The risk factors for severe patients with COVID-19 in China: A systematic review and meta-analysis

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Abstract
COVID-19 is spreading exponentially. In order to optimize medical resources allocation and reduce mortality, biomarkers are needed to differentiate between COVID-19 patients with or without severe diseases early as possible. We searched Ovid MEDLINE(R), Ovid EMBASE, CNKI, Wanfang, VIP databases, the Cochrane Library, and medRxiv for primary articles in English or Chinese up to March 30, 2020 to systematically evaluate the risk factors for severe patients in China. Mean difference or standardize mean difference and odds ratio with 95% confidence intervals were performed by random-effect or fixed models in cases of significant heterogeneity between studies. We used I² to evaluate the magnitude of heterogeneity. A total of 54 articles involving about 7000 patients were eligible for this meta-analysis. In total, 52 of 67 parameters between severe and non-severe cases were significantly different. Elderly male patients with comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease (COPD) cardiovascular disease, cerebrovascular disease, chronic kidney disease, or cancer were more common in severe COVID-19 patients. Regarding the clinical manifestations on admission, fever, cough, expectoration, dyspnea, chest distress, fatigue, headache, chills, anorexia, or abdominal pain were more prevalent in severe COVID-19 patients. The results of the clinical examination showed that high C-reactive protein (CRP), high lactate dehydrogenase (LDH), high D-dimer, and decreased T lymphocytes cells subsets, decreased lymphocyte may help clinicians predict the progression of severe illness in patients with COVID-19. Our findings will be conducive for clinician to stratify the COVID-19 patients to reduce mortality under the relative shortage of medical resources.

Keywords
clinical features, coronavirus disease 2019, meta-analysis, risk factors, severity

Introduction
On 31 December 2019, a cluster of pneumonia of unknown cause were reported in Wuhan, Hubei Province, China. The pneumonia named for coronavirus disease 2019 (COVID-19) was sustained by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Nowadays, the pandemic coronavirus spread across the world exponentially and the global number of cases are rising sharply, especially in United States, Italy, and Turkey. There have been 3,435,894 confirmed
cases, including 239,604 deaths in 213 countries or territories according to the report of the World Health Organization (WHO) until 4 May 2020.¹

As COVID-19 pandemic rages on in the world, our understanding of the new disease is still very limited. So far, the pathogenesis of COVID-19 remains unknown, and there have been no specific drugs or vaccine for SARS-CoV-2. Therefore, the WHO endorses supportive care only.² A wide range of variability in the case fatality rate (CFR) of COVID-19 was observed in different places. A report based on 72,314 COVID-19 cases published by the Chinese Center for Disease Control and Prevention showed the overall CFR was 2.3%, which was 49.0% among critical cases.³ Therefore, facing the global outbreak of COVID-19 and the relative shortage of medical resources, it is essential to distinguish severe patients from infected cases as early as possible for reducing the CFR.

Since the COVID-19 outbreak, a large number of research reports and case series have already been published in major international scientific and medical journals. Whereas all available clinical studies have significant limitations in sample size and the same patient might be reported in more than one article.⁴ It is obligatory to take a deeper look at the clinical evidence, because the overlapped data could affect the real understanding of this infectious disease. In addition, previous systematic reviews have shown inconclusive or incomplete results due to limited sample size and statistical power, which missed important clinical manifestation such as fatigue, cough, anorexia.⁵⁻⁷ To identify the severe patients from infected cases and address the limitations of the previous reviews, we performed a systematic literature review with meta-analysis to consolidate what has been learned from each study. All documents reporting information on the clinical manifestation, comorbidities and the laboratory characteristics in COVID-19 patients with a clinically validated definition of severe disease were finally included to evaluate the risk factors of COVID-19 in China.

Methods
This article was evaluated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO #CRD42020177229) and was available online. Prior to the analysis, we conducted subgroup analyzes by age group, and each of the variables of interest including the proportion of males, region, sample size, and the proportion of severe COVID-19 patients.

Search strategy
We systematically searched Ovid MEDLINE(R), Ovid EMBASE, CNKI, Wanfang, VIP databases, and the Cochrane Library for studies in English or Chinese language from January 1, 2020, to March 30, 2020, using the search terms: “2019 novel coronavirus,” “2019-nCoV infection,” “2019-nCoV disease,” “COVID-19,” “coronavirus disease-19,” “coronavirus disease 2019,” “novel coronavirus,” “SARS-CoV-2,” “COVID-19 virus,” “SARS2,” and “2019-nCoV.” The searches were limited to humans. We also searched the preprint servers medRxiv website for studies between January 1, 2020 and March 30, 2020 given that this field is developing rapidly. In addition, relevant clinical systematic reviews, meta-analysis, and references of relevant publications were scrutinized manually with the aim to identify additional potentially eligible literature.

