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Review Article

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# Comparison of Comorbidities in Relation to Critical Conditions among Coronavirus Disease 2019 Patients: A Network Meta-Analysis

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**Ethics approval and consent to participate**
All the data were obtained from published articles and were therefore not subject to ethics approval.

**Data Availability Statement**
Data for all the analyses are available in Supplementary Table 2.

**Conflict of Interest**
No conflict of interest.

## ABSTRACT

Severe illness and poor outcome are mainly associated with aging or certain medical comorbidities, especially chronic diseases. However, factors for unfavorable prognosis have not been well described owing to relatively small sample sizes and single-center reports. Therefore, this study aimed to compare the contribution of comorbidities in the development of critical conditions in coronavirus disease 2019 (COVID-19) patients. Pooled estimates of relative risks (RRs) and their 95% confidence intervals (CIs) were calculated by conducting a meta-analysis and network meta-analysis of 18 studies. Chronic obstructive pulmonary disease (COPD) was most strongly associated with the overall critical condition (RR = 4.22, 95% CI = 3.12 – 5.69), followed by cardiovascular disease (CVD) (RR = 3.00, 95% CI = 2.41 – 3.73), malignancy (RR = 2.91, 95% CI = 2.16 – 3.91), cerebrovascular accident (CVA) (RR = 2.86, 95% CI = 1.95 – 4.19), diabetes (RR = 2.10, 95% CI = 2.16 – 3.91), hypertension (RR = 2.02, 95% CI = 1.82 – 2.23), and chronic kidney disease (RR = 2.00, 95% CI = 1.36 – 2.94). The presence of comorbidities except for chronic liver disease and chronic kidney disease significantly increased the risk of severe infection, intensive care unit (ICU) admission, and cardiac injury in the subgroup analysis by types of critical conditions. Preexisting hypertension and diabetes additionally increased the risk of acute respiratory distress syndrome (ARDS). Among comorbidities, COPD had the highest probability of leading to severe COVID-19, ICU admission, and liver injury, while malignancy was most likely to cause ARDS and cardiac injury. In summary, preexisting COPD, CVD, CVA, hypertension, diabetes, and malignancy are more likely to worsen the progression of COVID-19, with severe infection, ICU admission requirement, and cardiac injury development.

**Keywords:** COVID-19; Comorbidity; Severity; Intensive care unit; Acute respiratory distress syndrome

## INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first reported in Wuhan in December 12, 2019, spread rapidly worldwide [1, 2]. Although stringent measures of isolation, social distancing, quarantine, and local/national lockdown for prevention were enacted to curb its spread in many countries [3, 4], this infectious

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disease emerged to become a global pandemic with approximately 11,169,802 confirmed cases and 528,232 deaths as of July 4, 2020 [5].

Coronavirus disease 2019 (COVID-19) patients are asymptomatic or mildly symptomatic in most cases; however, the presentation of critical cases is a concern as it leads to considerable number of deaths [6, 7]. In the epicenter of an outbreak region, the number of patients who required hospitalization and intensive treatment exceeded the capacity of the health system [8, 9]. Given that clinical evidence of current treatment options for COVID-19 is limited [10-12], it is essential to identify the characteristics of the population at high risk of developing critical conditions for designating priority checks, hospitalization, and more intensive management. Previous studies indicate that severe illness and poor outcome are mainly associated with aging [13] or certain medical comorbidities, especially chronic diseases [6, 14, 15]. However, factors for unfavorable prognosis have not been well described owing to relatively small sample sizes and single-center reports. In this study, we investigated possible comorbidities related to the progression of critical conditions among COVID-19 patients by conducting a meta-analysis and network meta-analysis (NMA) using eligible published data.

## MATERIALS AND METHODS

### 1. Search strategy

Relevant studies from PubMed, EMBASE, and the Cochrane Library databases were searched from the database's inception until April 17, 2020. We additionally reviewed the bibliographies of relevant publications. The keywords for literature search were as follows: ("COVID-19" OR "SARS-CoV-2") AND ("severe" OR "intensive care unit" OR "acute respiratory distress syndrome" OR "injury" OR "complication") AND ("condition" OR "characteristic" OR "epidemiology" OR "comorbidity"). The language of publication was restricted to English only.

### 2. Eligibility criteria

Eligibility criteria included all published case series, retrospective or prospective observational studies, and clinical trials that compare the prevalence of comorbidities between critical and non-critical patients admitted owing to COVID-19. The pre-specified underlying diseases were chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), cerebrovascular accident (CVA), hypertension, diabetes, chronic liver disease, chronic kidney disease, and malignancy. The pre-specified severity outcomes were severe infection, intensive care unit (ICU) admission, acute respiratory distress syndrome (ARDS), cardiac injury, and liver injury. The number of patients enrolled in each individual study was not limited. Reviews, letters, commentaries, conference abstracts, and editorials were not eligible for our study.

### 3. Data extraction

Relevant data were independently extracted by two investigators (TH and TTTA) according to the pre-determined search strategy. Disagreements between reviewers were discussed until a conclusion was reached. The following information was extracted: first author, recruitment period and location, median age (years), male proportion (%), number of patients having specific comorbidities in critical and non-critical groups.


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### 4. Statistical analysis

*1) Meta-analysis and meta-regression*

We performed a meta-analysis using the Mantel–Haenzel method to investigate the association between specific comorbidities and the risk of developing a critical condition among COVID-19 patients. We used data of patients with comorbidities in critical and non-critical groups from individual studies to calculate the pooled effect size of relative risk (RR) and its 95% confidence interval (CI). To measure the total variation due to heterogeneity, the Higgins $I^2$ statistic was computed where evidence was available for at least two studies [16]. The $I^2$ value when greater than 50% represents substantial heterogeneity [16]. Subgroup analyses were performed by types of critical conditions, including severe infection, ICU admission, ARDS, cardiac injury, and liver injury. Additionally, potential publication bias regarding studies in the final analysis was examined by performing Begg's funnel plot [17] and using Egger's test [18]. Furthermore, we tested the linear trend of RRs to determine the association between comorbidity and critical conditions according to the age and sex by performing a meta-regression [19].

