Archives of Virology (2021) 166:2071–2087
https://doi.org/10.1007/s00705-021-05012-2

REVIEW

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

Li Zhang[1] · Jie Hou[1] · Fu-Zhe Ma[1] · Jia Li[1] · Shuai Xue[2] · Zhong-Gao Xu[1]

Received: 27 October 2020 / Accepted: 10 January 2021 / Published online: 2 April 2021
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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

Handling Editor: Tim Skern.

Shuai Xue and Zhong-Gao Xu contributed equally to this work.

✉ Shuai Xue
xueshuai@jlu.edu.cn

✉ Zhong-Gao Xu
zhonggao@jlu.edu.cn

[1] Department of Nephrology, The First Hospital of Jilin University, Changchun 130021, Jilin, People's Republic of China

[2] Department of Thyroid Surgery, The First Hospital of Jilin University, Changchun 130021, Jilin, People's Republic of China

prognosis [6]. 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/and moderate disease were included in the non-severe group, and patients with severe or/and critical disease were included in the severe group. Moreover, patients in an intensive care unit (ICU) or with $SpO_2 \leq 90\%$ 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

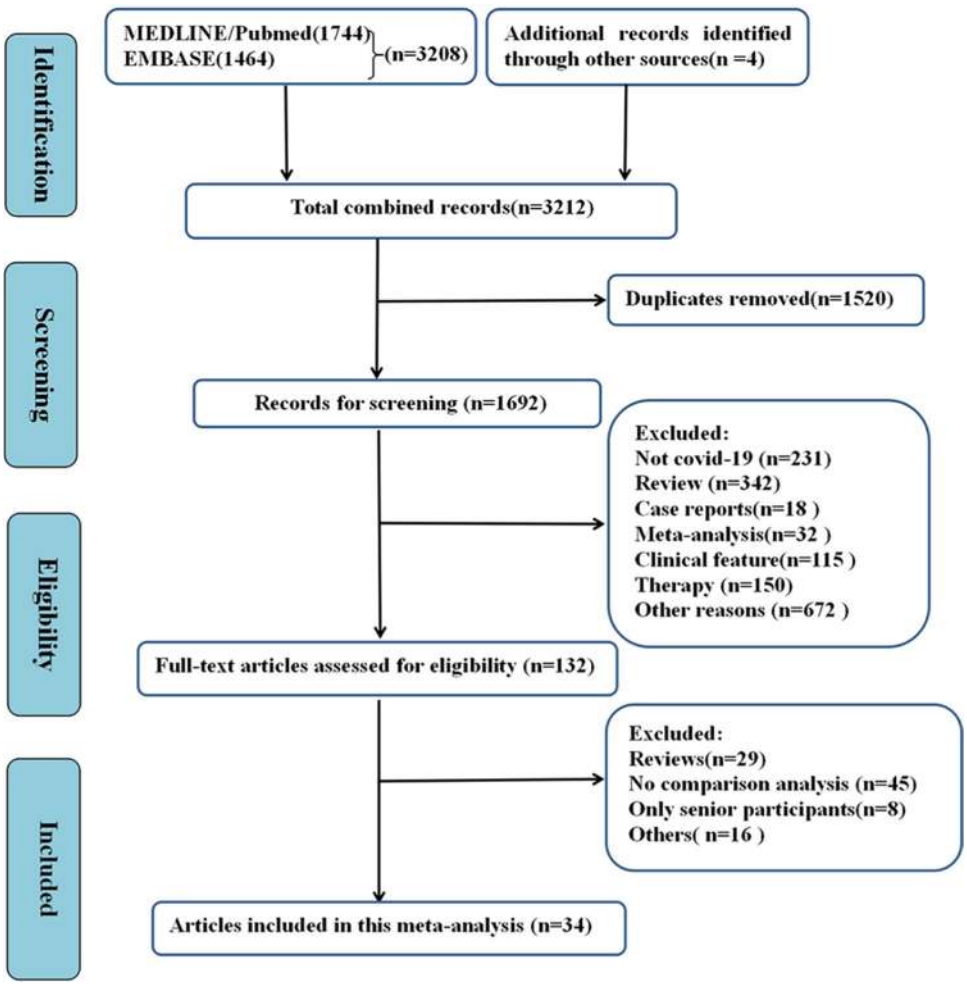


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow chart of the study selection process, showing the number of studies excluded at each step and the reasons for exclusion from the systematic review and meta-analysis