Eligibility criteria
Studies were deemed eligible for inclusion if they were (1) case-control, cross-sectional, clinical, or cohort studies including patients diagnosed with COVID-19 and (2) described the demographics, clinical manifestations, comorbidities or laboratory features of non-severe, and severe COVID-19 patients separately. We excluded expert recommendations, reviews, editorials, case reports, family-based studies, child cases, duplicates, studies lacking in information on quality assessment and data analysis.

Study selection
Two reviewers (JL, YL) independently screened the titles and abstracts of all the records and coded them as “retrieve” (eligible or potentially eligible or unclear) or “do not retrieve” based on the inclusion criteria. However, studies and reviews that might include relevant data or information were retained initially and the full-text version was analyzed. We retrieved the full texts and publications of the “retrieve” records. Two review authors (JL, YL) independently screened the full texts for
inclusion and recorded reasons for the ineligible studies. All disagreements were resolved by consensus, if not, by discussion with a third review author (XC). We recorded the selection process in sufficient detail and the protocol followed the recommendations established by the PRISMA (Figure 1).

**Data extraction and risk of bias assessment**

Data were extracted using a standardized electronic data entry form by two investigators (JL, YL) independently. Data extraction forms included information on authors, the area, the number of non-severe and severe COVID-19 patients in each group, study period, age, sex, unhealthy lifestyle habits (e.g. smoking), vital signs (e.g. body temperature, pulse, respiration rate, mean arterial pressure (MAP)), clinical manifestations (e.g. fever, chills, fatigue, cough, expectoration, dyspnea, chest distress, hemoptysis, nasal congestion and rhinorrhea, sore throat, headache, nausea, vomiting, dizziness, myalgia or arthralgia ache, anorexia, abdominal pain, and diarrhea), comorbidities (e.g.
hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVD), cerebrovascular disease (CeVD), chronic liver disease (CLD), digestive system disease (DSD), malignancy, chronic renal disease (CKD)), and laboratory features (white blood cells count (WBC), lymphocyte count, monocyte count, platelet count, hemoglobin, neutrophil count, neutrophil/lymphocyte ratio (NLR), percentage of neutrophil (N%), CD3 T-lymphocyte count (CD3), CD4 T-lymphocyte count (CD4), CD8 T-lymphocyte count (CD8), C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), serum ferritin, interleukin-6 (IL-6), lactic dehydrogenase (LDH), creatine kinase (CK), creatine kinase-MB (CK-MB), hypersensitive troponin I (hTnI), aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin (Tbil), albumin (ALB), creatinine (Cr), blood urea nitrogen (BUN), activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer, fibrinogen (FIB), serum sodium, serum potassium, serum chlorine, and serum calcium). Disagreements were resolved by consensus or a third reviewer (XC) when needed. Two authors (GZ, HQ) cross-checked all the information retrieved. To ensure that patients were not being counted more than once and minimize the inaccuracy of data, when more than one eligible article reported patients in the same hospital and addressed the same outcome, we included the article with the largest number of participants.

Quality of each included study was assessed using the JBI-MAStARI (JBI Meta Analysis of Statistics Assessment and Review Instrument). The questionnaire consists of eight questions that were answered with yes, no, unclear, or not applicable. The included studies were classified into three categories based on the result of each questionnaire: high methodological quality (>5 “yes” responses), moderate methodological quality (3–4 “yes” responses), or low methodological quality (0–2 “yes” responses).\(^8\)

