The common risk factors for progression and mortality in COVID-19 patients: a meta-analysis

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Abstract
Coronavirus disease 2019 (COVID-19), defined by the World Health Organization (WHO), has affected more than 50 million patients worldwide and caused a global public health emergency. Therefore, there is a recognized need to identify risk factors for COVID-19 severity and mortality. A systematic search of electronic databases (PubMed, Embase and Cochrane Library) for studies published before September 29, 2020, was performed. Studies that investigated risk factors for progression and mortality in COVID-19 patients were included. A total 344,431 participants from 34 studies were included in this meta-analysis. Regarding comorbidities, cerebrovascular disease (CVD), chronic kidney disease (CKD), coronary heart disease (CHD), and malignancy were associated with an increased risk of progression and mortality in COVID-19 patients. Regarding clinical manifestations, sputum production was associated with a dramatically increased risk of progression and mortality. Hemoptysis was a risk factor for death in COVID-19 patients. In laboratory examinations, increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased C-reactive protein (CRP), coinfection with bacteria or fungi, increased alanine aminotransferase (ALT) and creatine kinase (CK), increased N-terminal pronatriuretic peptide (NT-proBNP), and bilateral pneumonia in CT/X-ray were significantly more frequent in the severe group compared with the non-severe group. Moreover, the proportion of patients with increased CRP and total bilirubin (TBIL) was also significantly higher in the deceased group than in the survival group. CVD, CKD, sputum production, increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased CRP, coinfection with bacteria or fungi, increased ALT and CK, increased NT-proBNP, and bilateral pneumonia in CT/X-ray were associated with an increased risk of progression in COVID-19 patients. Moreover, the proportion of patients with increased sputum production, hemoptysis, CRP and TBIL was also significantly higher in the deceased group.

Introduction
Since December 2019, an outbreak of pneumonia caused by a novel coronavirus has affected China and spread all over the world [1, 2]. Coronavirus disease 2019 (COVID-19), defined by the World Health Organization (WHO), has infected more than 50 million patients worldwide and caused a global public health emergency [3]. Some patients develop adverse complications and exhibit poor prognosis, and deaths outside of China are increasing persistently. By November 17, 2020, there were 54,771,888 confirmed COVID-19 cases, including more than 1.32 million deaths, and the fatality rate was greater than 10% in some countries according to the WHO 2020 report [4, 5].

Therefore, there is a recognized need to identify risk factors for COVID-19 severity and mortality. Patients with risk factors might be identified earlier, and intensive surveillance or treatment could be administered in advance to improve
Several studies have documented some clinical characteristics and laboratory test values as risk factors for severe and fatal COVID-19 [7–9]. However, various limitations were apparent in these articles, such as reliance on single-center studies and small sample sizes, which might lead to some bias and restrict the generality and applicability of their conclusions. Predictive factors for severe cases and fatal outcome continue to be debated [10]. A meta-analysis of populations from different studies with a larger sample size is needed.

In this article, the clinical characteristics and laboratory test values of COVID-19 patients with severe/fatal illness compared with those with mild/nonfatal illness were compared in 34 studies with 344,431 patients to identify risk factors for severe disease or death in COVID-19 patients. Based on these data, we can predict disease progression and provide intensive surveillance and rapid treatment to effectively improve the prognosis of COVID-19 patients.

Materials and methods

This meta-analysis was registered in the International Prospective Register of Systematic Reviews (CRD42020179903). This meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions guidelines [11].

Search strategy

The PubMed, EMBASE, and MEDLINE databases were systematically searched from December 1, 2019, to September 29, 2020, with English language limitations. We searched studies using Medical Subject Headings (MeSH) terms, and the main key words included “Covid-19”, “Coronavirus Disease 2019”, “Wuhan Pneumonia”, “SARS-CoV-2”, “New Coronavirus Pneumonia”, “NCP”, “progression”, “severity”, “bad outcome*”, “mortality”, “death”, and “risk factor* or association*”. Additional records were identified manually through other sources.

Inclusion and exclusion criteria

Inclusion criteria: (1) comparative studies: groups involving severity and non-severity, survival and death; (2) study type: randomized controlled trials, case-control studies, cross-sectional studies and cohort studies; (3) study population: patients should be definitely infected with SARS-CoV2, and studies with more than 20 participants were included; (4) parameters: at least one result was reported among basic characteristics, laboratory examinations, comorbidities, and clinical manifestations in the study. Case reports and animal studies were excluded.

Data extraction and quality assessment

All the search results were imported into the EndNote reference management software (Clarivate Analytics) by L.Z. Duplicate records were removed by the software and hand-checked. Two reviewers (L.Z. and J.L.) independently screened the titles and abstracts of the remaining records for relevance against the protocol criteria and labeled these records as excluded, included, or uncertain. In cases of uncertainty, the full texts were retrieved to review the study in detail. Any disagreements were resolved by consulting a third reviewer. After confirming the included articles, data were extracted by two reviewers (L.Z. and S.X.) independently using a standardized form. Quality assessment of the included studies was conducted according to the Newcastle-Ottawa Scale [12] score by F.Z.M. and J.H. Any disagreements in the process of data extraction and quality assessment were discussed with other reviewers.

Statistical analysis

We calculated the odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous data and mean differences (MDs) with 95% CIs for continuous data. The I² statistic was used to assess the heterogeneity test across studies, and $P < 0.1$ or $I^2 > 50\%$ indicates statistical significance. If no statistical heterogeneity was noted, we used a fixed-effects model; otherwise, we chose a random-effects model. Publication bias was assessed using Egger’s regression [13] and Begg’s rank correlation analysis [14]. A significance of $P < 0.05$ indicated the possibility of publication bias [15]. When the $P$-value was less than 0.05, we adopted a trim-and-fill method to confirm the result. After supplementing several possible missing studies, the meta-analysis was conducted again. If the estimated value of the combined-effect size did not change significantly, the impact of publication bias was not significant [16]. Moreover, we conducted sensitivity analysis to explore sources of heterogeneity. Sensitivity analysis was performed by excluding single studies one at a time to assess its influence on the pooled effects. All statistical analysis was performed using Stata/SE software 15.0 (StataCorp LP) and Review Manager (RevMan) 5.3 (Nordic Cochrane Centre).