Table 1 Baseline characteristics of the included studies

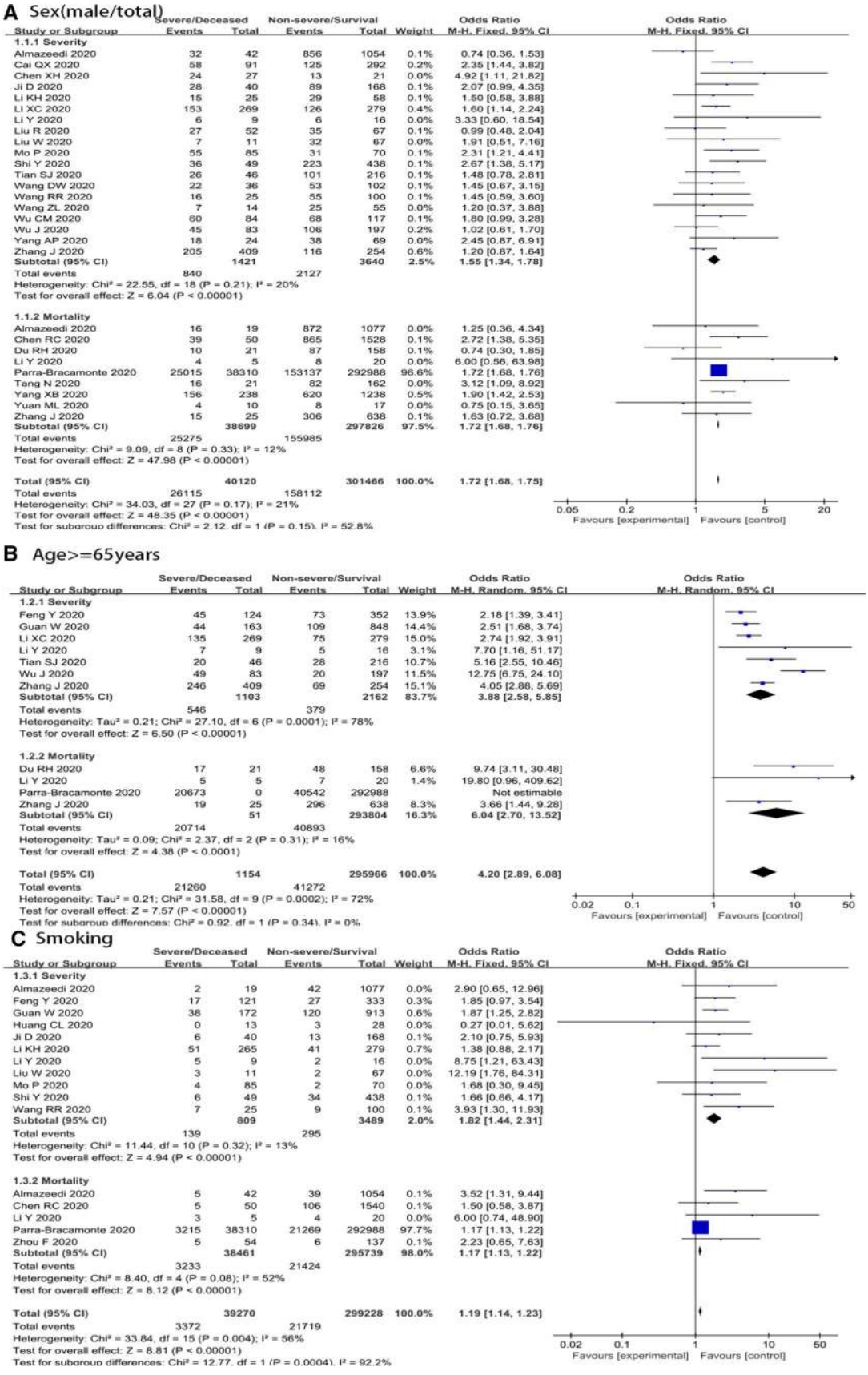
Author	Region/country	No. of patients	Sex (male/total)	Mean age (SD)/mean (IQR)	NOS
Chen RC*	Throughout China	1590	904/1578	69 (51-86)	8
Chen XH	Wuhan, China	48	37/48	64.6 ± 18.1	7
Cheng YC	Wuhan, China	701	367/701	63 (50-71)	7
Du RH	Wuhan, China	179	97/179	57.6 ± 13.7	8
Feng Y	Wuhan,Shanghai and Anhui	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 (36-65)	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