**Data synthesis and statistical analysis**

We extrapolated mean and standard deviation (SD) from median and interquartile range (IQR) values, or the median and the minimum and maximum values, according to the method presented by Luo et al.\(^9\) and Wan et al.\(^10\) respectively. We compared severe patients with non-severe ones in the demographics, clinical manifestations, comorbidities, and laboratory features. When COVID-19 patients were classified into more than two groups (mild, moderate, severe, and critical group), we combined mild and moderate as a non-severe group, severe, and critical/death as a severe group. The weight or standardized mean difference (WMD or SMD) and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by a random-effect or fixed-effect model based on between-study heterogeneity for continuous data and dichotomous data, respectively. Heterogeneity was assessed using the \(I^2\) test and the \(Q\) test: \(>50\%\) represented substantial heterogeneity. The random-effect model was used if \(I^2 > 50\%\) and the fixed-effect model was used if \(I^2 \leq 50\%\). To evaluate potential publication bias, funnel plots, and Egger’s test were used. Sensitivity analysis was conducted employing a leave-one-out analysis. Subgroup analysis with significant difference and substantial heterogeneity were performed based on age (>50 years vs \(\leq 50\) years old), region (Hubei vs other regions), samples size (\(\leq 100\) patients, 100–200 patients, or \(>200\) patients), the proportion of male (>50%, \(\leq 50\%\), or no reported), and the proportion of severe patients (>30% vs \(\leq 30\%\)). All statistical analysis was performed with the Stata SE version 12.1 software packages (Stata Corp, College Station, TX).

**Results**

**Study search and selection**

The PRISMA flow diagram of this meta-analysis is presented in Figure 1. A total number of 4305 unique publications were initially identified. We assessed 282 full-text records excluding duplicates and non-relevant citations based on title and abstract. Fifty-six of were selected by two review authors (JL, YL) and numbered. Prior to the data extraction, two studies were excluded because patients were classified into ICU and non-ICU groups.\(^11,12\) Finally, the pooled analysis included 54 studies.\(^13–17,18–66\)

**Study characteristics**

The characteristics of included studies are described in Supplemental Table S1. All articles were cross-sectional studies. Guan et al.\(^13\) study, included 1099 patients from 552 hospitals in 30 provinces, was excluded in the manuscript due to patient overlap.
Patients included in the 54 studies were from 14 provinces in China. A total of 33 articles were English language and 21 were Chinese language. The minimum sample size was 21 and maximum sample size was 918 participants. The mean ages ranged from 29.2 to 72.5 years, and the percentage of male ranged from 33.7% to 81.0%. The severity of COVID-19 was defined according to 42, 4, 3 studies which were established by China’s National Health Commission, WHO’s interim guidelines, the American Thoracic Society guideline respectively (Supplemental Table S1). In addition, three studies divided COVID-19 patients into severe and non-severe group already, two articles did not report the degree of severity (Supplemental Table S1). Of 54 studies, 46 and eight were identified fair and high quality according to the JBI-MAStARI, respectively (Supplemental Table S1 and S2). The demographics, clinical manifestations, comorbidities, and laboratory features of COVID-19 patients are presented in Supplemental Table S3. We analyzed 67 variables for the meta-analyzes. The forest plots, sensitivity analysis and funnel plots were showed in Supplemental Figure S1.

Demographics outcomes

The pooled results indicated that the proportion of male was significantly higher in severe group compared to female without significant heterogeneity (OR = 0.65, 95% CI = 0.58–0.73, \( F^2 = 29.6\% \)). In addition, severe cases were older than non-severe ones (WMD = 10.77 years, 95% CI = 9.25–12.30, \( F^2 = 64.3\% \)), and patients aged more than 65 years were associated with greater risk of severe disease (OR = 3.43, 95% CI = 2.57–4.59; \( F^2 = 22.4\% \)). Besides, smoker did not have higher odds of COVID-19 progression than non-smokers (OR = 1.35, 95% CI = 0.96–1.91; \( F^2 = 0\% \)).

Sensitivity analysis for age, sex showed that the results were robust by sequentially removal of each study. However, sensitivity analysis for smoking revealed that the results were not statistically significant.\(^{14–18,67}\) There was publication bias in sex, but not in age (Supplemental Figure S1).

Vital signs outcomes

Body temperature and pulse were higher among critical patients compared to non-critical ones ((body temperature: WMD = 0.29, 95% CI = 0.12–0.46; pulse: WMD = 4.19, 95% CI = 1.64–6.74; \( F^2 = 47.7\% \))) (Table 1 and Supplemental Figure S1), while respiratory rate and MAP were not statistically significant. Moreover, the sensitivity analysis showed that the estimate of pulse were not robust.