Results

Literature search

We identified 3212 articles by searching EMBASE, PubMed, and MEDLINE, and four additional records were identified.
using other sources. After excluding 1520 duplicated records and reviewing the titles and abstracts, we had 132 eligible articles. Thirty-four studies were included after screening the full text [7, 9, 17–48]. The process of identification and selection is presented Figure 1.

**Study characteristics**

A total of 344,431 participants were included in this meta-analysis. All of the articles were retrospective studies published in 2020. Eighteen studies were performed in Wuhan, 12 studies were conducted outside Wuhan in China, and four studies were done in other countries. The characteristics of the selected studies are presented in Table 1. Thirteen articles included survival and non-survival groups, and 24 included severe and non-severe groups. Subgroups analysis was performed based on severity or mortality. Three studies used the same or a similar population to investigate different aspects. Therefore, data from those studies were not included at the same time in the following comparisons.

COVID-19 severity was classified according to the Guidelines for the Diagnosis and Treatment of COVID-19 by the National Health Commission. In this meta-analysis, patients with mild or moderate disease were included in the non-severe group, and patients with severe or critical disease were included in the severe group. Moreover, patients in an intensive care unit (ICU) or with SpO₂ ≤ 90% or progressive or refractory illness were included in the severe group in several studies.

**Study quality**

A summary of the quality assessment of the included studies is presented in Figure S1. With the exception of two trials with a score of 6, the quality of the selected studies was generally high. All of the scores were greater than 5 and therefore could be included in this meta-analysis.

**Basic characteristics**

We compared demographic characteristics between the two groups based on sex (male/total), age ≥ 65 years, and smoking. These results are shown in Figure 2. Twenty-eight studies reported a male/total ratio among 341,586 subjects.
The proportion of males (65.09%) in the severe and deceased groups was significantly higher than in the non-severe and survival group (52.45%) (pooled OR = 1.72, 95% CI 1.68 to 1.75, \( P < 0.00001 \)) without heterogeneity (I^2 = 21%) (Fig. 2A). Furthermore, 10 and 15 studies reported the proportion of patients older than 65 years and those who smoked, respectively, between the two groups (Fig. 2B and C). The proportion of patients in the severe or deceased group was significantly higher than in the non-severe or survival group (both \( P < 0.00001 \)) (Fig. 2B and C). Smoking patients included current and former smokers.

### Table 1 Baseline characteristics of the included studies

| Author       | Region/country                  | No. of patients | Sex (male/total) | Mean age (SD)/mean (IQR) | NOS |
|--------------|---------------------------------|-----------------|------------------|--------------------------|-----|
| Chen RC*     | Throughout China                | 1590            | 904/1578         | 69 (51-86)               | 8   |
| Chen XH      | Wuhan, China                    | 48              | 37/48            | 64.6 ± 18.1              | 7   |
| Cheng YC     | Wuhan, China                    | 701             | 367/701          | 63 (50-71)               | 7   |
| Du RH        | Wuhan, China                    | 179             | 97/179           | 57.6 ± 13.7              | 8   |
| Feng Y       | Wuhan, Shanghai and Anhui      | 476             | 271/476          | 53 (40-64)               | 8   |
| Guan W*      | Throughout China                | 1099            | 637/1096         | 47.0(35.0-58.0)          | 8   |
| Guan WJ*     | Throughout China                | 1590            | 904/1578         | 48.9 ± 16.3              | 7   |
| Huang CL     | Wuhan, China                    | 41              | 30/41            | 49.0 (41.0-58.0)         | 7   |
| Ji D         | Anhui, Beijing                  | 208             | 117/208          | 44.0 ± 16.3              | 8   |
| Li KH        | Chongqing, Jinan                | 83              | 44/83            | 45.5 (12.3)              | 7   |
| Li XC        | Wuhan, China                    | 548             | 279/548          | 60 (48-69)               | 8   |
| Li Y         | Wuhan, China                    | 25              | 12/25            | N/A                      | 8   |
| Liu R        | Wuhan, China                    | 119             | 85/119           | N/A                      | 6   |
| Liu W        | Wuhan, China                    | 78              | 39/78            | 38 (33-57)               | 7   |
| Liu Y        | Wuhan, China                    | 383             | 162/383          | 46 (34-61)               | 7   |
| Mo P         | Wuhan, China                    | 155             | 86/155           | 54 (42-66)               | 7   |
| Qu R         | Huizhou, China                  | 30              | 16/30            | 50.5 (36-67)             | 7   |
| Shi Y        | Zhejiang, China                 | 487             | 259/487          | 46 (19)                  | 6   |
| Tang N       | Wuhan, China                    | 183             | 98/183           | 54.1 ± 16.2              | 7   |
| Tian SJ      | Beijing, China                  | 262             | 127/262          | 47.5 (1-94)              | 7   |
| Wang DW      | Wuhan, China                    | 138             | 75/138           | 56(42-68)                | 7   |
| Wang RR      | Fuyang                          | 125             | 71/125           | 38.76 ± 13.799           | 7   |
| Wang ZL      | Wuhan, China                    | 69              | 32/69            | 42.0 (35.0-62.0)         | 7   |
| Wu CM        | Wuhan, China                    | 201             | 128/201          | 51(43-60)                | 8   |
| Wu J         | Yancheng, Fuyang, Wuxi          | 280             | 151/280          | 43.12 ± 19.02            | 8   |
| Yang AP      | Zhejiang, China                 | 93              | 56/93            | 46.4 ± 17.6              | 8   |
| Yang XB      | Wuhan, China                    | 1476            | 776/1476         | 57 (47-67)               | 7   |
| Yuan ML      | Wuhan, China                    | 27              | 12/27            | 60 (47-69)               | 7   |
| Zhang J      | Wuhan, China                    | 663             | 321/663          | 55.6 (44-69)             | 8   |
| Zhou F       | Wuhan, China                    | 191             | 119/191          | 56.0 (46.0-67.0)         | 8   |
| Almazeedi    | Kuwait                          | 1096            | 888/1096         | 41 (25-57)               | 7   |
| Cai QX       | Guangdong, China                | 383             | 183/383          | N/A                      | 7   |
| Chang MC     | Daegu, South Korea              | 106             | 54/106           | 67.6 ± 15.3              | 8   |
| Parra-Bracamonte | Mexico           | 331,298         | 178,155/331,298  | 44 (33-56)               | 7   |