*2) Network meta-analysis*

Details of the application of NMA are described in our previous study [20]. In general, a generalized linear model for Bayesian NMA was used to calculate the pairwise effect of comorbidities on the risk of severe infection, ICU admission, ARDS, cardiac injury, and liver injury.

First, we converted the arm-based data into contrast-based data of the natural logarithm RRs and their standard errors (SE) using the following formula:

$$RR = \frac{i/ni}{p/np};\ SE = \sqrt{\frac{1}{i} - \frac{1}{ni} + \frac{1}{p} - \frac{1}{np}}$$

where *ni* and *np* are total number of patients in the critical and non-critical groups, and *i* and *p* are the number of patients with comorbidities in the critical and non-critical groups, respectively.

The normal likelihood and identity link function were then used to generalize the pooled network estimates. Between-study heterogeneity was evaluated using the $I^2$ statistic as well. Last, the surface under the cumulative ranking curve (SUCRA) was calculated to address the contribution of each underlying disease to a critical condition.

All the statistical analyses were conducted using STATA SE version 14.0 (StataCorp, College Station, TX, USA) and R version 3.6.0. Package 'metan' was applied for meta-analysis and meta-regression and package 'gmtc' was applied for NMA.

### 5. Ethical consideration

All the data were obtained from published articles and were therefore not subject to ethics approval.

## RESULTS

### 1. Literature search

**Figure 1** shows the flow diagram of how we identified studies included in the final meta-analysis. A total of 1,916 articles were identified by searching PubMed (N = 1,492), Embase


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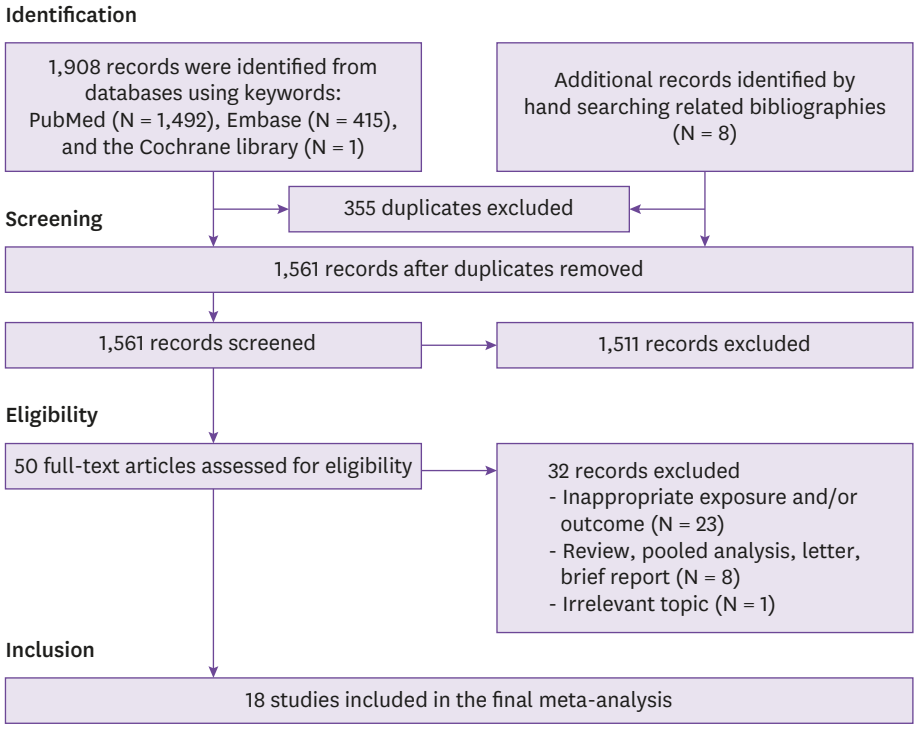


**Figure 1.** Flowchart of study selection.

(N = 415), the Cochrane Library (N = 1) databases and manually searching from relevant bibliographies (N = 8). We excluded 355 duplicated publications and additional 1,511 studies that did not satisfy the eligibility criteria. After reviewing full-texts of 50 articles, 18 observational studies were included in the final analysis [21-38].

## 2. Study characteristics

**Supplementary Table 1** and **2** show the general characteristics of studies in the final meta-analysis. The median age in the 18 studies was 38 – 64 years. All participants were recruited in China between December 2019 and February 2020. Among the 5,179 participants, there were 2,875 men, which accounted for 55.5% of the study population. Data on severe infection, ICU admission, ARDS, cardiac injury, and liver injury were available in 13, 4, 3, 2, and 2 studies, respectively. Most individual studies were observational studies, except the study by Liu Y et al [29].

## 3. Meta-analysis

**Table 1** summarizes the effect of comorbidities on the risk of developing critical conditions among COVID-19 patients and the results are detailed in **Supplementary Figure 1 – 8**. While COPD, CVD, CVA, hypertension, diabetes, chronic kidney disease, and malignancy were found to be significantly associated with an increased risk of the overall critical condition, with pooled RRs (95% CIs) of 4.22 (3.12 – 5.69), 3.00 (2.41 – 3.73), 2.86 (1.95 – 4.19), 2.02 (1.82 – 2.23), 2.10 (1.82 – 2.43), 2.00 (1.36 – 2.94), and 2.91 (2.16 – 3.91), respectively, the association between chronic liver disease and critical conditions was not significant (pooled RR = 1.05, 95% CI = 0.70 – 1.58). No publication bias was detected for studies revealing an association between comorbidities and critical conditions among COVID-19 patients ($P$ >0.05, **Fig. 2**).


