Mortality and Clinical Interventions in Critically ill Patient With Coronavirus Disease 2019: A Systematic Review and Meta-Analysis

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Objective: The aims of this systematic review and meta-analysis were to summarize the current existing evidence on the outcome of critically ill patients with COVID-19 as well as to evaluate the effectiveness of clinical interventions. Data Sources: We searched MEDLINE, the Cochrane library, Web of Science, the China Biology Medicine disc, China National Knowledge Infrastructure, and Wanfang Data from their inception to May 15, 2021. The search strings consisted of various search terms related to the concepts of mortality of critically ill patients and clinical interventions. Study Selection: After eliminating duplicates, two reviewers independently screened all titles and abstracts first, and then the full texts of potentially relevant articles were reviewed to identify cohort studies and case series that focus on the mortality of critically ill patients and clinical interventions. Main Outcomes and Measures: The primary outcome was the mortality of critically ill patients with COVID-19. The secondary outcomes included all sorts of supportive care. Results: There were 27 cohort studies and six case series involving 42,219 participants that met our inclusion criteria. All-cause mortality in the intensive care unit (ICU) was 35% and mortality in hospital was 32% in critically ill patients with COVID-19 for the year 2020, with very high between-study heterogeneity ($I^2 = 97\%$; $p < 0.01$). In a subgroup analysis, the mortality during ICU hospitalization in China was 39%, in Asia—except for China—it was 48%, in Europe it was 34%, in America it was 15%, and in the Middle East it was 39%. Non-surviving patients who had an older age (–8.10, 95% CI (–9.31 to –6.90)), a higher APACHE II score (–4.90, 95% CI (–6.54 to –3.27)), a higher SOFA score (–2.27, 95% CI (–2.95 to –1.59)), and a lower PaO$_2$/FiO$_2$ ratio (34.77, 95% CI (14.68 to 54.85)) than those who survived. Among clinical interventions, invasive mechanical ventilation...
INTRODUCTION

With the rapid spread of coronavirus disease 2019 (COVID-19) globally, as of June 2, 2021, a total of 171,222,477 confirmed cases had been reported in 215 countries, areas, or territories, and COVID-19 has been responsible for at least 3,686,142 deaths (1). Critically ill patients are always accompanied by a high risk of lives, which may be complicated by an uncontrolled systemic inflammatory response leading to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction. Patients with ARDS and requirement for respiratory support need urgently to be transferred to the intensive care unit (ICU). It is reported that nasal cannula or mask, high-flow nasal cannula, non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), and veno-venous extracorporeal membrane oxygenation (VV-ECMO) were widely used in COVID-19 according to the severity of respiratory dysfunction (2–4). Cardiac injury is common in COVID-19, with an incidence of 36% and closely related to a higher risk of mortality (5). It is reported that, in a systematic review and meta-analysis, the pooled incidence of acute kidney injury (AKI) was 28.6% among hospitalized COVID-19 patients from the USA and Europe and 5.5% among patients from China. Kidney replacement therapy (KRT) was used in 20.6% of patients admitted to the intensive care unit (6).

As is universally known, the mortality of critically ill patients is higher than that of ordinary patients. A systematic review reported that the summary estimate for all-cause mortality was 10% for adult patients with COVID-19 and 34% for critically ill patients within minor countries (7). In order to gain a clearer picture of the mortality of critically ill patients within major countries and clinical interventions or supportive care for organ dysfunction in the ICU, we meta-analyzed the relevant literature. The results may provide a narrative for the mortality of critically ill patients with COVID-19 as well as the effect of clinical characteristics and interventions between surviving and non-surviving patient groups.

METHODS

This systematic review was performed in compliance with the Centre of Reviews and Dissemination guidelines (8) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (9). In order to complete the systematic review and provide some references for clinical intervention during COVID-19 as soon as possible, this review was not registered.

Eligibility Criteria

We included studies that focused on the mortality of critically ill patients with laboratory-confirmed COVID-19, clinical characteristics, and interventions or supportive care of organ dysfunction.

We included original studies that fulfill the following criteria: (1) the type of study was cohort, case–control, or case–series designs, (2) the study topic was related to the mortality, clinical characteristics, and interventions or supportive care of critically ill patients with COVID-19, which is defined as a positive result of a real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs (10), and (3) the study was published or posted in English or Chinese. We excluded duplicates, conference abstracts, letters, and studies for which we could not access the full text and missing data of outcomes. In order to avoid a small size, only studies of more than 50 patients were included. If there were two or more studies that included the same population, only the study with the largest sample size was chosen.