N/A, not applicable; SD, standard deviation; IQR, interquartile range; NOS, Newcastle-Ottawa Scale (score)

*Three studies included the same or similar population but investigated different aspects. Therefore, their data were not included at the same time in one comparison.
# Risk factors for critical COVID-19

## A Sex(male/total)

| Study Subgroup | Sex | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H. Fixed | 95% CI |
|----------------|-----|-----------------|---------------------|------------|------------|-------|
|                |     | Total | Events | Total | Weight |        |
|                |     |      |        |       |         |       |
|                |     | Total | Events |        |         |       |
|                |     | Total | Weight |         |         |       |

### 1.1 Mortality

| Study Subgroup | Sex | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H. Fixed | 95% CI |
|----------------|-----|-----------------|---------------------|------------|------------|-------|
|                |     | Total | Events | Total | Weight |        |
|                |     |      |        |       |         |       |
|                |     | Total | Events |        |         |       |
|                |     | Total | Weight |         |         |       |

### 1.2 Smoking

| Study Subgroup | Sex | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H. Fixed | 95% CI |
|----------------|-----|-----------------|---------------------|------------|------------|-------|
|                |     | Total | Events | Total | Weight |        |
|                |     |      |        |       |         |       |
|                |     | Total | Events |        |         |       |
|                |     | Total | Weight |         |         |       |

## B Age=<65 years

| Study Subgroup | Sex | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H. Fixed | 95% CI |
|----------------|-----|-----------------|---------------------|------------|------------|-------|
|                |     | Total | Events | Total | Weight |        |
|                |     |      |        |       |         |       |
|                |     | Total | Events |        |         |       |
|                |     | Total | Weight |         |         |       |

### 1.1 Mortality

| Study Subgroup | Sex | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H. Fixed | 95% CI |
|----------------|-----|-----------------|---------------------|------------|------------|-------|
|                |     | Total | Events | Total | Weight |        |
|                |     |      |        |       |         |       |
|                |     | Total | Events |        |         |       |
|                |     | Total | Weight |         |         |       |

### 1.2 Smoking

| Study Subgroup | Sex | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H. Fixed | 95% CI |
|----------------|-----|-----------------|---------------------|------------|------------|-------|
|                |     | Total | Events | Total | Weight |        |
|                |     |      |        |       |         |       |
|                |     | Total | Events |        |         |       |
|                |     | Total | Weight |         |         |       |
Fig. 3 Comorbidity risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) diabetes, (B) COPD, (C) hypertension, (D) CHD, (E) CVD, (F) CKD, (G) malignancy, (H) Hep B infection, (I) abnormal liver function, and (J) immunodeficiency.

Comorbidities

We compared 10 comorbidities—diabetes, chronic obstructive pulmonary disease (COPD), hypertension, coronary heart disease (CHD), cerebrovascular disease (CVD), chronic kidney disease (CKD), malignancy, hepatitis B virus infection (HepB), abnormal liver function, and immunodeficiency—between the two groups in this study. The outcomes are shown in Figure 3.

Eighteen studies with a total of 339,975 COVID-19 patients were included in the diabetes comorbidity comparison between the two groups. The proportion of patients with diabetes comorbidity was dramatically higher in the severe or deceased group than in the non-severe or survival group (OR = 3.39, 95% CI 2.73 to 4.22, pooled OR < 0.00001) without heterogeneity (I² = 44%) (Fig. 3A). Patients with diabetes had a 3.55-fold higher risk of progression and 3.83-fold higher risk of mortality compared with those without diabetes among the SARS-CoV-2-infected population. Similarly, we identified an increased risk of progression and mortality in COVID-19 patients with COPD, hypertension, CHD, CVD, or CKD (all subgroups and total P-values < 0.00001) (Fig. 3B-F). Thus, these results confirmed that diabetes, COPD, hypertension, CHD, CVD, and CKD were all associated with an increased risk of progression and mortality in COVID-19 patients.

Moreover, subgroup analysis indicated that malignancy could increase the risk of progression (OR = 2.73, 95% CI 1.83 to 4.07, P < 0.00001) but did not increase the risk of mortality (OR = 2.13, 95% CI 1.02 to 4.47, P = 0.05) in COVID-19 patients without obvious heterogeneity (both I² = 0%) (Fig. 3G). Immunodeficiency was also correlated with an increased risk of severity (P = 0.0006) and mortality (P < 0.00001) without heterogeneity (Fig. 3J). Furthermore, we found that HepB infection and abnormal liver function were only correlated with severity in COVID-19 patients (Fig. 3H and I).