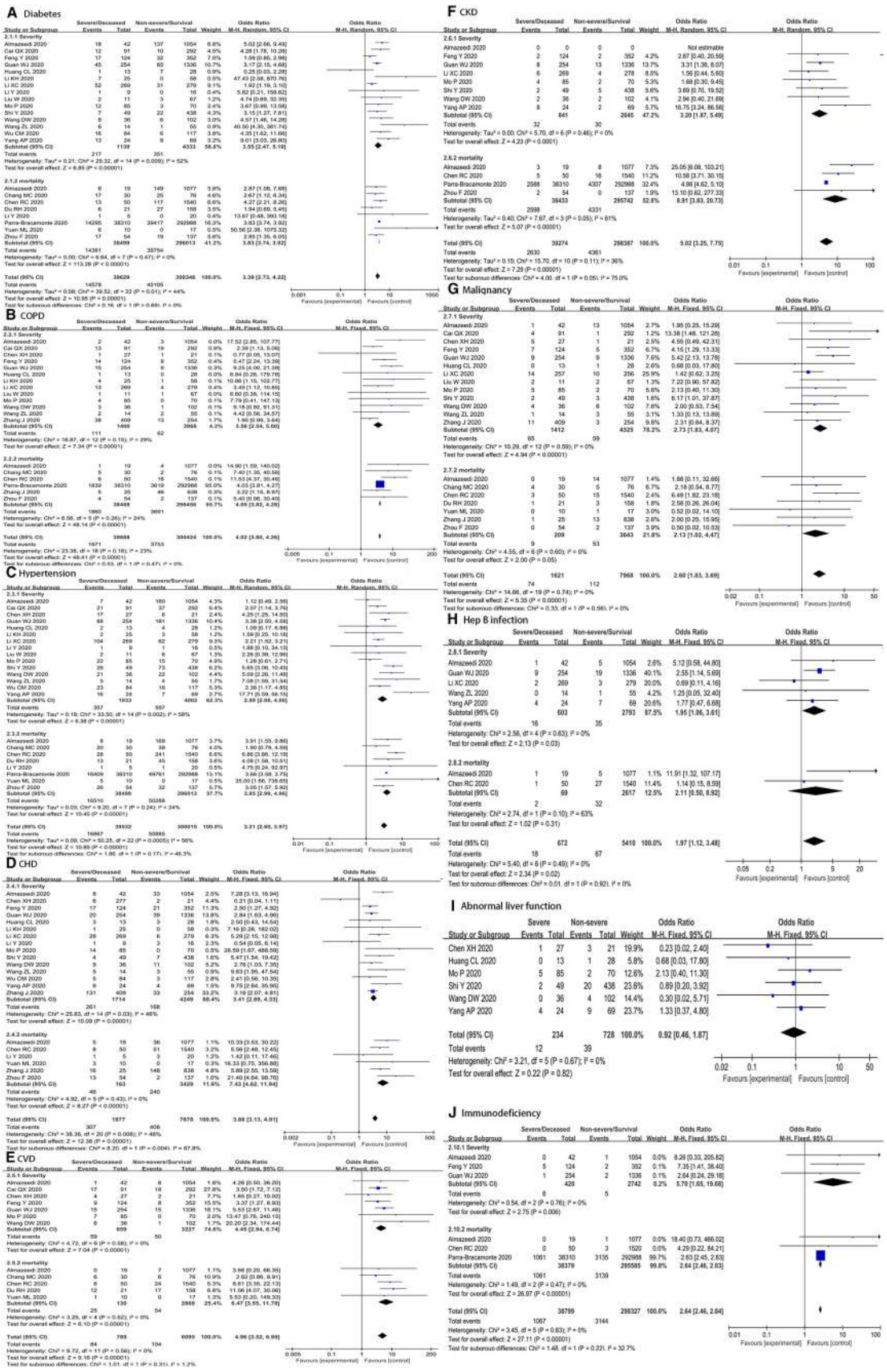
N/A, not applicable; SD, standard deviation; IQR, interquartile range; NOS, Newcastle-Ottawa Scale (score)