In this review, the primary outcome was the mortality of critically ill patients with COVID-19. The secondary outcomes included all sorts of supportive care, including non-invasive respiratory support, IMV, KRT, and vasopressor. Critically or severely ill patients were defined as those patients who were admitted to the ICU or required respiratory support. Surviving patients were defined as those discharged from the ICU or hospital or who remained hospitalized. Non-surviving patients were defined as those who died in the ICU or hospital. Immunoregulation therapy includes corticosteroids, interferon, and intravenous immunoglobulin G.

Search of Studies

Two reviewers (ZQ and SL) carried out the search independently in the following six electronic databases from their inception to May 15, 2021: MEDLINE (via PubMed), the Cochrane library, Web of Science, China Biology Medicine disc, China National Knowledge Infrastructure, and Wanfang Data. The main terms were “mortality,” “critically ill patient,” “severely ill patient,” “novel coronavirus,” “2019-novel coronavirus,” “Novel CoV,” “SARS-CoV-2,” “COVID-19,” “2019-CoV,” “invasive mechanical ventilation,” “high flow nasal cannula,” “non-invasive ventilation,” “extracorporeal membrane oxygenation,” “renal replacement therapy,” “ARDS,” and “ARDS severity.”

Conclusions: Mortality was high in critically ill patients with COVID-19 based on low-quality evidence and regional difference that existed. The early identification of critical characteristics and the use of support care help to indicate the outcome of critically ill patients.
"renal replacement therapy," "kidney replacement therapy," "vasopressor," and so on (the details of the search strategy can be found in Supplementary File 1). Moreover, we also searched the clinical trial registry platforms, the Google Scholar, the reference lists of the identified reviews, and the preprint platforms [including SSRN (https://www.ssrn.com/index.cfm/en/), medRxiv (https://www.medrxiv.org/), and bioRxiv (https://www.biorxiv.org/)] for further potential studies.

**Selection of Studies**
After eliminating duplicates by using EndNote X9.3.2 software, two reviewers independently screened all titles and abstracts first, and then the full texts of potentially relevant articles were
| Study               | Events | Total | Proportion | 95%-CI          |
|--------------------|--------|-------|------------|-----------------|
| **subgroup = China** |        |       |            |                 |
| Hu 2020            | 16     | 55    | 0.29       | [0.18; 0.43]    |
| Li 2021            | 57     | 123   | 0.46       | [0.37; 0.56]    |
| Random effects model | 178    |       | 0.39       | [0.28; 0.52]    |
| Heterogeneity: $I^2 = 56\%$, $\tau^2 = 0.0760$, $p = 0.03$ |
| **subgroup = Asia** |        |       |            |                 |
| Fawad 2021         | 157    | 204   | 0.77       | [0.71; 0.83]    |
| Chaisith 2021      | 12     | 60    | 0.20       | [0.11; 0.32]    |
| Random effects model | 264    |       | 0.48       | [0.13; 0.85]    |
| Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.6601$, $p < 0.01$ |
| **subgroup = Europe** |        |       |            |                 |
| Alejandro 2021     | 660    | 2022  | 0.33       | [0.31; 0.35]    |
| Gamberini 2020     | 141    | 391   | 0.36       | [0.31; 0.41]    |
| Giovanna 2021      | 35     | 78    | 0.45       | [0.34; 0.57]    |
| Grasselli2020      | 405    | 1581  | 0.26       | [0.23; 0.28]    |
| Sandra 2021        | 43     | 152   | 0.28       | [0.21; 0.36]    |
| Josef 2021         | 21     | 92    | 0.23       | [0.15; 0.33]    |
| Aleva 2020         | 13     | 50    | 0.26       | [0.15; 0.40]    |
| Yannick 2021       | 31     | 114   | 0.27       | [0.19; 0.36]    |
| Ramazan 2021       | 82     | 209   | 0.39       | [0.33; 0.46]    |
| Viseslav 2021      | 96     | 160   | 0.60       | [0.52; 0.68]    |
| Christina 2021     | 16     | 50    | 0.32       | [0.20; 0.47]    |
| Random effects model | 4899  |       | 0.34       | [0.28; 0.40]    |
| Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.1713$, $p < 0.01$ |
| **subgroup = Americas** |        |       |            |                 |
| Mitra 2020         | 18     | 117   | 0.15       | [0.09; 0.23]    |
| Random effects model | 117    |       | 0.15       | [0.10; 0.23]    |
| Heterogeneity: not applicable |
| **subgroup = Middle East** |        |       |            |                 |
| Muhammed 2021      | 281    | 465   | 0.60       | [0.56; 0.65]    |
| Mostafa 2021       | 7      | 60    | 0.12       | [0.05; 0.23]    |
| Arshia 2021        | 77     | 133   | 0.58       | [0.49; 0.66]    |
| Abdurrahman 2021   | 113    | 352   | 0.32       | [0.27; 0.37]    |
| Random effects model | 1010  |       | 0.39       | [0.20; 0.62]    |
| Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.8696$, $p < 0.01$ |
| **Random effects model** | 6468  |       | 0.35       | [0.28; 0.43]    |
| **Prediction interval** |       |       |            | [0.10; 0.73]    |
| Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.5343$, $p < 0.01$ |
| Residual heterogeneity: $I^2 = 94\%$, $p < 0.01$ | 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 |