Clinical manifestations

We explored 14 common clinical manifestations of COVID-19 patients in this analysis (Fig. S1 and Table 2). Thirteen studies with a total of 5407 COVID-19 patients were included in the comparison of sputum production between the two groups. The incidence of sputum production was significantly higher in the severe or deceased group than in the non-severe or survival group (pooled OR = 2.08, 95% CI 1.55 to 2.80, pooled P < 0.00001). Sputum production was associated with dramatically increased risks of progression and mortality (Fig. S1G). Similarly, we found that the incidence of dyspnea was clearly elevated in the severe and deceased subgroup compared with the non-severe and survival subgroup (severity subgroup: OR = 5.33, 95% CI 3.36 to 8.45, P < 0.00001; mortality subgroup: OR = 8.55, 95% CI 2.70 to 27.72, P = 0.0003) with significant heterogeneity (I² = 62% and I² = 77%, respectively) (Fig. S1H).

We found the proportion of patients with anorexia, fatigue, or shortness of breath to be significantly higher in the severe group than in the non-severe group (P = 0.0004, P = 0.04, and P < 0.00001, respectively). However, we did not identify similar evidence in the mortality subgroup (Fig. S1B, C, and J). The results also showed that the proportion of patients with hemoptysis was significantly higher in the survival group than in the non-survival group (P < 0.00001). Moreover, compared with the non-severe group, the proportion of patients with fever, pharyngalgia, cough, hemoptysis, dizziness, or nausea/vomiting was higher, and the proportion with myalgia/arthritis, diarrhea, or headache was lower in the severe group; however, the differences were not statistically significant. Similarly, compared with the survival group, the proportion of patients with cough, myalgia/arthritis, diarrhea, headache, or nausea/vomiting was higher, and the proportion of patients with fever was lower in the deceased group. However, these differences were not statistically significant (Fig. S1 and Table 2).

Laboratory tests

We investigated 20 common laboratory examinations of COVID-19 patients in this analysis. Given that there were too many results to be presented, we divided laboratory results into four aspects as follows: Laboratory values greater than the upper limit of the locally defined reference range were regarded as elevated, and those lower than the lower limit were considered decreased.

Routine blood tests

In total, 13 studies with 5252 participants investigated the proportion of patients with elevated white blood cell (WBC) counts in each of the two groups of COVID-19 patients. The proportion of patients with elevated WBC counts was
significantly higher in both the severe and mortality subgroups (OR = 3.22, 95% CI 2.03 to 5.11, \( P < 0.00001 \); OR = 6.87, 95% CI 4.59 to 10.29, \( P < 0.00001 \), respectively) without statistical heterogeneity (\( I^2 = 50\% \) and \( I^2 = 5\% \) respectively) (Fig. 4A). Moreover, the proportion of patients with a reduced WBC count was lower in the severe/deceased group than in the non-severe/survival group, but the results were only statistically significant for the mortality subgroup (OR = 0.45, 95% CI 0.21 to 0.96, \( P = 0.04 \)) (Fig. 4B). Similarly, the rates of increased neutrophil counts and reduced lymphocyte counts were significantly higher in both the severe and deceased groups than in the non-severe and survival groups (both pooled \( P < 0.00001 \), Fig. 4 C and F); however, some heterogeneity was noted in the subgroups (neutrophil increased: severity subgroup \( I^2 = 61\% \); lymphocyte decreased: mortality subgroup \( I^2 = 88\% \)). Compared with the non-severe group, the proportion of patients with a reduced platelet count was significantly increased, and the proportion of patients with reduced neutrophil levels was lower in the severe group (\( P = 0.01 \), \( P = 0.04 \), and \( P = 0.03 \), respectively). However, we did not identify similar evidence in the mortality subgroup (Fig. 4D and E).

Infection-related results

Four infection-related factors – C-reactive protein (CRP), procalcitonin (PCT), IL-6, and coinfection with another pathogen – were investigated in this study (Fig. 5). The proportion patients with elevated CRP, elevated PCT, and coinfection with bacteria or fungi was significantly higher in the severe group than in the non-severe group (\( P < 0.00001 \), \( P < 0.00001 \), \( P = 0.03 \), and \( P = 0.01 \), respectively) without significant heterogeneity (Fig. 5A, B and D). The proportion of patients with elevated CRP or PCT was also significantly higher in deceased group than in the survival group (\( P = 0.003 \) and \( P = 0.005 \), respectively) without significant heterogeneity (Fig. 5A, B and D). The proportion of patients with elevated CRP or PCT was also significantly higher in deceased group than in the survival group (\( P = 0.003 \) and \( P = 0.005 \), respectively) without significant heterogeneity (Fig. 5A, B and D). Sufficient evidence was not enough available to determine the effect of IL-6, a common inflammatory cytokine, on the risk of progression and mortality (Fig. 5C).

Blood biochemistry

Six common blood biochemistry results were studied in this meta-analysis (Fig. 6). The proportion of patients with increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and serum creatinine (sCr), was significantly higher in the severe/deceased

| Clinical manifestation | OR (95% CI) | \( P \)-value |
|-----------------------|-------------|-------------|
| Fever                 | 1.33 (0.83 to 2.12) | 0.23        |
| Anorexia              | 2.78 (1.58 to 4.89) | 0.0004      |
| Fatigue               | 1.22 (1.01 to 1.47) | 0.04        |
| Myalgia/arthritis     | 0.77 (0.47 to 1.26) | 0.30        |
| Pharyngalgia          | 1.24 (0.82 to 1.88) | 0.30        |
| Cough                 | 1.26 (0.88 to 1.80) | 0.22        |
| Sputum                | 2.11 (1.40 to 3.19) | 0.0004      |
| Dyspnea               | 5.33 (3.36 to 8.45) | < 0.00001   |
| Hemoptylosis          | 3.89 (0.95 to 15.91)| 0.06        |
| Shortness of breath   | 6.63 (3.05 to 14.41)| < 0.00001   |
| Diarrhea              | 0.95 (0.75 to 1.22) | 0.71        |
| Nausea/vomiting       | 1.11 (0.76 to 1.62) | 0.58        |
| Headache              | 0.79 (0.56 to 1.12) | 0.18        |
| Dizziness             | 2.44 (0.83 to 7.14) | 0.10        |
| Fever                 | 0.81 (0.47 to 1.38) | 0.43        |
| Fatigue               | 1.40 (0.98 to 2.00) | 0.06        |
| Myalgia/arthritis     | 1.22 (0.77 to 1.95) | 0.39        |
| Cough                 | 1.10 (0.56 to 2.17) | 0.78        |
| Sputum                | 1.98 (1.31 to 3.01) | 0.001       |
| Dyspnea               | 8.55 (2.70 to 27.12)| 0.0003      |
| Hemoptylosis          | 165.82 (22.73 to 1209.81)| < 0.0001   |
| Shortness of breath   | 4.65 (0.42 to 51.96)| 0.21        |
| Diarrhea              | 1.03 (0.54 to 1.95) | 0.93        |
| Nausea/vomiting       | 1.52 (0.74 to 3.11) | 0.25        |
| Headache              | 1.43 (0.81 to 2.53) | 0.22        |
| Dizziness             | 1.17 (0.15 to 9.02) | 0.88        |