Clinical manifestations

We found the following clinical manifestations were risk factors of severe diseases: fever (OR = 1.96, 95% CI = 1.29–2.99; \( F^2 = 72.6\% \)), chills (OR = 2.30, 95% CI = 1.50–3.52; \( F^2 = 0\% \)), cough (OR = 1.22, 95% CI = 1.07–1.41; \( F^2 = 49\% \)), expectoration (OR = 1.36, 95% CI = 1.13–1.65; \( F^2 = 37.8\% \)), dyspnea (OR = 5.83, 95% CI = 3.65–9.31; \( F^2 = 80.8\% \)), chest distress (OR = 4.09, 95% CI = 2.41–6.92; \( F^2 = 24.8\% \)), fatigue (OR = 1.56, 95% CI = 1.15–2.10; \( F^2 = 61.7\% \)), headache (OR = 1.36, 95% CI = 1.07–1.73; \( F^2 = 41.0\% \)), anorexia (OR = 2.25, 95% CI = 1.32–3.84; \( F^2 = 74.2\% \)), abdominal pain (OR = 2.76, 95% CI = 1.56–4.89; \( F^2 = 0\% \)). There was no significant correlation between hemoptysis, nasal congestion or rhinorrhea, sore throat, diarrhea, nausea or vomiting, myalgia and dizziness, and severe COVID-19 (Figure 2 and Supplemental Figure S1).

Sensitivity analysis were robust excluding sore throat, headache, nausea, or vomit. The funnel plot and Egger’s test showed there was no significant publication bias except for chest distress, cough, and fever. The associations of fever, fatigue, anorexia, dyspnea, myalgia, nausea, or vomit with the risk of severe COVID-19 were inconsistent in subgroup analysis (Supplemental Table S4–S8).

Comorbidities

Comorbidities outcomes are presented in Figure 2 and Supplemental Figure S1. The proportion of hypertension, diabetes, CVD, CKD, COPD, CeVD, and cancer was statistically significant higher in severe COVID-19 patients compared to the non-severe patients (hypertension (OR = 3.11, 95% CI = 2.38–4.08; \( F^2 = 58.4\% \)), diabetes (OR = 2.44, 95% CI = 1.99–3.00; \( F^2 = 40.3\% \)), CVD (OR = 3.98, 95% CI = 3.00–5.27; \( F^2 = 0\% \)), CKD (OR = 2.19, 95% CI = 1.37–3.49; \( F^2 = 20.8\% \)), COPD (OR = 4.25, 95% CI = 2.63–6.88; \( F^2 = 0\% \)), CeVD (OR = 3.06, 95% CI = 1.93–4.85; \( F^2 = 33.8\% \)), cancer (OR = 1.48, 95% CI = 0.93–2.35; \( F^2 = 0\% \)), but not DSD or CLD. Between-study heterogeneity was low for all comorbidities except for hypertension.
## Table 1. Meta-analysis of the continuous variables for severe versus non-severe patients with COVID-19.