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**Table 1.** Meta-analysis for the association among comorbidities and critical conditions among COVID-19 patients

| | Severe infection | | ICU admission | | ARDS | | Cardiac injury | | Liver injury | | Overall critical condition | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N ($I^2$) | RR (95% CI) | N ($I^2$) | RR (95% CI) | N ($I^2$) | RR (95% CI) | N ($I^2$) | RR (95% CI) | N ($I^2$) | RR (95% CI) | N ($I^2$) | RR (95% CI) |
| COPD | 10 (0%) | 3.97 (2.77 - 5.69) | 4 (0%) | 4.76 (2.44 - 9.27) | 1 (NA) | 3.00 (0.15 - 61.7) | 2 (0%) | 4.87 (1.79 - 13.3) | 1 (NA) | 11.0 (0.58 - 207) | 18 (0%) | 4.22 (3.12 - 5.69) |
| CVD | 9 (29.6%) | 3.15 (2.34 - 4.25) | 4 (0%) | 2.59 (1.61 - 4.16) | 2 (0%) | 2.51 (0.80 - 7.87) | 2 (57.2%) | 4.30 (2.56 - 7.20) | 2 (0%) | 0.90 (0.27 - 2.95) | 19 (15.7%) | 3.00 (2.41 - 3.73) |
| CVA | 5 (0%) | 2.72 (1.84 - 4.02) | | | 1 (NA) | 10.7 (1.06 - 108) | | | | | 6 (0%) | 2.86 (1.95 - 4.19) |
| Hypertension | 13 (49.8%) | 1.90 (1.68 - 2.16) | 4 (1.9%) | 2.64 (2.03 - 3.44) | 3 (0%) | 1.72 (1.10 - 2.68) | 2 (0%) | 2.51 (1.93 - 3.26) | 2 (2.3%) | 1.00 (0.42 - 2.37) | 24 (42.2%) | 2.02 (1.82 - 2.23) |
| Diabetes | 13 (51.1%) | 2.01 (1.70 - 2.39) | 4 (44.5%) | 2.44 (1.66 - 3.60) | 3 (0%) | 3.35 (1.70 - 6.59) | 2 (0%) | 2.04 (1.27 - 3.27) | 2 (0%) | 1.06 (0.31 - 3.64) | 24 (32.3%) | 2.10 (1.82 - 2.43) |
| Chronic liver disease | 8 (29.1%) | 1.10 (0.71 - 1.70) | 3 (0%) | 0.50 (0.12 - 2.06) | | | 1 (NA) | 4.07 (0.58 - 28.5) | | | 12 (17.8%) | 1.05 (0.70 - 1.58) |
| Chronic kidney disease | 7 (0%) | 2.09 (1.33 - 3.28) | 3 (0%) | 1.56 (0.47 - 5.12) | 1 (NA) | 1.00 (0.08 - 12.6) | 1 (NA) | 2.26 (0.78 - 6.57) | | | 12 (0%) | 2.00 (1.36 - 2.94) |
| Malignancy | 9 (8.0%) | 2.45 (1.67 - 3.58) | 4 (31.5%) | 2.26 (1.27 - 4.01) | 1 (NA) | 32.2 (4.28 - 241) | 1 (NA) | 14.3 (3.02 - 67.4) | | | 15 (37.7%) | 2.91 (2.16 - 3.91) |

COVID-19, coronavirus disease 2019; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; N, number of studies; RR, relative risk; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CVA, cerebrovascular accident; NA, not applicable.

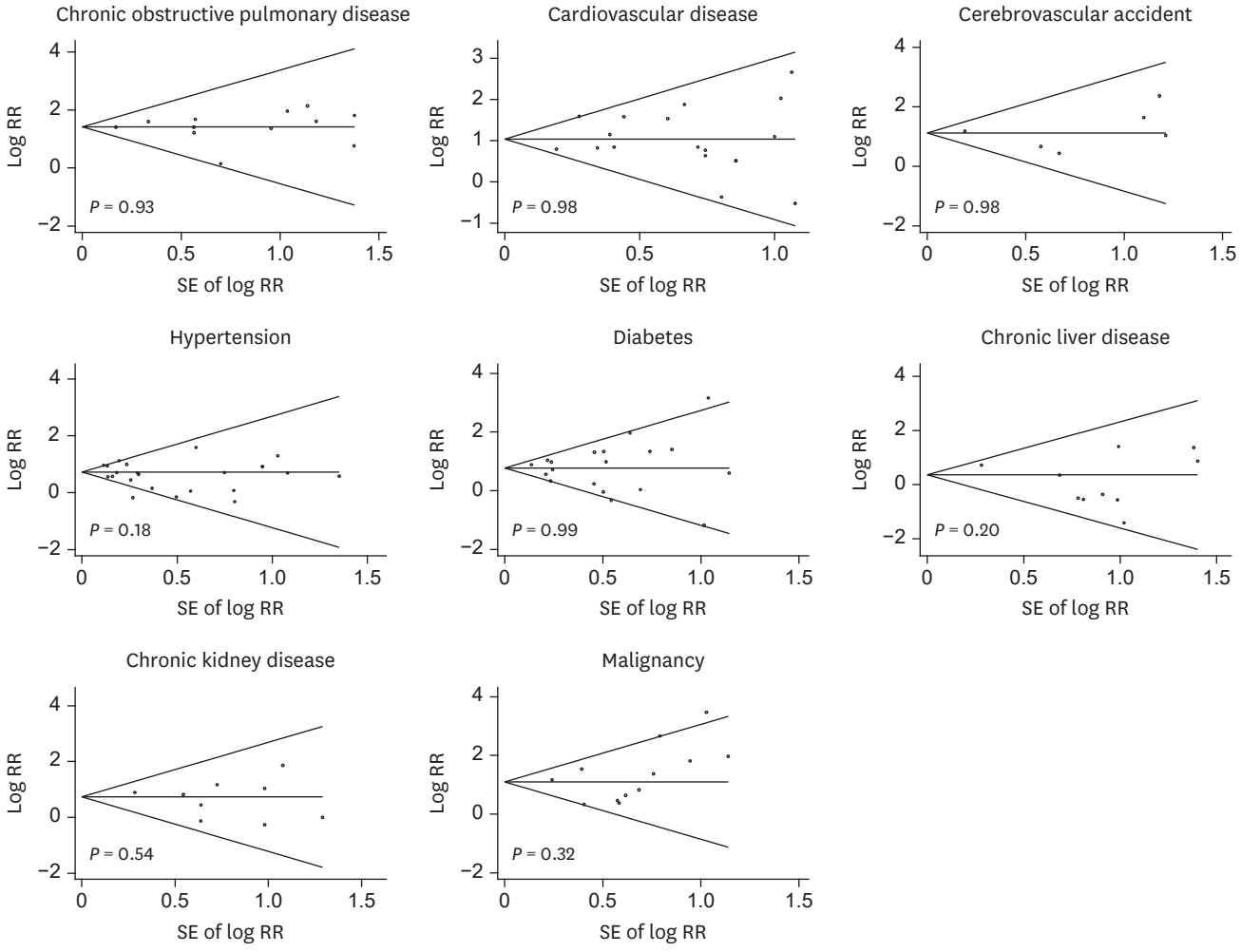


**Figure 2.** Publication bias for different comorbidities and their association between critical conditions among COVID-19 patients.
COVID-19, coronavirus disease 2019; RR, relative risk; SE, standard error.