Fig. 4 Routine blood test risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated WBC, (B) decreased WBC, (C) elevated neutrophils, (D) decreased neutrophils, (E) decreased platelets, and (F) decreased lymphocytes.

Table 2 Results of meta-analysis of the clinical manifestations
### Risk factors for critical COVID-19

#### A. WBC elevated

| Study Subgroup | Events | Total | Non-events | Survival | Odds Ratio | Odds Ratio |
|----------------|--------|-------|------------|----------|------------|------------|
| Non-neutrophil | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |
| Neutrophil     | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |

#### B. WBC decreased

| Study Subgroup | Events | Total | Non-events | Survival | Odds Ratio | Odds Ratio |
|----------------|--------|-------|------------|----------|------------|------------|
| Non-neutrophil | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |
| Neutrophil     | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |

#### C. Neutrophil elevated

| Study Subgroup | Events | Total | Non-events | Survival | Odds Ratio | Odds Ratio |
|----------------|--------|-------|------------|----------|------------|------------|
| Non-neutrophil | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |
| Neutrophil     | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |

#### D. Neutrophil decreased

| Study Subgroup | Events | Total | Non-events | Survival | Odds Ratio | Odds Ratio |
|----------------|--------|-------|------------|----------|------------|------------|
| Non-neutrophil | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |
| Neutrophil     | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |

#### E. Platelet decreased

| Study Subgroup | Events | Total | Non-events | Survival | Odds Ratio | Odds Ratio |
|----------------|--------|-------|------------|----------|------------|------------|
| Non-neutrophil | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |
| Neutrophil     | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |

#### F. Lymphocyte decreased

| Study Subgroup | Events | Total | Non-events | Survival | Odds Ratio | Odds Ratio |
|----------------|--------|-------|------------|----------|------------|------------|
| Non-neutrophil | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |
| Neutrophil     | 124    | 361   | 239        | 11.4%    | 3.78 (9.07, 9.08) | 3.78 (9.07, 9.08) |
### A elevated CRP

| Study or Subgroup | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|-----------------|---------------------|------------|---------------------|
| **4.7.1 severity** |                 |                     |            |                     |
| Feng Y 2020       | 97              | 108                 | 169        | 307                 | 10.5% | 7.20 [3.71, 13.97] |
| Guan W 2020       | 110             | 135                 | 371        | 658                 | 27.3% | 3.40 [2.15, 5.40] |
| Li K 2020         | 23              | 25                  | 27         | 58                  | 1.5%  | 13.20 [2.85, 61.24] |
| Li K 2020         | 255             | 268                 | 205        | 272                 | 11.5% | 6.41 [3.44, 11.94] |
| Li Y 2020         | 7               | 9                   | 9          | 16                  | 1.6%  | 2.72 [0.43, 17.42] |
| Zhang J 2020      | 324             | 459                 | 94         | 254                 | 28.1% | 6.49 [4.58, 9.20] |
| Subtotal (95% CI) | 954             |                      |            | 1565                | 80.6% | 5.57 [4.41, 7.34] |
| **Total events**  | 816             |                     |            | 875                 |       |                   |

### 4.7.2 mortality

| Study or Subgroup | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|-----------------|---------------------|------------|---------------------|
| Chen RC 2020      | 33              | 33                  | 655        | 1039                | 0.7%  | 39.30 [2.40, 643.22] |
| Du RH 2020        | 20              | 21                  | 138        | 158                 | 1.8%  | 2.90 [0.37, 22.80] |
| Li Y 2020         | 3               | 5                   | 13         | 20                  | 2.4%  | 0.81 [0.11, 6.04] |
| Zhang J 2020      | 14              | 25                  | 374        | 638                 | 14.5% | 0.90 [0.40, 2.01] |
| Subtotal (95% CI) | 84              |                      |            | 1855                | 19.4% | 2.48 [1.37, 4.56] |
| **Total events**  | 70              |                     |            | 1190                |       |                   |

### B elevated PCT

| Study or Subgroup | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H, Random, 95% CI |
|-------------------|-----------------|---------------------|------------|---------------------|
| **4.8.1 severity** |                 |                     |            |                     |
| Guan W 2020       | 16              | 11                  | 179        | 516                 | 17.0% | 4.14 [2.06, 8.33] |
| Huang CL 2020     | 3               | 12                  | 12         | 27                  | 3.7%  | 20.29 [0.96, 429.41] |
| Li K 2020         | 21              | 25                  | 23         | 58                  | 12.4% | 7.99 [2.43, 26.30] |
| Li K 2020         | 43              | 239                 | 3          | 249                 | 12.4% | 18.18 [5.55, 59.47] |
| Wang DW 2020      | 27              | 36                  | 22         | 102                 | 15.2% | 10.91 [4.48, 26.66] |
| Wang ZL 2020      | 0               | 12                  | 4          | 50                  | 3.9%  | 0.41 [0.02, 8.20] |
| Subtotal (95% CI) | 110             |                      |            | 1062                | 64.6% | 7.63 [3.66, 15.47] |
| **Total events**  | 110             |                     |            | 1062                |       |                   |