| Laboratory results                        | No. of studies | No. of patients | WMD/SMD (95% CI) | Model  | $I^2$ (%) | Egger’s |
|-------------------------------------------|----------------|-----------------|------------------|--------|-----------|---------|
| **Demographic**                           |                |                 |                  |        |           |         |
| Age                                       | 27             | 5107            | 10.77 (9.25, 12.30) | Random | 64.30     | 0.00    |
| **Vital signs**                            |                |                 |                  |        |           |         |
| Body temperature (°C)                     | 7              | 1249            | 0.29 (0.12, 0.46) | Random | 67.50     | 0.35    |
| Pulse (bpm)                               | 6              | 733             | 4.19 (1.64, 6.74) | Fixed  | 47.70     | 0.85    |
| Respiratory rate (bpm)                    | 6              | 733             | 2.20 (–0.13, 4.54) | Random | 91.90     | 0.07    |
| MAP (mmHg)                                | 3              | 556             | 0.76 (–1.58, 3.11) | Random | 33.30     | 0.43    |
| **Blood routine**                         |                |                 |                  |        |           |         |
| WBC (×10^9/L)                             | 19             | 3228            | 0.75 (0.26, 1.24) | Random | 85.50     | 0.00    |
| Lymphocyte (×10^9/L)                      | 20             | 4145            | –0.39 (–0.46, –0.33) | Random | 75.60     | 0.18    |
| Platelets (×10^9/L)                       | 19             | 2858            | –23.19 (–32.61, –13.77) | Random | 65.50     | 0.00    |
| Hemoglobin (g/L)                          | 14             | 1362            | –4.03 (–6.44, –1.61) | Fixed  | 22.50     | 0.92    |
| Neutrophil (×10^9/L)                      | 16             | 2230            | 1.25 (0.79, 1.72) | Random | 78.20     | 0.02    |
| Monocyte (×10^9/L)                        | 8              | 1211            | 0.01 (–0.06, 0.08) | Random | 79.00     | 0.93    |
| NLR                                       | 5              | 1161            | 2.04 (1.18, 2.90) | Random | 73.60     | 0.67    |
| N%                                        | 8              | 1311            | 13.38 (10.91, 15.86) | Random | 51.90     | 0.56    |
| **T cells subsets**                       |                |                 |                  |        |           |         |
| CD3 (×10^9/L)                             | 4              | 404             | –443.0 (–702.1, –183.9) | Random | 91.30     | 0.17    |
| CD4 (×10^9/L)                             | 6              | 888             | –227.6 (–344.8, –110.5) | Random | 90.60     | 0.74    |
| CD8 (×10^9/L)                             | 6              | 888             | –138.9 (–207.6, –70.2) | Random | 88.90     | 0.79    |
| **Inflammation-related biomarkers**       |                |                 |                  |        |           |         |
| CRP (mg/L)                                | 21             | 3053            | 38.21 (31.95, 44.47) | Random | 67.80     | 0.59    |
| PCT (ng/mL)                               | 19             | 2933            | 0.891 (0.67, 1.12) | Random | 84.50     | 0.00    |
| ESR (mm/h)                                | 8              | 1342            | 14.18 (6.53, 21.83) | Random | 69.70     | 0.69    |
| IL-6 (pg/mL)                              | 5              | 1254            | 1.681 (0.68, 2.68) | Random | 98.20     | 0.00    |
| Ferritin (ng/mL)                          | 3              | 1016            | 328.0 (139.2, 516.8) | Random | 3.80      | 0.04    |
| **Myocardial enzymes**                    |                |                 |                  |        |           |         |
| hTnI (pg/mL)                              | 4              | 574             | 18.60 (11.90, 25.4) | Fixed  | 0.00      | 0.37    |
| LDH (U/L)                                 | 15             | 1935            | 1.221 (0.91, 1.53) | Random | 85.70     | 0.08    |
| CK (U/L)                                  | 15             | 1934            | 0.511 (0.30, 0.72) | Random | 76.30     | 0.89    |
| CK-MB (U/L)                               | 5              | 780             | 0.741 (0.30, 1.17) | Random | 83.00     | 0.73    |
| **Biochemical findings**                  |                |                 |                  |        |           |         |
| AST (U/L)                                 | 19             | 2385            | 1.041 (0.66, 1.42) | Random | 92.20     | 0.48    |
| ALT (U/L)                                 | 20             | 2695            | 0.451 (0.24, 0.65) | Random | 77.90     | 0.07    |
| Tbil (μmol/L)                              | 10             | 1739            | 1.32 (0.08, 2.56) | Random | 68.40     | 0.72    |
| ALB (g/L)                                 | 16             | 2346            | –4.33 (–5.35, –3.30) | Random | 76.90     | 0.01    |
| Cr (μmol/L)                               | 18             | 2709            | 5.77 (1.58, 9.97) | Random | 75.20     | 0.14    |
| BUN (mmol/L)                              | 13             | 2162            | 1.16 (0.77, 1.55) | Random | 64.70     | 0.00    |
| **Coagulation function**                  |                |                 |                  |        |           |         |
| D-dimer (mg/L)                            | 16             | 2183            | 1.041 (0.73, 1.36) | Random | 88.10     | 0.05    |
| PT (s)                                    | 12             | 1192            | 0.401 (0.10, 0.69) | Random | 76.70     | 0.61    |
| FIB (g/L)                                 | 5              | 1002            | 0.32 (0.06, 0.57) | Random | 63.70     | 0.22    |
| APTT (s)                                  | 10             | 1244            | –0.01 (–1.45, 1.44) | Random | 76.60     | 0.34    |
| **Electrolyte**                            |                |                 |                  |        |           |         |
| Sodium (mmol/L)                           | 6              | 814             | –2.09 (–2.70, –1.48) | Fixed  | 0.00      | 0.20    |
| Potassium (mmol/L)                        | 9              | 1426            | –0.02 (–0.15, 0.10) | Random | 72.10     | 0.51    |
| Chlorine (mmol/L)                         | 5              | 616             | –0.44 (–2.24, 1.36) | Random | 71.60     | 0.61    |
| Calcium (mmol/L)                          | 6              | 870             | –0.13 (–0.21, –0.04) | Random | 89.70     | 0.07    |

1Presented SMD.