**FIGURE 2** All-cause mortality in intensive care unit with COVID-19.
reviewed to identify the final inclusion. Discrepancies were settled by discussion or consultation with a third reviewer. All reasons for exclusion of ineligible studies were recorded, and the process of study selection was documented using a PRISMA flow diagram (11).

### Data Extraction

Two reviewers (ZQ and SL) extracted data independently with a standard data collection form. Any disagreements were resolved by consensus, and a third reviewer (XL) checked the consistency and accuracy of all data. The following data and information were extracted for each included study: basic information (title, first author, publication year, funding, and study design), information on the participants (sample size, age, and inclusion/exclusion criteria of participants), details of the intervention and control conditions, outcome information [for dichotomous data, we abstracted the number of events and total participants per group; for continuous data, we abstracted the means, standard deviations (SD), and number of total participants per group].

### Risk of Bias in Individual Studies

Two reviewers (ZQ and SL) assessed the potential risk of bias of each included study independently. Discrepancies were resolved by discussion and consensus with a third researcher (XL). We assessed the risk of bias in cohort studies using Newcastle–Ottawa Scale (12), which contains eight domains: representativeness of exposure cohorts, selection of non-exposure cohorts, determination of exposure, outcome events that did not occur before study initiation, comparability of cohort based on design or analysis, assessment of outcome events, adequacy of follow-up time, and completeness of follow-up. For case series, we used the Joanna Briggs Institute critical appraisal checklist for case series (13), which consists of 10 domains. Each domain was graded as one score if reported.
Statistical Analysis
All statistical analyses were performed using RStudio, version 1.3.1056. Comparable data from studies with one outcome were pooled using forest plots according to the Cochrane Handbook by using random-effects model separately (14). Mortality in the ICU and in hospital was used for a detailed description. A subgroup analysis was performed according to different regions. For dichotomous outcomes, we calculated the risk ratios (RR) and the corresponding 95% confidence intervals (CI) and P-values. For continuous outcomes, we calculated the standardized mean difference and its corresponding 95% CI if means and SD were reported. Furthermore, 95% prediction interval (PI) was used to evaluate the range that, we assert with 95% certainty, will fall into during a future validation test. We reported the effect size with 95% CI by using random-effects models. Two-sided $P < 0.05$ were considered statistically significant. Heterogeneity was defined as $P < 0.10$ and $I^2 > 50\%$. When effect sizes could not be pooled due to only one study for a comparison, we reported the study findings narratively. We used sensitivity analyses to evaluate the stability of mortality outcomes of the included studies. For a result that included more than 10 studies, publication bias was tested by visual funnel plots.

Quality of the Evidence
The quality of evidence for each outcome was assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The
judgments of quality for specific outcomes were based on five main factors: study design and execution limitations, inconsistency, indirectness, imprecision of results (random-effects model), and publication bias across all studies (15, 16). The quality of evidence for each outcome was graded as high, moderate, low, or very low (17) and presented in “GRADE Evidence Profiles” (18).

RESULTS

Search Results

The literature search retrieved 9,362 records through database searching and 51 additional records through other sources, which included 36 from the Google Scholar and 15 from preprint platforms. After removing duplicates, we screened the titles and abstracts of 5,138 records and reviewed the full text of 101 articles. Finally, we included 33 studies (cohort studies and case-series) (19–51) that reported either the mortality of critically ill patients or the clinical interventions between surviving and non-surviving patients with COVID-19 (Figure 1). All of them were published in English.