*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.

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.

Fig. 2 Association of general characteristics with progression and mortality in COVID-19. Forest plots are shown for the effects of (A) sex (male/total), (B) age ≥ 65 years, and (C) smoking.


A Sex(male/total)
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.1.1 Severity
Almazeedi 2020 32 42 856 1054 0.1% 0.74 [0.36, 1.53]
Cai QX 2020 58 91 125 292 0.2% 2.35 [1.44, 3.82]
Chen XH 2020 24 27 13 21 0.0% 4.92 [1.11, 21.82]
Ji D 2020 28 40 89 168 0.1% 2.07 [0.99, 4.35]
Li KH 2020 15 25 29 58 0.1% 1.50 [0.58, 3.88]
Li XC 2020 153 269 126 279 0.4% 1.60 [1.14, 2.24]
Li Y 2020 6 9 6 16 0.0% 3.33 [0.60, 18.54]
Liu R 2020 27 52 35 67 0.1% 0.99 [0.48, 2.04]
Liu W 2020 7 11 32 67 0.0% 1.91 [0.51, 7.16]
Mo P 2020 55 85 31 70 0.1% 2.31 [1.21, 4.41]
Shi Y 2020 36 49 223 438 0.1% 2.67 [1.38, 5.17]
Tian SJ 2020 26 46 101 216 0.1% 1.48 [0.78, 2.81]
Wang DW 2020 22 36 53 102 0.1% 1.45 [0.67, 3.15]
Wang RR 2020 16 25 55 100 0.1% 1.45 [0.59, 3.60]
Wang ZL 2020 7 14 25 55 0.0% 1.20 [0.37, 3.88]
Wu CM 2020 60 84 68 117 0.1% 1.80 [0.99, 3.28]
Wu J 2020 45 83 106 197 0.2% 1.02 [0.61, 1.70]
Yang AP 2020 18 24 38 69 0.0% 2.45 [0.87, 6.91]
Zhang J 2020 205 409 116 254 0.6% 1.20 [0.87, 1.64]
Subtotal (95% CI) 1421 3640 2.5% 1.55 [1.34, 1.78]
Total events 840 2127
Heterogeneity: Chi² = 22.55, df = 18 (P = 0.21); I² = 20%
Test for overall effect: Z = 6.04 (P < 0.00001)
1.1.2 Mortality
Almazeedi 2020 16 19 872 1077 0.0% 1.25 [0.36, 4.34]
Chen RC 2020 39 50 865 1528 0.1% 2.72 [1.38, 5.35]
Du RH 2020 10 21 87 158 0.1% 0.74 [0.30, 1.85]
Li Y 2020 4 5 8 20 0.0% 6.00 [0.56, 63.98]
Parra-Bracamonte 2020 25015 38310 153137 292988 96.6% 1.72 [1.68, 1.76]
Tang N 2020 16 21 82 162 0.0% 3.12 [1.09, 8.92]
Yang XB 2020 156 238 620 1238 0.5% 1.90 [1.42, 2.53]
Yuan ML 2020 4 10 8 17 0.0% 0.75 [0.15, 3.65]
Zhang J 2020 15 25 306 638 0.1% 1.63 [0.72, 3.68]
Subtotal (95% CI) 38699 297826 97.5% 1.72 [1.68, 1.76]
Total events 25275 155985
Heterogeneity: Chi² = 9.09, df = 8 (P = 0.33); I² = 12%
Test for overall effect: Z = 47.98 (P < 0.00001)
Total (95% CI) 40120 301466 100.0% 1.72 [1.68, 1.75]
Total events 26115 158112
Heterogeneity: Chi² = 34.03, df = 27 (P = 0.17); I² = 21%
Test for overall effect: Z = 48.35 (P < 0.00001)
Test for subgroup differences: Chi² = 2.12, df = 1 (P = 0.15), I² = 52.8%
0.05 0.2 1 5 20
Favours [experimental] Favours [control]
B Age>=65years
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 Severity
Feng Y 2020 45 124 73 352 13.9% 2.18 [1.39, 3.41]
Guan W 2020 44 163 109 848 14.4% 2.51 [1.68, 3.74]
Li XC 2020 135 269 75 279 15.0% 2.74 [1.92, 3.91]