MAP: Mean arterial pressure; WBC: White blood cell; NLR: Neutrophils/lymphocytes ratio; N%: percentage of neutrophils; CD3: CD3 T-lymphocyte count; CD4: CD4 T-lymphocyte count; CD8: CD8 T-lymphocyte count; CRP: C-reactive protein; PCT: Procalcitonin; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactic dehydrogenase; CK: Creatine kinase; CK-MB: Creatine kinase-MB; hTnI: Hypersensitive troponin I; AST: Aspartate aminotransferase; ALT: Alanine transaminase; Tbil: Total bilirubin; ALB: Albumin; Cr: Creatinine; BUN: Blood urea nitrogen; APTT: Activated partial thromboplastin time; PT: Prothrombin time; FIB: Fibrinogen; WMD = weighted mean difference; SMD: standardized mean difference.
The sensitivity analysis for hypertension, diabetes, CVD, CKD, COPD, CeVD, DSD, or CLD confirmed that none of the exclusion of a specific study would change the final results. For cancer, although sensitivity analysis remained consistent, the 95% CI included the null effect when we omitted studies of Shi et al., Cheng et al., Zhang et al., or Hu et al. A funnel plot and results of Egger’s test showed significant evidence of publication bias for hypertension, COPD, and CKD, and no significant evidence of publication bias for CVD, CeVD, DSD, and CLD. Subgroup analysis for hypertension still generated significant associations comparable with those of the overall analysis (Supplemental Table S4–S8).

**Laboratory features**

The WMDs/SMDs indicated that 21 laboratory findings including WBC, neutrophil, NLR, N%, CRP, PCT, ESR, IL-6, LDH, ferritin, hTnI, CK, CK-MB, AST, ALT, Tbil, Cr, BUN, PT, D-dimer, and FIB were significantly increased, and nine laboratory findings including lymphocyte, platelets, hemoglobin, CD3, CD4, CD8, ALB, serum sodium, and serum calcium were significantly decreased \( (p < 0.01) \), but four laboratory findings including monocyte, APTT, serum potassium, and serum chloride levels did not differ in severe patients versus non-severe patients (Table 1). However, only differences in lymphocyte (WMD = −0.39, 95% CI = −0.64 to −0.33; \( I^2 = 75.6\% \)), CD4 (WMD = −227.6, 95% CI = −344.8 to −110.5; \( I^2 = 90.6\% \)), CD8 (WMD = −138.9, 95% CI = −207.6 to −70.2; \( I^2 = 88.9\% \)), CRP (WMD = 38.21, 95% CI = 31.95–44.47; \( I^2 = 67.8\% \)), LDH (SMD = 1.27, 95% CI = 0.95–1.60; \( I^2 = 85.7\% \)), and D-dimer (WMD = 1.04, 95% CI = 0.73–1.36; \( I^2 = 88.10\% \)) between severe and non-severe patients showed clinical significance. Non-severe patients had normal or slightly abnormal

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**Figure 2.** The outcomes of the meta-analysis for risk factors of dichotomous data in severe patients with COVID-19.

COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular diseases; CeVD: Cerebrovascular diseases; CLD: Chronic liver diseases; CKD: Chronic kidney diseases; DSD: Digestive system disease.
mean/median values of lymphocyte, CD3, CD4, CD8, CRP, LDH, and D-dimer, while severe patients had significantly abnormal mean/median values of the aforementioned indicators (Supplemental Figure S1–38, S1-44, S1-45, S1-46, S1-51, S1-63). Between-study heterogeneity was high for all laboratory findings except for MAP, sodium, hTnI, ferritin, hemoglobin.

Regarding sensitivity analysis, the WMDs/SMDs for the majority of laboratory findings remained consistent. By contrast, the estimates of Tbil and FIB were not robust after sequentially omitting each study. A funnel plot and results of Egger’s test showed significant evidence of publication bias for WBC, platelets, neutrophil, PCT, ferritin, IL-6, ALB, and BUN, and no significant evidence of publication bias for the other laboratory findings. Considering between-study heterogeneity and clinical significance, we further conducted subgroup analysis for lymphocyte, CD4, CD8, CRP, LDH, and D-dimer, which showed that lymphocyte, CD4, CRP, LDH, and D-dimer still remained a substantial difference regardless of each subgroup, but CD8 did not suggest any significant difference in patients aged less than 50 years old between severe and non-severe disease (Supplemental Table S4–S8).