### CIL-6

| Study or Subgroup | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H, Random, 95% CI |
|-------------------|-----------------|---------------------|------------|---------------------|
| **4.9.1 severity** |                 |                     |            |                     |
| Chen XH 2020      | 124             | 56                  | 27         | 58                  | 16.4% | 16.55 [7.71, 35.55] |
| Wang NH 2020      | 44.4             | 27.3               | 25         | 61.61               | 17.89 | 100                 | 25.0% | -0.94 [-1.29, -0.39] |
| Wu CM 2020        | 12.13            | 3.9                 | 6.82       | 1.83                | 117   | 25.4% | 1.83 [1.56, 2.17] |
| Subtotal (95% CI) | 136             |                      |            | 238                 | 74.7% | 0.57 [1.14, 2.27] |

### D Co-infection

| Study or Subgroup | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|-----------------|---------------------|------------|---------------------|
| **4.10.1 Bacteria** |                 |                     |            |                     |
| Chen XH 2020      | 1               | 27                  | 0          | 21                  | 31.0% | 2.43 [0.09, 62.82] |
| Liu W 2020        | 0               | 11                  | 0          | 67                  | Not estimable |
| Wu J 2020         | 5               | 83                  | 1          | 197                 | 32.5% | 12.56 [1.44, 109.27] |
| Subtotal (95% CI) | 128             |                      |            | 285                 | 63.5% | 7.63 [1.29, 45.22] |
| **Total events**  | 6               |                     |            | 1                   |       |                   |

| Study or Subgroup | Severe/Deceased | Non-severe/Survival | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|-----------------|---------------------|------------|---------------------|
| **4.10.2 Fungi**  |                 |                     |            |                     |
| Chen XH 2020      | 12              | 27                  | 1          | 21                  | 36.5% | 16.00 [1.87, 136.95] |
| Liu W 2020        | 0               | 11                  | 0          | 67                  | Not estimable |
| Wu J 2020         | 0               | 83                  | 0          | 197                 | Not estimable |
| Subtotal (95% CI) | 121             |                      |            | 285                 | 38.5% | 16.00 [1.87, 136.95] |
| **Total events**  | 12              |                     |            | 1                   |       |                   |

### Conclusion

- For overall effect: Z = 4.14 [0.00001] P = 0.001
- For subgroup differences: CH = 0.37, df = 1 (P = 0.60), P = 0%
Infection-related risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated CRP, (B) elevated PCT, (C) elevated IL-6, (D) and co-infection.

Sensitivity analysis

Although subgroup analysis was used in this study, heterogeneity was still noted for some factors. We performed leave-one-out sensitivity analysis to identify possible explanations for heterogeneity (Table S3). High heterogeneity with an I² > 50% and P < 0.05 was found in the analysis of some risk factors. Additionally, after the removal of each study from the analysis, similar results were obtained, and the heterogeneity of most risk factors changed significantly. The high heterogeneity was not reduced by sensitivity analysis in three comparisons (diabetes, decreased WBC, and LDH) in the severity or mortality group. However, after the removal of each study from the analysis of diabetes, decreased WBC, and LDH, the results were stable.

Discussion

Within several months, COVID-19 spread across the world and became a serious health threat to all humans [3]. The number of critical patients and deaths increased substantially, although the majority of infected individuals survived [49]. Early diagnosis and treatment are essential in severe cases, which underscores the importance of identifying predictive factors of disease progression and death. Several studies have investigated risk factors for critical/fatal COVID-19 with a limited number of patients [7, 10]. However, these studies yielded conflicting results due to small sample sizes. To provide less-biased estimates on this specific topic, a meta-analysis, which is an objective, quantitative method, was employed.

Recently, a meta-analysis from China that included 13 studies from Jan 1, 2020, to Mar 20, 2020, was published [10]. Some risk factors for critical/fatal COVID-19 cases were identified. However, another 21 original studies on this topic were published subsequently within several months. An updated meta-analysis is needed to explore new risk factors for critical/fatal COVID-19. In addition to common risk factors, such as male sex, age over 65 years, smoking, hypertension, diabetes, cardiovascular disease, and respiratory diseases, shortness of breath or dyspnea, WBC, AST, Cr, PCT, LDH, hs-cTnI and D-dimer, we also identified some new factors in this study.

Regarding comorbidities, diabetes was one leading risk factor for progression in COVID-19 patients [50]. Zhu et al. also found that well-controlled blood glucose levels correlated with a reduced risk of detrimental complications and all-cause mortality in subjects with COVID-19 and pre-existing diabetes [51]. Uncontrolled glycemia and diabetes have been reported as important predictors.
### A elevated AST Severe/Deceased Non-severe/Survival Odds Ratio

| Study or Subgroup     | Events | Total | Events | Total | Weight | M.H. Random, 95% CI | M.H. Random, 95% CI |
|-----------------------|--------|-------|--------|-------|--------|---------------------|---------------------|
| 4.1.1 mortality       |        |       |        |       |        |                     |                     |
| Chen RH 2000          | 24      | 35    | 988    | 1012  | 0.076  | 2.36 (1.67, 3.35)   | 2.36 (1.67, 3.35)   |
| USHC 2003             | 8       | 16    | 7      | 23    | 1.6    | 2.2 (1.16, 3.97)    | 2.2 (1.16, 3.97)    |
| UY 2020               | 5       | 9     | 8      | 16    | 1.7    | 1.2 (0.74, 2.04)    | 1.2 (0.74, 2.04)    |
| Wang ZG 2012          | 135     | 142   | 655    | 797   | 3.1    | 3.58 (1.93, 6.63)   | 3.58 (1.93, 6.63)   |
| Subtotal (95% CI)     | 222     |       | 1243   |       | 78.6%  | 2.87 [2.16, 3.83]   | 2.87 [2.16, 3.83]   |
| Total events          | 222     |       | 1243   |       | 78.6%  | 2.87 [2.16, 3.83]   | 2.87 [2.16, 3.83]   |