Li Y 2020 7 9 5 16 3.1% 7.70 [1.16, 51.17]
Tian SJ 2020 20 46 28 216 10.7% 5.16 [2.55, 10.46]
Wu J 2020 49 83 20 197 11.5% 12.75 [6.75, 24.10]
Zhang J 2020 246 409 69 254 15.1% 4.05 [2.88, 5.69]
Subtotal (95% CI) 1103 2162 83.7% 3.88 [2.58, 5.85]
Total events 546 379
Heterogeneity: Tau² = 0.21; Chi² = 27.10, df = 6 (P = 0.0001); I² = 78%
Test for overall effect: Z = 6.50 (P < 0.00001)
1.2.2 Mortality
Du RH 2020 17 21 48 158 6.6% 9.74 [3.11, 30.48]
Li Y 2020 5 5 7 20 1.4% 19.80 [0.96, 409.62]
Parra-Bracamonte 2020 20673 0 40542 292988 Not estimable
Zhang J 2020 19 25 296 638 8.3% 3.66 [1.44, 9.28]
Subtotal (95% CI) 51 293804 16.3% 6.04 [2.70, 13.52]
Total events 20714 40893
Heterogeneity: Tau² = 0.09; Chi² = 2.37, df = 2 (P = 0.31); I² = 16%
Test for overall effect: Z = 4.38 (P < 0.0001)
Total (95% CI) 1154 295966 100.0% 4.20 [2.89, 6.08]
Total events 21260 41272
Heterogeneity: Tau² = 0.21; Chi² = 31.58, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 7.57 (P < 0.00001)
Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%
0.02 0.1 1 10 50
Favours [experimental] Favours [control]
C Smoking
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.3.1 Severity
Almazeedi 2020 2 19 42 1077 0.0% 2.90 [0.65, 12.96]
Feng Y 2020 17 121 27 333 0.3% 1.85 [0.97, 3.54]
Guan W 2020 38 172 120 913 0.6% 1.87 [1.25, 2.82]
Huang CL 2020 0 13 3 28 0.0% 0.27 [0.01, 5.62]
Ji D 2020 6 40 13 168 0.1% 2.10 [0.75, 5.93]
Li KH 2020 51 265 41 279 0.7% 1.38 [0.88, 2.17]
Li Y 2020 5 9 2 16 0.0% 8.75 [1.21, 63.43]
Liu W 2020 3 11 2 67 0.0% 12.19 [1.76, 84.31]
Mo P 2020 4 85 2 70 0.0% 1.68 [0.30, 9.45]
Shi Y 2020 6 49 34 438 0.1% 1.66 [0.66, 4.17]
Wang RR 2020 7 25 9 100 0.1% 3.93 [1.30, 11.93]
Subtotal (95% CI) 809 3489 2.0% 1.82 [1.44, 2.31]
Total events 139 295
Heterogeneity: Chi² = 11.44, df = 10 (P = 0.32); I² = 13%
Test for overall effect: Z = 4.94 (P < 0.00001)
1.3.2 Mortality
Almazeedi 2020 5 42 39 1054 0.1% 3.52 [1.31, 9.44]
Chen RC 2020 5 50 106 1540 0.1% 1.50 [0.58, 3.87]
Li Y 2020 3 5 4 20 0.0% 6.00 [0.74, 48.90]
Parra-Bracamonte 2020 3215 38310 21269 292988 97.7% 1.17 [1.13, 1.22]
Zhou F 2020 5 54 6 137 0.1% 2.23 [0.65, 7.63]
Subtotal (95% CI) 38461 295739 98.0% 1.17 [1.13, 1.22]
Total events 3233 21424
Heterogeneity: Chi² = 8.40, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 8.12 (P < 0.00001)
Total (95% CI) 39270 299228 100.0% 1.19 [1.14, 1.23]
Total events 3372 21719
Heterogeneity: Chi² = 33.84, df = 15 (P = 0.004); I² = 56%
Test for overall effect: Z = 8.81 (P < 0.00001)
Test for subgroup differences: Chi² = 12.77, df = 1 (P = 0.0004), I² = 92.2%
0.02 0.1 1 10 50
Favours [experimental] Favours [control]