Discussion

Previously, older age and male have been reported as important independent predictors of severe disease or death in SARS-CoV.13 The current study confirmed that severe COVID-19 patients were older and more likely to be males, which was similar to previous systematic review.5 The study was in accordance with the previous study of Guan et al.,13 which based on 1099 cases from 552 hospitals in 30 provinces of China in the early period of outbreak. Moreover, this study provided further evidence that COVID-19 patients aged more than 65 years were at a higher risk of severe disease. These findings shared similar conclusions with the study of Wu et al.,68 which included 201 confirmed COVID-19 patients, Wu reported a 3.26 times and 6.17 times higher risk of the progression of ARDS to death for patients aged more than 65 years and patients aged less than 65 years, respectively. These phenomena may ascribe to the lower expression of angiotensin-converting enzyme 2 (ACE2), a catalytic breakdown enzyme of Ang-II, in elderly and male individuals. Lower level of ACE2 could increase the concentration of Ang II, which leads to inflammatory response.69 Consistent with our findings, previous meta-analysis studies, which consisted of only 412 COVID-19 patients, reported that smoking also was not a risk factor for severe illness.5

In concert with recent studies, we found fever, cough, dyspnea, fatigue, myalgia, anorexia were the predominant symptoms of COVID-19 patients infected by SARS-CoV-2,11,13,68,70 while chill, chest distress, hemoptysis, sore throat, nasal congestion or rhinorrhea, gastrointestinal symptoms were rare, which was different from seasonal influenza and SARS-CoV or MERS-CoV.13,71,72 Previous pooled analysis further indicated that severe COVID-19 patients had more frequent fever and dyspnea compared to non-severe patients,5,73 as it was in our findings. In addition, our study improves upon prior meta-analysis by exploring gastrointestinal and other clinical symptoms. Up to date, there were more frequent respiratory symptoms such as cough, expectoration, and chest distress in severe patients than non-severe patients. It was consistent with patients infected by SARS-CoV-2, which were recognized as an acute lung injury whereby an initial and rapidly developed significant respiratory distress like SARS and MERS.74 What’s more, we found general clinical manifestations including fatigue, chills and headache as well as gastrointestinal symptoms such as anorexia and abdominal pain, not hemoptysis, sore throat, myalgia, dizziness, nasal congestion/rhinorrhea, nausea/vomit, and diarrhea, were more common in severe patients than non-severe patients. However, the latest meta-analysis indicated that cough, expectoration, headache, and fatigue were not associated with the risk of severe disease.73 This latest published systematic review and meta-analysis may reflect less accurate results due to the inclusion of a study by Guan et al.,13 which was likely to overlap with the other included articles in the pooled analysis. Symptoms difference between severe patients and non-severe patients showed that the clinical manifestations besides respiratory illness were maybe also early signs of multiple organ injuries and were also associated with high risk of development into serious illness.

Our results indicated that patients coexisting with comorbidities such as hypertension, diabetes, CVD, cancer, and COPD had higher risk of severe
COVID-19, as it was in previous studies. Hypertension, diabetes, CVD, and cancer showed a few common characteristics with infectious diseases. Similarly the body was in a state of the proinflammatory and in the attenuation of the innate immune response, the long-term history of diabetes, hypertension, CVD, and cancer damaged the vascular structure, and it was more likely to develop into critical disease in infection. Furthermore, once patients underlying CVD or hypertension infected by SARS-CoV-2, ACE2 consumption would accelerate the deterioration of CVD or hypertension. At the same time, the loss of ACE2 may also promoted endothelial dysfunction and inflammation in diabetes patients. What our research is superior to previous research is that we also found that CKD and CeVD are also risk factors for the occurrence of severe COVID-19, while DSD and CLD are not. A review suggested that the expression of ACE2 was lower in patients with underlying chronic diseases, especially CKD, CVD, than those without underlying chronic diseases. This may be one of the reasons why patients with CKD and CeVD have a higher risk of severe disease in SARS-CoV-2 infection.