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**Table 2.** Meta-regression for the association among comorbidities and critical conditions among COVID-19 patients

| | Age (years) | | Male (%) | |
|---|---|---|---|---|
| | Coefficient | *P*-value | Coefficient | *P*-value |
| COPD | −0.020 | 0.46 | 0.010 | 0.79 |
| CVD | 0.021 | 0.20 | −0.046 | 0.03 |
| CVA | −0.019 | 0.76 | 0.090 | 0.40 |
| Hypertension | −0.009 | 0.58 | −0.009 | 0.62 |
| Diabetes | −0.039 | 0.002 | −0.002 | 0.93 |
| Chronic liver disease | −0.023 | 0.59 | −0.079 | 0.38 |
| Chronic kidney disease | −0.025 | 0.44 | 0.028 | 0.60 |
| Malignancy | −0.037 | 0.15 | −0.006 | 0.92 |

COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CVA, cerebrovascular accident.

In the subgroup meta-analysis by types of critical conditions, similar significant findings were found for COPD, CVD, CVA, hypertension, diabetes, and malignancy with respect to associations with severe infection, ICU admission, and cardiac injury (**Table 1**). CVA (RR = 10.7, 95% CI = 1.06 – 108), hypertension (pooled RR = 1.72, 95% CI = 1.10 – 2.68), and diabetes (pooled RR = 3.35, 95% CI = 1.70 – 6.59) were additionally observed to increase the risk of ARDS. Chronic kidney disease was associated with a 109% increased risk of severe infection (pooled RR = 2.09, 95% CI = 1.33 – 3.28).

## 4. Meta-regression

The linear association between the log RR measurements and covariates of age and sex is shown in **Table 2**. The log RR for the association between CVD and critical conditions significantly decreased by 0.046 ($P$ = 0.03) for each 1% increase of men in the study population. The log RR for the association between diabetes and critical conditions decreased by 0.039 ($P$ = 0.002) for each 1-year increase in median age in the study population.

## 5. Network meta-analysis

The network geometry according to different types of severity conditions is shown in **Figure 3**. Overall, the risk of underlying hypertension and diabetes was commonly elucidated for all severity outcomes. Additionally, data on the effect of COPD and CVD on ICU admission and cardiac injury were frequently reported, whereas those on the effect of CVD on liver injury was seldom reported.

**Table 3** shows the comparative effect of comorbidities on the risk of critical conditions in patients with COVID-19. Similar to findings from the meta-analysis, underlying diseases of COPD, CVD, CVA, hypertension, diabetes, chronic kidney disease, and malignancy were observed to significantly lead to severe COVID-19, with RRs (95% CIs) of 4.05 (2.62 – 6.24), 3.01 (2.04 – 4.47), 2.81 (1.64 – 4.61), 1.80 (1.39 – 2.29), 2.02 (1.52 – 2.67), 2.12 (1.25 – 3.59), and 2.65 (1.69 – 4.19), respectively. The effect of COPD, CVD, hypertension, diabetes, and malignancy on ICU admission was also observed, with RRs (95% CIs) of 4.87 (2.32 – 9.85), 2.48 (1.43 – 4.30), 2.55 (1.65 – 3.61), 2.62 (1.56 – 4.38), and 2.66 (1.39 – 5.03), respectively. Including CVA in the NMA of the ARDS outcome resulted in extremely high point estimates and SE (data not shown) owing to the effect of a single study [36]; thus, CVA was excluded in the NMA of the association between comorbidities and ARDS. Therefore, diabetes was observed to be associated with an approximate 2-fold increased risk of ARDS progression (RR = 3.22, 95% CI = 1.25 – 8.28).

In the pairwise effect of comorbidities on critical conditions, COPD was associated with a significantly higher risk of severe infection than hypertension (RR = 2.25, 95% CI = 1.38