A Diabetes
B COPD
C Hypertension
D CHD
E CVD
F CKD
G Malignancy
H Hep B infection
I Abnormal liver function
J Immunodeficiency

◂**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 then in the non-severe or survival group (OR = 3.39, 95% CI 2.73 to 4.22, pooled $P < 0.00001$) without heterogeneity ($I^2 = 44\%$) (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 $I^2 = 0\%$) (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 ($I^2 = 62\%$ and $I^2 = 77\%$, 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/arthralgia, 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/arthralgia, 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

Table 2 Results of meta-analysis of the clinical manifestations

Clinical manifestation	OR (95% CI)	*P*-value
Severity subgroup		
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/arthralgia	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
Hemoptysis	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
Mortality subgroup		
Fever	0.81 (0.47 to 1.38)	0.43
Fatigue	1.40 (0.98 to 2.00)	0.06
Myalgia /arthralgia	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
Hemoptysis	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

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).

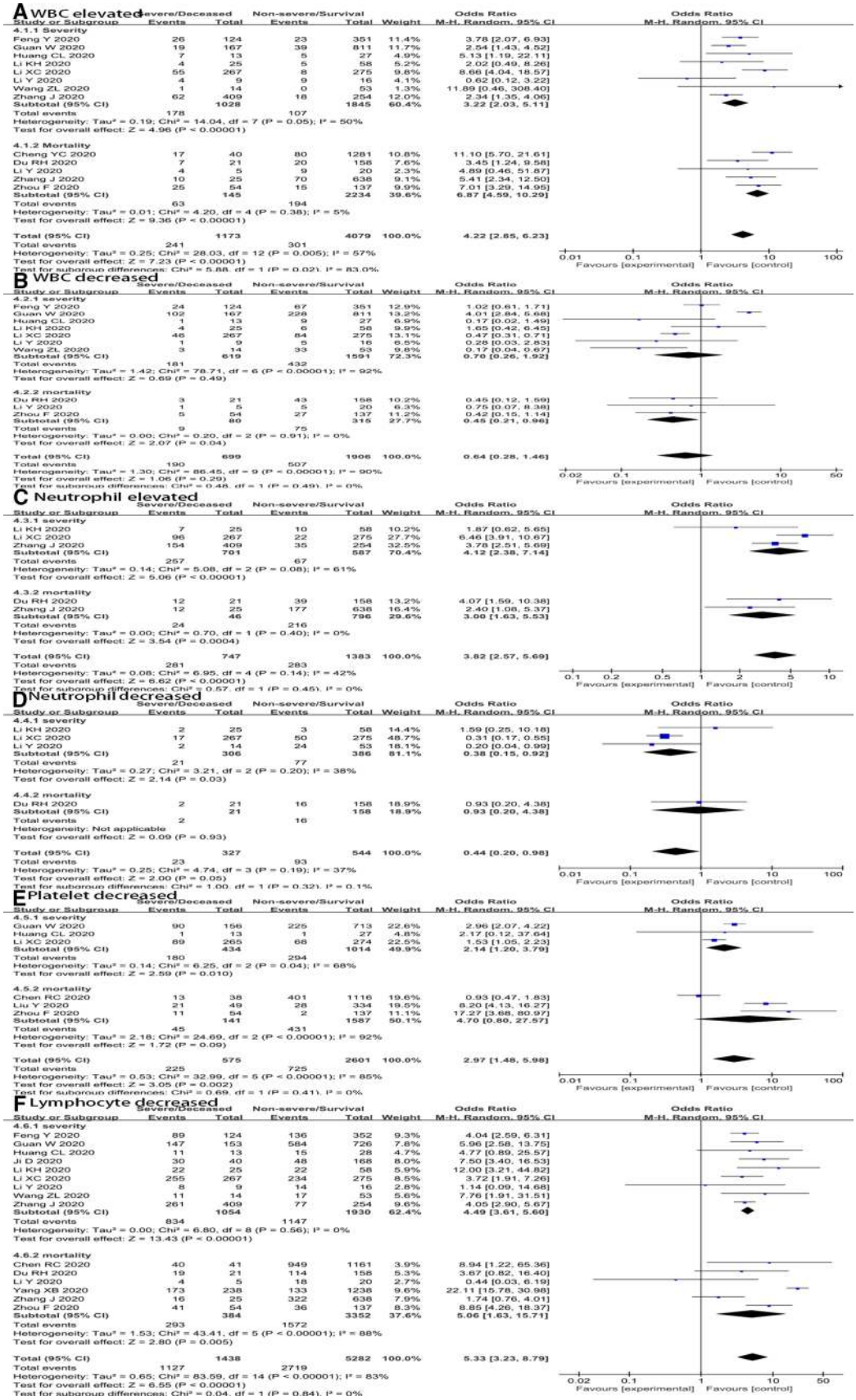
Fig. 4 Routine blood test risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated WBC, (B) decreased WBC, (C) elevated neutrophils, (D) decreased neutrophils, (E) decreased platelets, and (F) decreased lymphocytes. ▶