The pathogenesis of SARS-CoV-2-induced infection is still not completely understood. Cytokine storm and dysregulated immune responses are thought to play important roles in disease severity. Inflammatory biomarker was also a feature associated with severity of COVID-19 disease. It is consistent with previous studies, our research found CRP, PCT, ESR, and serum ferritin was higher in severe patients than non-severe. Although all inflammatory biomarkers are non-specific for severe COVID-19, patients with elevated inflammatory biomarkers need special attention of clinicians. In addition, IL-6, a key mediator regulating cytokine storm, was also associated with the severity of COVID-19, IL-6 was considered as a predictor for mortality. At present, IL-6 has not been conducted in meta-analysis, our findings suggested the level of IL-6 was higher in severe patients than non-severe patients, which demonstrated that severe patients may present more severe systemic inflammatory response. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, may improve the serious injuries of COVID-19 patients with very high IL-6 and reduce mortality. Furthermore, we found that severe patients manifested cellular immune deficiency with increased neutrophil-to-lymphocyte ratio (NLR) and decreased lymphocyte, monocyte, platelets, CD3, CD4, and CD-8 T-cell counts, which was consistent with the results that serious COVID-19 patients presented with lymphocytopenia. These results indicated that severe patients with COVID-19 were associated with more serious damage of immune system. Moreover, previous studies shown that SARS-CoV-2 induced myocardial damage, which lined with our results that severe patients had higher level of myocardial enzymatic (hTnI, LDH, CK, CK-MB). Finally, we also pooled analysis of the biochemical findings, coagulation function, and electrolyte. The tests results reported as WMDs/SMDs made the clinical utility limited. But the clinicians might still pay more attentions to COVID-19 patients with abnormal biochemical findings, coagulation function, and electrolyte.

Limitations
The review applied a systematic and rigorous analysis based on the largest sample size of COVID-19 patients so far, the conclusions are highly credible. However, there are still some limitations in this meta-analysis. First, all studies included in our meta-analysis were retrospective cross-sectional, and factors for severe patients reported in different literatures varied greatly. Second, studies included are of large heterogeneity because of the severity of COVID-19 defined and the method for laboratory tests differently among studies and hospitals. What’s more, we didn’t analyze the interaction of the different comorbidities and clinical manifestations owing to lack of individual patient data and the information on the types of clusters of clinical manifestations and diseases of each study. The future studies may focus on the types of clusters of clinical manifestations and diseases, and developing a risk score to predict severe disease in patients with COVID-19 that could alert clinicians to patients at greatest risk, such that steps could be taken to mitigate the risk. Third, most patients in our study are from China, risk factors of COVID-19 severity may vary by race and regions, as it was reported in our subgroup studies. Therefore, the conclusions of our meta-analysis still need to be verified by larger sample size and more relevant studies involved COVID-19 cases in the worldwide.

Conclusions
In this meta-analysis, we summarized and analyze 67 parameters of patient features, vital signs, symptoms, comorbidities and laboratory tests between
severe and non-severe patients in about 7000 COVID-19 confirmed cases reported by 54 studies. First, we found older age and male were associated with a higher risk of development of severe COVID-19 disease. And further analysis indicated that the symptoms of fever, chills, dyspnea, cough, expectoration, chest distress, fatigue, headache, anorexia, or abdominal pain are risk factors for severe illness. In addition, the observation also reminded us that patients with underlying diseases, especially hypertension, diabetes, CVD, CeVD, CKD, COPD, and cancer were associated with higher odds of severe illness. Finally, compared to non-severe patients with COVID-19, severe patients were older and presented a higher body temperature, pulse, and levels of WBC, neutrophil, NLR, N%, inflammation-related biomarkers, myocardial enzymes, AST, ALT, Tbil, Cr, BUN, PT, D-dimer, but showed a lower levels of lymphocyte, T lymphocytes cells subsets, platelets, hemoglobin, albumin, serum sodium, and calcium. Our findings will be conducive for clinician to stratify the COVID-19 patients to reduce mortality under the relative shortage of medical resources.

Author contributions
JL, YL had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: JL and YL. Selection of studies: JL, YL, and XC. Extraction of data: JL, YL, and XC. Checked all the information retrieved: GZ and HQ. Analysis or interpretation of data: JL and YL. Drafting of manuscript: JL and YL. Critical revision of the manuscript for important intellectual content: JL, YL, XC, GZ, HQ, HY, WJ. Obtaining funding: YL, HY, and XC. Study supervision: JL.

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