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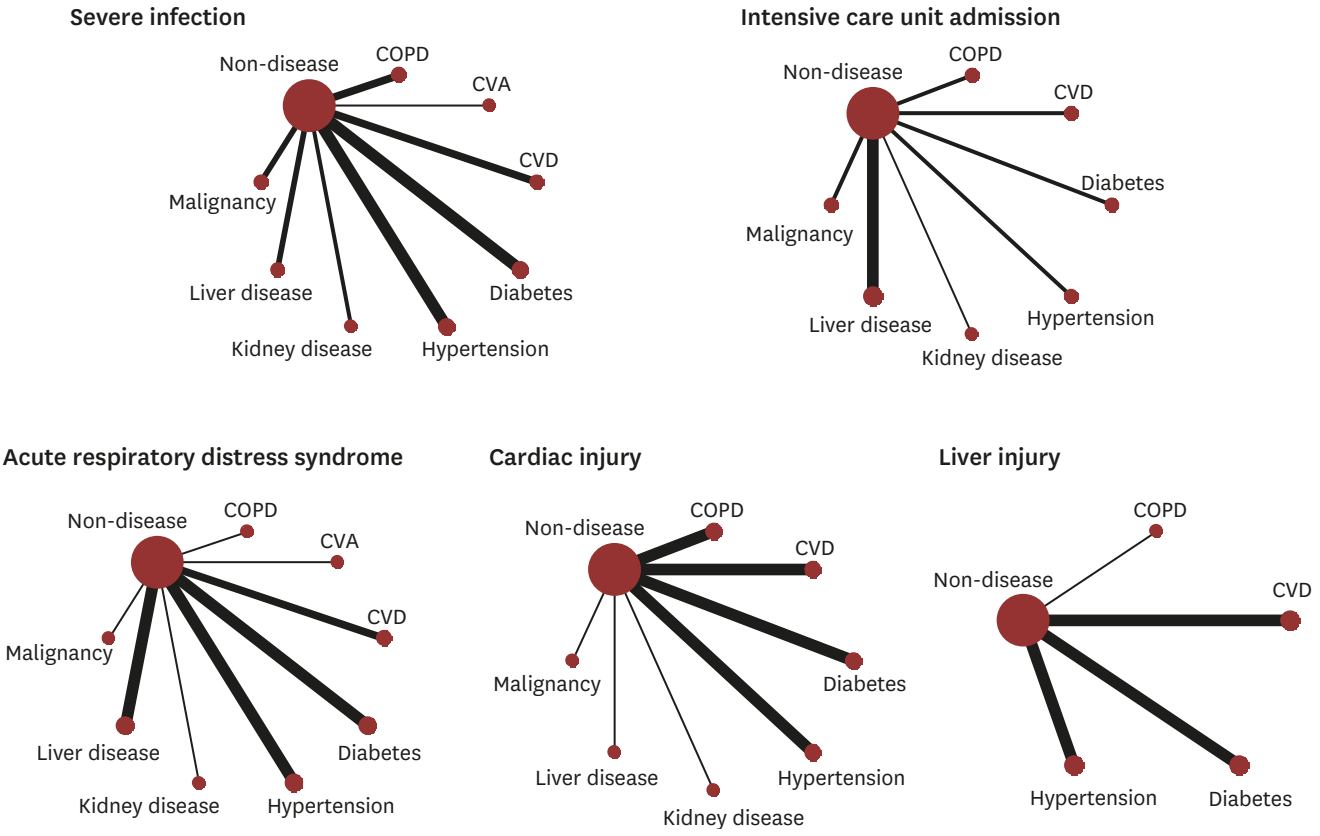


**Figure 3.** Network geometry of associations among comorbidities and critical conditions.
Thickness of edge is proportional to the number of direct underlying disease comparisons. Size of node is proportional to the number of direct underlying disease comparisons included in that node.
COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CVD, cardiovascular disease.

**Table 3.** Network meta-analysis for the association of comorbidities with critical conditions and surface under the cumulative ranking curve values of comorbidities

| | COPD | CVD | CVA | Hypertension | Diabetes | Liver disease | Kidney disease | Malignancy | None | SUCRA |
|---|---|---|---|---|---|---|---|---|---|---|
| Severe infection ($I^2$ = 30%) | | | | | | | | | | |
| COPD | | 0.74 (0.41 - 1.35) | 0.69 (0.34 - 1.35) | 0.44 (0.27 - 0.73) | 0.50 (0.30 - 0.83) | 0.31 (0.16 - 0.61) | 0.52 (0.26 - 1.03) | 0.66 (0.35 - 1.21) | 0.25 (0.16 - 0.38) | 0.98 |
| CVD | 1.34 (0.74 - 2.41) | | 0.93 (0.47 - 1.74) | 0.60 (0.37 - 0.93) | 0.67 (0.41 - 1.07) | 0.42 (0.21 - 0.80) | 0.70 (0.36 - 1.34) | 0.88 (0.48 - 1.58) | 0.33 (0.22 - 0.49) | 0.71 |
| CVA | 1.44 (0.74 - 2.91) | 1.07 (0.57 - 2.13) | | 0.64 (0.37 - 1.15) | 0.72 (0.41 - 1.33) | 0.45 (0.22 - 0.94) | 0.75 (0.37 - 1.60) | 0.94 (0.49 - 1.92) | 0.36 (0.22 - 0.61) | 0.78 |
| Hypertension | 2.25 (1.38 - 3.74) | 1.67 (1.07 - 2.70) | 1.56 (0.87 - 2.73) | | 1.12 (0.78 - 1.65) | 0.71 (0.39 - 1.26) | 1.18 (0.66 - 2.13) | 1.47 (0.89 - 2.50) | 0.55 (0.44 - 0.72) | 0.32 |
| Diabetes | 2.01 (1.20 - 3.37) | 1.49 (0.93 - 2.45) | 1.40 (0.75 - 2.46) | 0.89 (0.61 - 1.29) | | 0.63 (0.34 - 1.13) | 1.05 (0.58 - 1.91) | 1.31 (0.78 - 2.25) | 0.50 (0.37 - 0.66) | 0.41 |
| Liver disease | 3.19 (1.63 - 6.42) | 2.37 (1.25 - 4.71) | 2.21 (1.06 - 4.60) | 1.42 (0.79 - 2.57) | 1.59 (0.89 - 2.94) | | 1.66 (0.80 - 3.57) | 2.08 (1.05 - 4.29) | 0.79 (0.47 - 1.36) | 0.15 |
| Kidney disease | 1.91 (0.97 - 3.81) | 1.42 (0.75 - 2.78) | 1.33 (0.62 - 2.72) | 0.85 (0.47 - 1.51) | 0.95 (0.52 - 1.74) | 0.60 (0.28 - 1.25) | | 1.25 (0.63 - 2.53) | 0.47 (0.28 - 0.80) | 0.46 |
| Malignancy | 1.52 (0.82 - 2.87) | 1.14 (0.63 - 2.07) | 1.06 (0.52 - 2.05) | 0.68 (0.40 - 1.13) | 0.76 (0.44 - 1.28) | 0.48 (0.23 - 0.95) | 0.80 (0.40 - 1.60) | | 0.38 (0.24 - 0.59) | 0.68 |
| None | 4.05 (2.62 - 6.24) | 3.01 (2.04 - 4.47) | 2.81 (1.64 - 4.61) | 1.80 (1.39 - 2.29) | 2.02 (1.52 - 2.67) | 1.27 (0.74 - 2.13) | 2.12 (1.25 - 3.59) | 2.65 (1.69 - 4.19) | | 0.01 |
| ICU admission ($I^2$ = 0%) | | | | | | | | | | |
| COPD | | 0.51 (0.21 - 1.30) | | 0.52 (0.23 - 1.16) | 0.53 (0.23 - 1.33) | 0.11 (0.02 - 0.58) | 0.35 (0.08 - 1.44) | 0.55 (0.21 - 1.41) | 0.21 (0.10 - 0.43) | 0.95 |