The Characteristics of the Included Studies

The basic characteristics of the included studies of the mortality of critically ill patients are summarized in Table 1 (Supplementary File 2). These 28 studies involving 40,195 participants were admitted between January 1 and December 30, 2020, which covered Asia, Europe, and America. Of the 28 studies, 19 were single-center studies and nine were multi-center studies in design. Mortality was demonstrated and concluded with a follow-up of more than 7 days and expressed as mortality in the ICU or in hospital. Among 33 studies, 17 studies (22, 25, 50, 51) with 6,414 participants compared clinical interventions between surviving and non-surviving patients. All studies assessed the risk of bias with scores of 3–9, indicating low to high quality (Supplementary File 3). A visual analysis of the
funnel plot indicated that no publication bias was suspected in the results of age and mortality in the ICU. The results of IMV, PaO$_2$/FiO$_2$ ratio, and SOFA source were suggestive of publication bias (Supplementary File 4).

Clinical Outcome of Critically Ill Patients
Figures 2, 3 show all-cause mortality in the ICU and in hospital as per peer-reviewed studies from countries around the world. In the present study, all-cause mortality in the ICU was 35% in critically ill patients (95% PI, 10–73%) with very high between-study heterogeneity. In a subgroup analysis, the mortality in China was 39%, in Asia—except for China—it was 55%, in Europe it was 26%, and in America it was 24%.

Basic Clinical Characteristics Between Two Different Outcome Groups
Figures 4–7 show the basic clinical characteristics including age, acute physiological and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, and PaO$_2$/FiO$_2$ ratio between surviving and non-surviving patients. Patients who did not survive had an older age [−8.10, 95% CI (−9.31 to −6.90)], a higher APACHE II score [−4.90, 95% CI (−6.54 to −3.27)], a higher SOFA score [−2.27, 95% CI (−2.95 to −1.61)], and a lower PaO$_2$/FiO$_2$ ratio [0.85, 95% CI (0.70 to 0.99)].
| Region   | Nation | Study            | No. patients | Study design               | Single- or multi-center | Date        | Follow-up               | Outcome                                      |
|----------|--------|------------------|--------------|-----------------------------|-------------------------|-------------|------------------------|----------------------------------------------|
| Asia     | China  | Xie et al. (51)  | 733          | Retrospective case series   | Multi-center            | Jan. 1 to Feb. 29 | 28-days               | 394 patients died                            |
| China    | Li et al. (38) | 268 | Retrospective, cohort study | Single-center | Jan. 26 to Feb. 5 | 32-days | 87 patients died, 85 discharged from hospital |
| China    | Hu et al. (33) | 55  | Retrospective case series | Single-center | Jan. 8 to Mar. 12 | 28-days | 16 patients died, 33 discharged home. Six transferred to isolation wards |
| China    | Chen et al. (24) | 192 | Retrospective case series | Single-center | Jan. 28 to Mar. 13 | Until Mar. 13 | 50 died in the hospital and 142 were discharged |
| China    | Geng et al. (29) | 123 | Retrospective observational study | Single-center | Feb. 9 to Apr. 6 | Until Apr. 6 | 57 died in ICU hospitalization and 66 were discharged |
| Pakistan | Rahim et al. (44) | 204 | Cross-sectional study | Single-center | Apr. 1 to Aug. 31 | Until Aug. 31 | 157 died in ICU hospitalization and 47 shifting from the ICU to a general isolation ward |
| India    | Mahendra et al. (39) | 560 | Retrospective observational study | Single-center | Jun. 1 to Oct. 30 | 30-days | 306 died in hospital |
| Thailand | Sivakorn et al. (52) | 60  | Prospective observational study | Single-center | Jan. 1 to 31 | Until Jan. 31 | 12 died and 48 patients were alive at ICU discharge. |
| Middle East | Qatar | Najim et al. (41) | 60 | Prospective observational study | Single-center | Jun. 26 to Aug. 5 | 60-days or died or discharged from the ICU | Seven died |
| Europe   | Europe | Wendel Garcia et al. (50) | 398 | Prospective cohort study | Multi-center | Mar. 13 to Apr. 22 | 40-days | 97 patients died and 301 discharged |
| Europe   | France | Fond et al. (27) | 14,351 | Retrospective cohort study | Multi-center | Feb. 1 to Jun. 9 | until Jun. 9 | 3,790 died in hospital |
| Spain    | Rodríguez et al. (45) | 2,022 | Prospective observational | Multi-center | Feb. 22 to May 11 | 90-days | 660 died in ICU and 1,362 discharged from ICU |
| Italy    | Gamberrini et al. (28) | 391 | Retrospective observational study | Multi-center | Feb. 22 to May 4 | Until May 15 | 141 died in ICU hospitalization, 39 still in ICU |
| Italy    | Carpagnano et al. (23) | 78  | Retrospective observational study | Single-center | Mar. 11 to Apr. 27 | Until Apr. 27 | 35 patients died during hospitalization, 43 discharge from the ICU |
TABLE 1 | Continued

