021;9(7):773–785.