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**Table 3.** (Continued) Network meta-analysis for the association of comorbidities with critical conditions and surface under the cumulative ranking curve values of comorbidities

| | COPD | CVD | CVA | Hypertension | Diabetes | Liver disease | Kidney disease | Malignancy | None | SUCRA |
|---|---|---|---|---|---|---|---|---|---|---|
| CVD | 1.96 (0.77 - 4.76) | | | 1.03 (0.50 - 1.93) | 1.06 (0.49 - 2.23) | 0.21 (0.04 - 1.05) | 0.67 (0.16 - 2.60) | 1.08 (0.46 - 2.46) | 0.40 (0.23 - 0.70) | 0.58 |
| Hypertension | 1.92 (0.86 - 4.42) | 0.97 (0.52 - 2.00) | | | 1.03 (0.55 - 1.99) | 0.20 (0.04 - 1.02) | 0.66 (0.17 - 2.53) | 1.06 (0.50 - 2.18) | 0.39 (0.28 - 0.61) | 0.60 |
| Diabetes | 1.87 (0.75 - 4.42) | 0.95 (0.45 - 2.04) | | 0.97 (0.50 - 1.83) | | 0.20 (0.04 - 1.02) | 0.64 (0.15 - 2.52) | 1.02 (0.44 - 2.33) | 0.38 (0.23 - 0.64) | 0.63 |
| Liver disease | 9.52 (1.72 - 49.2) | 4.85 (0.96 - 22.6) | | 4.94 (0.98 - 22.8) | 5.09 (0.98 - 24.2) | | 3.24 (0.44 - 23.0) | 5.30 (0.98 - 26.0) | 1.96 (0.41 - 8.49) | 0.06 |
| Kidney disease | 2.89 (0.69 - 13.1) | 1.48 (0.38 - 6.16) | | 1.52 (0.39 - 5.87) | 1.57 (0.40 - 6.47) | 0.31 (0.04 - 2.25) | | 1.61 (0.38 - 6.72) | 0.60 (0.17 - 2.27) | 0.40 |
| Malignancy | 1.81 (0.71 - 4.77) | 0.93 (0.41 - 2.18) | | 0.95 (0.46 - 2.00) | 0.98 (0.43 - 2.27) | 0.19 (0.04 - 1.02) | 0.62 (0.15 - 2.65) | | 0.38 (0.20 - 0.72) | 0.64 |
| None | 4.87 (2.32 - 9.85) | 2.48 (1.43 - 4.30) | | 2.55 (1.65 - 3.61) | 2.62 (1.56 - 4.38) | 0.51 (0.12 - 2.42) | 1.67 (0.44 - 5.99) | 2.66 (1.39 - 5.03) | | 0.15 |
| ARDS ($I^2$ = 0%) | | | | | | | | | | |
| COPD | | 0.85 (0.03 - 25.7) | | 0.54 (0.02 - 14.0) | 1.06 (0.04 - 28.0) | | 0.34 (0.01 - 22.0) | 9.70 (0.24 - 466) | 0.33 (0.01 - 7.92) | 0.54 |
| CVD | 1.17 (0.04 - 38.3) | | | 0.62 (0.13 - 3.06) | 1.25 (0.24 - 6.52) | | 0.40 (0.02 - 8.02) | 11.8 (0.76 - 179) | 0.39 (0.10 - 1.53) | 0.54 |
| Hypertension | 1.87 (0.07 - 47.7) | 1.61 (0.33 - 7.75) | | | 1.99 (0.58 - 6.52) | | 0.63 (0.04 - 10.2) | 18.6 (1.79 - 218) | 0.62 (0.28 - 1.36) | 0.38 |
| Diabetes | 0.95 (0.04 - 25.9) | 0.80 (0.15 - 4.21) | | 0.50 (0.15 - 1.72) | | | 0.32 (0.02 - 5.30) | 9.36 (0.86 - 116) | 0.31 (0.12 - 0.80) | 0.64 |
| Kidney disease | 2.98 (0.05 - 195) | 2.52 (0.12 - 54.2) | | 1.58 (0.10 - 26.7) | 3.15 (0.19 - 55.9) | | | 30.1 (0.94 - 1032) | 0.97 (0.07 - 14.7) | 0.28 |
| Malignancy | 0.10 (0.00 - 4.08) | 0.08 (0.01 - 1.31) | | 0.05 (0.00 - 0.56) | 0.11 (0.01 - 1.17) | | 0.03 (0.00 - 1.07) | | 0.03 (0.00 - 0.30) | 0.96 |
| None | 2.99 (0.13 - 72.0) | 2.58 (0.65 - 10.3) | | 1.61 (0.73 - 3.53) | 3.22 (1.25 - 8.28) | | 1.03 (0.07 - 14.8) | 30.0 (3.30 - 306) | | 0.15 |
| Cardiac injury ($I^2$ = 27%) | | | | | | | | | | |
| COPD | | 0.61 (0.02 - 6.05) | | 0.39 (0.01 - 4.19) | 0.37 (0.02 - 4.81) | 0.71 (0.02 - 22.0) | 0.41 (0.01 - 8.45) | 2.48 (0.07 - 63.5) | 0.18 (0.02 - 1.13) | 0.71 |
| CVD | 1.65 (0.17 - 52.4) | | | 0.63 (0.05 - 11.4) | 0.58 (0.05 - 13.4) | 1.21 (0.05 - 58.3) | 0.66 (0.04 - 24.7) | 4.14 (0.20 - 177) | 0.29 (0.06 - 3.03) | 0.55 |
| Hypertension | 2.59 (0.24 - 68.0) | 1.60 (0.09 - 20.6) | | | 0.92 (0.08 - 18.1) | 1.87 (0.07 - 79.4) | 1.05 (0.05 - 33.4) | 6.52 (0.29 - 232) | 0.44 (0.08 - 4.01) | 0.39 |
| Diabetes | 2.73 (0.21 - 59.8) | 1.73 (0.07 - 18.2) | | 1.09 (0.06 - 13.2) | | 1.99 (0.06 - 68.6) | 1.11 (0.04 - 28.9) | 6.86 (0.26 - 199) | 0.49 (0.07 - 3.47) | 0.37 |
| Liver disease | 1.41 (0.05 - 63.3) | 0.83 (0.02 - 21.7) | | 0.53 (0.01 - 15.2) | 0.50 (0.01 - 16.7) | | 0.57 (0.01 - 28.0) | 3.53 (0.06 - 205) | 0.25 (0.01 - 4.82) | 0.58 |
| Kidney disease | 2.46 (0.12 - 85.0) | 1.51 (0.04 - 26.3) | | 0.96 (0.03 - 18.8) | 0.90 (0.03 - 22.9) | 1.77 (0.04 - 90.1) | | 6.20 (0.14 - 263) | 0.44 (0.03 - 5.85) | 0.42 |
| Cancer | 0.40 (0.02 - 15.1) | 0.24 (0.01 - 5.01) | | 0.15 (0.00 - 3.49) | 0.15 (0.01 - 3.91) | 0.28 (0.00 - 15.4) | 0.16 (0.00 - 6.96) | | 0.07 (0.00 - 1.07) | 0.86 |
| None | 5.68 (0.89 - 54.6) | 3.50 (0.33 - 16.6) | | 2.25 (0.25 - 11.9) | 2.05 (0.29 - 14.2) | 4.04 (0.21 - 80.4) | 2.28 (0.17 - 29.5) | 14.0 (0.93 - 223) | | 0.12 |
| Liver injury ($I^2$ = 0%) | | | | | | | | | | |
| COPD | | 0.09 (0.00 - 4.67) | | 0.10 (0.00 - 5.42) | 0.09 (0.00 - 5.33) | | | | 0.09 (0.00 - 2.93) | 0.90 |
| CVD | 10.9 (0.21 - 541) | | | 1.16 (0.11 - 14.7) | 1.04 (0.08 - 13.3) | | | | 0.96 (0.16 - 5.51) | 0.39 |
| Hypertension | 9.54 (0.18 - 414) | 0.86 (0.07 - 9.18) | | | 0.89 (0.06 - 10.5) | | | | 0.84 (0.14 - 3.97) | 0.46 |
| Diabetes | 10.9 (0.19 - 568) | 0.96 (0.08 - 13.2) | | 1.12 (0.10 - 15.6) | | | | | 0.93 (0.14 - 6.20) | 0.41 |
| None | 11.7 (0.34 - 380) | 1.04 (0.18 - 6.36) | | 1.20 (0.25 - 7.33) | 1.07 (0.16 - 7.37) | | | | | 0.36 |