| Region | Nation | Study | No. patients | Study design | Single- or multi-center | Date | Follow-up | Outcome |
|--------|--------|-------|--------------|--------------|------------------------|------|-----------|---------|
| Italy  | Grasselli et al. (30) | 1,581 | Retrospective case series | Multi-center | Feb. 20 to Mar. 18 | 7-days | 405 patients died, 920 still in the ICU, 256 discharged |
| Sweden | Jonmarker et al. (35) | 152 | Retrospective observational study | Single-center | Mar. 1 to Apr. 31 | 28-days | 43 died in ICU |
| Sweden | Järhult et al. (34) | 92 | Prospective observational | Single-center | Mar. 1 to Jun. 30 | 30-days | 21 died in ICU |
| Netherland | Aleva et al. (19) | 50 | Retrospective case series | Single-center | Mar. 9 to Apr. 7 | 86-days | 13 patients died, 37 survived and discharged from ICU |
| Netherland | Vogels et al. (49) | 114 | Retrospective observational study | Single-center | Mar. 1 to Jun. 4 | 28-days | 31 died in ICU hospitalization |
| Turkey | Gunduz et al. (31) | 209 | Retrospective observational study | Single-center | Mar. 24 to Jul. 6 | Until their outcomes | 82 died in ICU hospitalization |
| Serbia | Popadic et al. (43) | 160 | Retrospective observational study | Single-center | Jun. 23 to Oct. 2 | Until their outcomes | 96 died in ICU hospitalization, 64 lived |
| Greece | Routsi et al. (47) | 50 | Prospective observational study | Single-center | Mar. 11 to Apr. 27 | Until Apr. 27 | 16 patients died, one still in the ICU, 33 discharged |
| America | Gupta et al. (32) | 3,924 | Retrospective cohort study | Multi-center | Mar. 4 to May 10 | 30-days | 1,544 patients died, 2,058 discharged alive, 322 remained hospitalized |
| Canada | Mitra et al. (40) | 117 | Retrospective case series | Multi-center | Feb. 21 to Apr. 14 | 21-days | 18 patients died, 12 remained in ICU, 16 discharged from ICU but remained in hospital, and 71 discharged home |
| Brazil | Kurtz et al. (36) | 13,301 | Retrospective cohort study | Multi-center | Feb. 27 to Oct. 28 | 60-days | 1,785 patients died during hospitalization, 82 remained hospitalized |

Quality of Evidence
We evaluated the quality of evidence for 11 outcomes. Among them, two outcomes (18%) were graded as of moderate quality, four outcomes (36%) were graded as of low quality, and five (45%) outcomes were graded as of very low quality. We produced “GRADE evidence profiles,” and the details of GRADE can be found in Supplementary File 5.

Sensitivity Analysis
We conducted a sensitivity analysis on each result by omitting one study at a time. No study had a significant impact on the results of the meta-analysis (Supplementary File 6). A sensitivity analysis showed that all studies had little or acceptable effect on the total combined effect and that the results were stable.

DISCUSSION
The epidemic of COVID-19 is not stopping yet, especially in western countries. In previous reports, the incidence of...
mortality associated with critically ill patients remains poorly characterized. The novel findings in this study include the mortality of critically ill patients with laboratory-confirmed COVID-19 worldwide and the clinical interventions between surviving and non-surviving patients. The results show that all-cause mortality in ICU was 35% and mortality in hospital was 32% around the world for the year 2020. Differences were distinct between regions. The incidence of mortality that occurred in Southeast Asia was as high as 48%, followed by 39% in China and the Middle East. The lowest incidence occurred in America, which is 15%. The plausible explanations for the high mortality in China and other Asia countries are that the arrival and peak of the COVID-19 pandemic in Asia were earlier than in any region, and there was a shortage of ICU resources and experience. Moreover, data may be subject to patient selection for ICU admission, and some nations adopted a stringent strategy (19). In addition, mortality also relates to the time of follow-up. Some of the participants remained in the hospital in mechanical ventilation even at the end of follow-up. A recent meta-analysis reported that all-cause mortality associated with COVID-19 was 10% overall and 34% in patients admitted to the ICU (7), but most of their participants were from China; in this part, we had a close result. This new meta-analysis included more participants and covered much wider regions.
Early identification and prompt organ function support care would provide relief in critical cases (53). Among the included studies, five identified independent risk factors were associated with ICU mortality from laboratory parameters to clinical intervention, but the results are not the same (22, 25, 38, 50, 51, 54). We compared the baseline clinical characteristics between surviving and non-surviving patients. What we found based on the univariate analysis was that old age, APACHEII score, and SOFA score displayed consistency with multivariate Cox regression analysis in these five studies. Besides these, the PaO$_2$/FiO$_2$ ratio is an important index to reflect the severity of respiratory failure. Our results also showed that the PaO$_2$/FiO$_2$ ratio is helpful to predict the outcome.