**Heterogeneity:** $I^2 = 0.00$, $Q = 2.08$, $df = 5$ ($P = 0.84$), $P = 0$
**Test for overall effect:** $Z = 3.97$ ($P = 0.0001$)

#### B elevated ALT Severe/Deceased Non-severe/Survival Odds Ratio

| Study or Subgroup     | Events | Total | Events | Total | Weight | M.H. Random, 95% CI | M.H. Random, 95% CI |
|-----------------------|--------|-------|--------|-------|--------|---------------------|---------------------|
| 4.1.2 mortality       |        |       |        |       |        |                     |                     |
| Chen RH 2000          | 395     | 20     | 726    | 92     | 0.53   | 1.09 (1.00, 1.20)   | 1.09 (1.00, 1.20)   |
| USHC 2003             | 94      | 24     | 54     | 112    | 0.24   | 1.11 (1.03, 1.20)   | 1.11 (1.03, 1.20)   |
| Wang ZG 2012          | 66      | 14     | 27     | 41     | 0.66   | 1.68 (1.00, 2.81)   | 1.68 (1.00, 2.81)   |
| Subtotal (95% CI)     | 565     |       | 1339   |       | 81.1%  | 1.91 [1.90, 1.92]   | 1.91 [1.90, 1.92]   |
| Total events          | 565     |       | 1339   |       | 81.1%  | 1.91 [1.90, 1.92]   | 1.91 [1.90, 1.92]   |

**Heterogeneity:** $I^2 = 3.67$, $df = 3$ ($P = 0.33$), $P = 16$
**Test for overall effect:** $Z = 3.60$ ($P = 0.0003$)

#### D elevated LDH Severe/Deceased Non-severe/Survival Odds Ratio

| Study or Subgroup     | Events | Total | Events | Total | Weight | M.H. Random, 95% CI | M.H. Random, 95% CI |
|-----------------------|--------|-------|--------|-------|--------|---------------------|---------------------|
| 4.1.3 mortality       |        |       |        |       |        |                     |                     |
| Chen RH 2000          | 17      | 30    | 99     | 116   | 0.05   | 1.06 (0.84, 1.33)   | 1.06 (0.84, 1.33)   |
| Subtotal (95% CI)     | 182     |       | 1188   |       | 64.2%  | 1.19 [1.18, 1.20]   | 1.19 [1.18, 1.20]   |
| Total events          | 182     |       | 1188   |       | 64.2%  | 1.19 [1.18, 1.20]   | 1.19 [1.18, 1.20]   |

**Heterogeneity:** $I^2 = 12.48$, $df = 3$ ($P = 0.006$), $P = 52$
**Test for overall effect:** $Z = 5.17$ ($P = 0.0001$)

#### E elevated CR Severe/Deceased Non-severe/Survival Odds Ratio

| Study or Subgroup     | Events | Total | Events | Total | Weight | M.H. Random, 95% CI | M.H. Random, 95% CI |
|-----------------------|--------|-------|--------|-------|--------|---------------------|---------------------|
| 4.1.4 mortality       |        |       |        |       |        |                     |                     |
| Chen RH 2000          | 10      | 32    | 120    | 132   | 0.15   | 1.71 (1.05, 2.79)   | 1.71 (1.05, 2.79)   |
| Subtotal (95% CI)     | 112     |       | 492    |       | 63.5%  | 1.60 [1.39, 1.95]   | 1.60 [1.39, 1.95]   |
| Total events          | 112     |       | 492    |       | 63.5%  | 1.60 [1.39, 1.95]   | 1.60 [1.39, 1.95]   |

**Heterogeneity:** $I^2 = 0.00$, $Q = 1.99$, $df = 8$ ($P = 0.07$), $P = 48$
**Test for overall effect:** $Z = 1.73$ ($P = 0.03$)

#### E elevated CR Severe/Deceased Non-severe/Survival Odds Ratio

| Study or Subgroup     | Events | Total | Events | Total | Weight | M.H. Random, 95% CI | M.H. Random, 95% CI |
|-----------------------|--------|-------|--------|-------|--------|---------------------|---------------------|
| 4.1.5 mortality       |        |       |        |       |        |                     |                     |
| Chen RH 2000          | 32      | 35    | 411    | 446   | 1.04   | 1.25 (1.04, 1.51)   | 1.25 (1.04, 1.51)   |
| Subtotal (95% CI)     | 105     |       | 1349   |       | 13.7%  | 1.16 [1.08, 1.25]   | 1.16 [1.08, 1.25]   |
| Total events          | 105     |       | 1349   |       | 13.7%  | 1.16 [1.08, 1.25]   | 1.16 [1.08, 1.25]   |

**Heterogeneity:** $I^2 = 0.00$, $Q = 1.99$, $df = 1$ ($P = 0.001$), $P = 0$
**Test for overall effect:** $Z = 2.21$ ($P = 0.03$)

#### E elevated CR Severe/Deceased Non-severe/Survival Odds Ratio

| Study or Subgroup     | Events | Total | Events | Total | Weight | M.H. Random, 95% CI | M.H. Random, 95% CI |
|-----------------------|--------|-------|--------|-------|--------|---------------------|---------------------|
| 4.1.6 mortality       |        |       |        |       |        |                     |                     |
| Chen RH 2000          | 10      | 10    | 100    | 110   | 0.09   | 1.62 (1.03, 2.52)   | 1.62 (1.03, 2.52)   |
| Subtotal (95% CI)     | 110     |       | 110    |       | 100%   | 1.62 [1.03, 2.52]   | 1.62 [1.03, 2.52]   |
| Total events          | 110     |       | 110    |       | 100%   | 1.62 [1.03, 2.52]   | 1.62 [1.03, 2.52]   |