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CVA, cerebrovascular accident; SUCRA, surface under the cumulative ranking curve; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.


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– 3.74), diabetes (RR = 2.01, 95% CI = 1.20 – 3.37), and chronic liver disease (RR = 3.19, 95% CI = 1.63 – 6.42). Additionally, the severe infection risk among patients with CVD was significantly higher than those with hypertension (RR = 1.67, 95% CI = 1.07 – 2.70) and chronic liver disease (RR = 2.37, 95% CI = 1.25 – 4.71). Furthermore, underlying CVA and malignancy were associated with a higher risk of severe infection than chronic liver disease (RR = 2.21, 95% CI = 1.06 – 4.60 and RR = 2.08, 95% CI = 1.05 – 4.29, respectively). Regarding ICU admission, preexisting COPD was shown to have a higher risk than chronic liver disease (RR = 9.52, 95% CI = 1.72 – 49.2).

Among comorbidities, COPD was revealed to have the highest probability of leading to severe COVID-19 (SUCRA = 0.98), ICU admission (SUCRA = 0.95), and liver injury (SUCRA = 0.90), while malignancy was observed to most likely contribute to the progression of ARDS (SUCRA = 0.96) and cardiac injury (SUCRA = 0.86).

## DISCUSSION

The effect of underlying diseases on the severity of COVID-19 has been previously reported in other systematic reviews and meta-analyses [39, 40]. However, only associations of comorbidities including COPD, CVD, hypertension, and diabetes were investigated with disease severity and ICU admission, but not for other outcomes. In the current systematic review, meta-analysis, and NMA of 18 studies, which included a total of 5,179 patients with COVID-19, we additionally included comorbidities of CVA, chronic liver disease, chronic kidney disease, and malignancy as well as critical conditions of ARDS, cardiac injury, and liver injury in the final analysis. Furthermore, we examined the comparative effect of comorbidities on each critical condition of COVID-19 in the NMA approach.

The risk of COPD, CVD, hypertension, and diabetes leading to severe COVID-19 and ICU admission among patients with COVID-19 was similar to the finding from a recent meta-analysis, which included 4 of the 18 studies in our meta-analysis [40]. Although comorbidities were consistently found to be associated with severe infection and ICU admission, we observed substantially smaller pooled effect sizes in our analysis (*e.g.* 3.97 *vs.* 6.42 for COPD and severe infection risk, and 4.76 versus 17.8 for COPD and ICU admission risk) [40]. The high expression of angiotensin-converting enzyme 2 (ACE-2) receptors on the surface of epithelial cells in the lung, heart, kidney, and blood vessels could be an important key since SARS-CoV-2 binds to this receptor for cell entry. With a specific binding domain that shows a higher affinity for the lower respiratory system than other coronaviruses [41], SAR-CoV-2 tends to cause lung infection and ARDS. COPD patients might be more susceptible to acquiring pneumonia because of long-term bronchitis with persistent mucus secretion, elevated inflammation, and activated immune response cascade. Besides, symptoms of pneumonia might be worse in patients with community acquired pneumonia or COPD [42-44].