With regard to the outcome of the clinical interventions of this meta-analysis, respiratory support is the most important part of life sustaining treatments. According to this study, HFNO during ICU hospitalization was more often used in non-surviving patients, and IMV was more often used in surviving patients. In previous studies, Auld and Capone (22, 54) reported that receipt of IMV was associated with a decreased likelihood of survival. When we discuss the difference of respiratory support, respiratory support as rescue therapy and the different severity levels of the two groups should not be ignored. HFNO and NIV can be safely used in COVID-19-related mild–moderate ARDS. In the study of non-COVID-19, HFNO has been associated with lower mortality in hypoxemic respiratory failure (55), but in some moderate–severe ARDS patients, HFNO or NIV should be used cautiously due to rapid progression to severe type and a high risk of treatment failure. According to Mukhtar et al. (56), the use of NIV with a predefined algorithm in subjects with moderate–severe COVID-19 ARDS was successful in 77% of the subjects. IMV is the most widely used therapy of severe hypoxemia. The population with IMV was larger than with non-invasive support in this study. The need of endotracheal intubation and invasive mechanical ventilation was eight times that of non-invasive ventilation in a previous study (30). Although the timing
of IMV is disputed, as evidenced in a recent publication, a meta-analysis reported that early intubation was not associated with improved survival (57). A latest meta-analysis (42) reported that the timing of intubation may not influence the mortality of critically ill patients with COVID-19. ECMO can be taken into consideration if the respiratory dysfunction of patients develop into severe ARDS, which cannot sustain with IMV, but this salvage treatment did not have a statistically significant difference between the two groups. In a study with a small sample (3), two of five patients survived by the support of ECMO. The appropriate time and eligible patients need to be evaluated.

In a previous research, as high as 31% of patients in a cohort developed severe acute kidney injury requiring renal replacement therapy during hospitalization (25). High creatinine level, AKI, and receipt of RRT were independent risk factors for the inhospital mortality of patients (22, 51, 58). Similarly, high-high sensitivity cardiac troponin I level, ischemic heart disease, cardiac injury, and vasopressor support were associated with death in patients (22, 38, 50, 51, 54). In the present study, the result shows that vasopressors and RRT were more often used in the surviving group.

There were some limitations in the current study that must be acknowledged. First is the high level of heterogeneity in the study. Plausible explanations for the heterogeneous risks of mortality include differences in age, nation and race, disease severity, and insufficient length of follow-up. It was difficult for us to control for the effects of these confounding factors. The heterogeneity in the component studies was addressed with random-effects models. Second, as for the secondary outcomes, is that this part of the clinical interventions was derived from an observational cohort, not a randomized controlled trial, so these results should be treated cautiously. The key purpose of this study is to describe the effect of the actual use of various clinical interventions in the surviving group and non-surviving group rather than the impact of individual measures on the prognosis. Third is that most studies were retrospective and recall bias might have occurred.

**CONCLUSIONS**

Mortality was high in critically ill patients with COVID-19 based on low-quality evidence, and intercontinental differences existed. The early identification of critical characteristics and the use of support care help to indicate the outcome of critically ill patients.

**DATA AVAILABILITY STATEMENT**

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

**AUTHOR CONTRIBUTIONS**

LL, YC, and ZQ: concept and design. LL: administrative, technical, or material support. ZQ and SL: statistical analysis and drafting of the manuscript. LL and YC: supervision. All authors critical revision of the manuscript for important intellectual content, acquisition, analysis, or interpretation of data.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.635560/full#supplementary-material

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