**Heterogeneity:** $I^2 = 14.95$, $df = 3$ ($P = 0.006$), $P = 82$
**Test for overall effect:** $Z = 3.72$ ($P = 0.0002$)

**Characteristics:** $Ch^2 = 0.07$, $df = 2$ ($P = 0.78$), $P = 48$
**Test for overall effect:** $Z = 2.97$ ($P = 0.003$)
of severity and death in subjects infected with SARS-CoV, H1N1 influenza virus, and MERS-CoV [52–54]. In addition, CVD and CKD were associated with an increased risk of progression and mortality in COVID-19 patients. A growing body of evidence shows that SARS-CoV-2 attaches to the cell membrane and attacks host cells via the ACE2 receptor [55, 56]. ACE2 receptors, which are mainly distributed in the cardiovascular system, lung, kidneys, and colon, have also been detected in glial cells and neurons in the brain; thus, these sites are potential targets of SARS-CoV-2 [57, 58]. ACE2 expression in brain and kidney cells is downregulated by mechanisms such as internalization, shedding, and viral replication [59]. An inflammatory response and exudation of immune cells are induced via increased Ang II concentrations, resulting in a cytokine storm and target-organ damage [60, 61]. If patients with CVD are infected with SARS-CoV-2, bleeding from cerebral capillaries due to endothelial ruptures could have fatal consequences [62]. The prevalence of acute kidney injury among COVID-19 patients is approximately 0.5%. The available data suggest that cytokine damage, organ crosstalk, and systemic effects might represent potential mechanisms of kidney injury in COVID-19 [63, 64]. Kidneys from CKD patients can experience a second hit via viral infection, and these patients are more likely to develop to renal failure [63]. In addition, malignancy and immunodeficiency increase the risk of disease progression or mortality. Compared to a 2.3% fatality rate for all COVID-19 patients, the fatality rate for infected cancer patients in China is 28.6% [65]. Patients with cancers are at an increased risk of severe complications of respiratory viruses because they are frequently immunosuppressed as a result of their disease and treatment [66]. The immune response plays important role in virus elimination and disease progression. For patients with malignancy or immunodeficiency, COVID-19 more often results in critical/fatal cases [67, 68].

Regarding clinical manifestations, sputum production was associated with a dramatically increased risk of progression and mortality. Exudation is a clinical manifestation of inflammation [69], and the volume of exudate is positively correlated with the severity of inflammation. We also found that the incidence of anorexia, fatigue, and shortness of breath was significantly higher in the severe group than in the non-severe group. In an European investigation, that also identified infection-related pulmonary symptoms such as dyspnea, fever were more prevalent in patients with moderate-to-severe COVID-19 [70]. Notably, except for dyspnea, we found hemoptysis to be another important risk factor for mortality. Thus, patients with hemoptysis should be given particular attention.

Regarding laboratory examination, several test values are associated with severity and mortality of COVID-19. Increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased CRP, coinfection with bacteria or fungi, increased ALT and CK, increased NT-proBNP, and bilateral pneumonia in CT/X-ray were significantly higher in the severe group than in the non-severe group. Moreover, the proportion of patients with increased CRP and TBIL was also significantly higher in the deceased group than in the survival group. When the body is infected or the tissue is damaged, CRP plasma levels increase rapidly as an acute protein indicator [71]. These increased levels increase phagocytosis and activate the complement cascade [72]. Moreover, damaged, necrotic, and apoptotic tissues and cells, as well as the pathogen, are eliminated by CRP. The CRP concentration is a reflection of the body’s response to infection [73]. Increased NT-proBNP and ALT indicate impaired cardiac function, and increased TBIL indicates impaired liver function. Coinfection with bacteria or fungi and bilateral pneumonia in CT/X-ray were associated with COVID-19 severity. This is consistent with the results of Li et al., showing that initial CT scores may be useful to stratify patients [74]. All of the risk factors are helpful for identifying possible severe cases and are potentially valuable for decisions regarding allocation of medical resources.

**Strengths and weaknesses**

To the best of our knowledge, this is the first updated meta-analysis to assess all of the common risk factors for progression and mortality in COVID-19 patients using a large study sample. In this study, more confounding factors were adjusted, and more risk factors were found for the first time. High heterogeneity was found in the analysis of some risk factors, and the majority of factors were compensated by sensitivity analysis. Some results (decreased WBC and LDH in severe and fatal cases as well as dizziness) should be interpreted with caution given the limited number of included articles and high heterogeneity. Further high-quality studies are needed to verify these results.

This meta-analysis has some potential limitations. First, the source of heterogeneity for some risk factors was not identified by sensitivity analysis. Second, the small sample size of patients hindered the implementation of meta-regression analysis. Third, the nonrandomized and retrospective
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nature of all studies should be taken into consideration as a source of bias. Randomized controlled trials are warranted in the future to provide high-quality evidence.

Conclusions

Some new risk factors were identified in our updated meta-analysis. Regarding comorbidities, CVD, CKD, CHD, and malignancy were associated with an increased risk of progression and mortality in COVID-19 patients. Regarding clinical manifestations, sputum production was associated with a dramatically increased risk of progression and mortality. Hemoptysis was a risk factor for death in COVID-19 patients. In laboratory examinations, increased neutrophil count, decreased lymphocyte count, decreased platelet count, increased CRP, coinfection with bacteria or fungi, increased ALT and CK, increased NT-proBNP, and bilateral pneumonia in CT/X-ray were significantly higher in the severe group than in the non-severe group. Moreover, the proportion of patients with increased CRP and TBIL was also significantly higher in the deceased group than in the survival group.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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