It is clear from our data that having CVD might increase the risk of severity of COVID-19. A summary report from the Chinese Center for Disease Control and Prevention also indicates that the mortality rate among COVID-19 patients with CVD was 10.5%, whereas that of the overall population was only 2.3% [6]. Activating the ACE-2 signaling pathway and the use of CVD treatment including ACE inhibitors and angiotensin receptor blockers (ARBs) during COVID-19 might be crucial for ensuring better outcomes [45]. These above drugs increase


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ACE-2 expression levels in several tissues, including cardiomyocytes [46, 47]. Subsequently, there is a potentially increased risk of developing COVID-19 or a critical condition in patients with ACE inhibitors/ARBs treatment history. Additionally, antivirals or other medications for COVID-19 might, in turn, worsen CVD symptoms to form a virtuous circle of critical progression. Lopinavir/ritonavir and hydroxychloroquine, which have been commonly used as "off-label" drugs for the treatment of COVID-19, were reported to have the undesirable effect of QT interval prolongation and drug-related sudden cardiac death [48]. This might not be clear whether the progression of cardiac injury was due to comorbidities or treatment-induced adverse events. Till date, adequate data are unavailable to strengthen this hypothesis, and the mechanism of critical progression in CVD patients has not been well established. Given that COPD and CVD are considered part of a multimorbidity disease network [49, 50], findings from our study highlighted the importance of the control strategy in COVID-19 patients with preexisting COPD and CVD.

It is noteworthy that including multiple studies in the final analysis allowed us to detect the significant effect of diabetes on the risk of severe infection and ICU admission, which was borderline (pooled RR = 3.12) for diabetes and severe infection risk or non-significant (pooled RR = 2.72) for diabetes and ICU admission in the study by Jian et al. [40]. Similarly consistent findings for the effect of diabetes on disease severity was also reported by Liu et al., with pooled RR = 2.61 [39]. Diabetes has been reported to be related to unfavorable outcomes in other viral infections including influenza, SARS-CoV, and Middle East Respiratory Syndrome (MERS)-CoV [51-53]. Several factors, including decreased chemotaxis, impaired phagocytic cell function, reduced T cell-mediated immune response, and inhibited microbial clearance, cause inappropriate immune response in patients with poorly controlled diabetes [54, 55]. Furthermore, as a potential mechanism, the amplification of pro-inflammatory cytokine response in diabetes, such as interferons, interleukins, and the tumor necrosis factor, might further be enhanced and result in a cytokine storm [56] seen in patients with critical COVID-19 symptoms. What needs to be clarified is whether the relationship between diabetes and severity of COVID-19 is independent from other confounding factors, including aging and renal comorbidities that are seen coexisting in both conditions. Besides, medications used in the ICU (such as steroids), which might also contribute to the unfavorable outcome of COVID-19 patients with preexisting diabetes, should be investigated.

According to another meta-analysis on preexisting hypertension and the critical condition of COVID-19 that included 10 of the 18 studies of our meta-analysis, hypertension was found to be associated with a nearly 2.5-fold increased risk of the overall critical condition (pooled odds ratio = 2.49), which was also higher than our estimate [57]. Experts suggest that the use of antihypertensive drugs including ACE inhibitors and ARBs should also be observed for further investigations [58].

In the current study, we additionally performed a subgroup analysis by types of critical conditions, especially ARDS, cardiac injury, and liver injury, which have not been investigated in previous studies. The effect of chronic liver disease, chronic kidney disease, and malignancy on critical conditions have been analyzed for the first time in our study, with an increased risk of severe infection among preexisting chronic kidney disease (pooled RR = 2.09) and malignancy (pooled RR = 2.45). Data show that patients with CKD are likely to be vulnerable to COVID-19 [59]. It might be explained by their impaired immune system [59, 60] and the use of ACE inhibitors and ARBs. However, discontinuation of these agents

is not recommended [61]. Furthermore, recent reports have demonstrated poor prognosis of COVID-19 patients with history of or active malignancy [62-64]. Here, cancer-associated immune deficiency could be one of the main mechanisms. Interestingly, one prospective cohort study from the United Kingdom illustrated that there was no significant difference in mortality among COVID-19 patients who received different anticancer treatments, including cytotoxic chemotherapy, radiation, targeted therapy, hormone therapy, and immunotherapy after adjusting for age, gender, and comorbidity [65]. Nevertheless, more data regarding cancer heterogeneity related to types and stages should be analyzed to better understand the impact of COVID-19 among cancer patients.

Although the current meta-analysis and NMA evaluated the comparative effect of several comorbidities on various critical conditions of COVID-19 patients, the analysis was limited owing to the lack of age- and sex-adjusted data with respect to each comorbidity and critical condition. However, in our meta-regression, significant RRs per 1-year increase in median age and 1% increase in men in the study population were seen for diabetes ($P = 0.002$) and CVD ($P = 0.03$) only. Further, we were not able to investigate the effect of coexisting chronic diseases because of the unavailability of primary data. Last, all individual studies were conducted on the Chinese population, which may limit generalization of the findings.

In summary, the findings from this meta-analysis indicate that preexisting COPD, CVD, CVA, hypertension, diabetes, and malignancy tend to worsen the progression of COVID-19 to severe infection, ICU admission requirement, and cardiac injury development. Disease control strategies are strongly needed to avoid critical conditions among patients with underlying COPD and CVD.

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## SUPPLEMENTARY MATERIALS

### Supplementary Table 1
Baseline characteristics of individual studies

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### Supplementary Table 2
Comorbidity distribution according to critical conditions from individual studies

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### Supplementary Figure 1
Fixed-effects meta-analysis of chronic obstructive pulmonary disease and critical conditions among COVID-19 patients.

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**Supplementary Figure 2**
Fixed-effects meta-analysis of cardiovascular disease and critical conditions among COVID-19 patients.

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**Supplementary Figure 3**
Fixed-effects meta-analysis of cerebrovascular accident and critical conditions among COVID-19 patients.

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**Supplementary Figure 4**
Fixed-effects meta-analysis of hypertension and critical conditions among COVID-19 patients.

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**Supplementary Figure 5**
Fixed-effects meta-analysis of diabetes and critical conditions among COVID-19 patients.

Click here to view

**Supplementary Figure 6**
Fixed-effects meta-analysis of chronic liver disease and critical conditions among COVID-19 patients.

Click here to view

**Supplementary Figure 7**
Fixed-effects meta-analysis of chronic kidney disease and critical conditions among COVID-19 patients.

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**Supplementary Figure 8**
Fixed-effects meta-analysis of malignancy and critical conditions among COVID-19 patients.

Click here to view

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