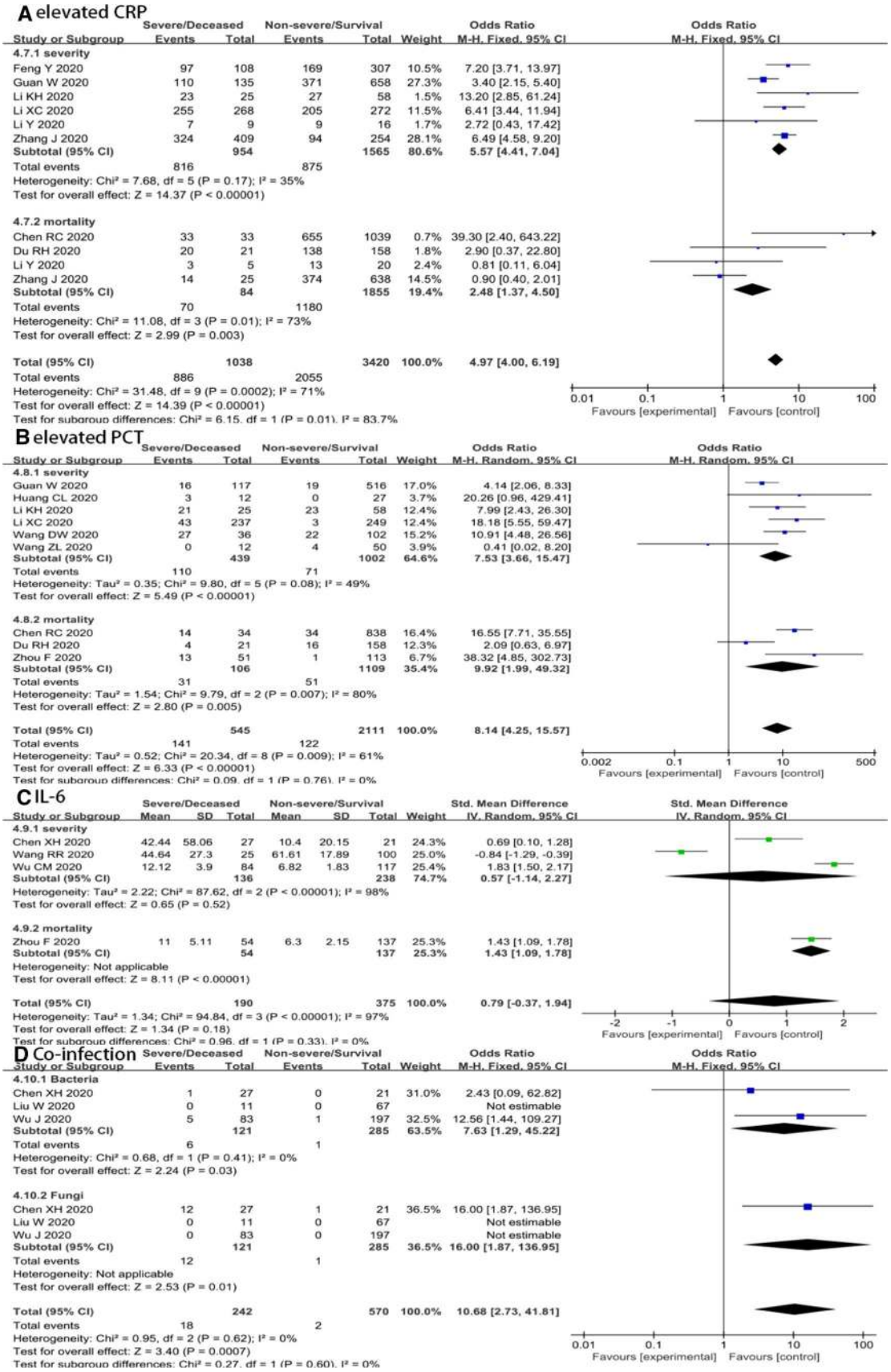
Infection-related results

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), but heterogeneity was noted ($I^2 = 73\%$ and $I^2 = 80\%$, respectively) (Fig. 5A and B). 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


A WBC elevated
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.1.1 Severity
Feng Y 2020 26 124 23 351 11.4% 3.78 [2.07, 6.93]
Guan W 2020 19 167 39 811 11.7% 2.54 [1.43, 4.52]
Huang CL 2020 7 13 5 27 4.9% 5.13 [1.19, 22.11]
Li KH 2020 4 25 5 58 5.2% 2.02 [0.49, 8.26]
Li XC 2020 55 267 8 275 9.8% 8.66 [4.04, 18.57]
Li Y 2020 4 9 9 16 4.1% 0.62 [0.12, 3.22]
Wang ZL 2020 1 14 0 53 1.3% 11.89 [0.46, 308.40]
Zhang J 2020 62 409 18 254 12.0% 2.34 [1.35, 4.06]
Subtotal (95% CI) 1028 1845 60.4% 3.22 [2.03, 5.11]
Total events 178 107
Heterogeneity: Tau² = 0.19; Chi² = 14.04, df = 7 (P = 0.05); I² = 50%
Test for overall effect: Z = 4.96 (P < 0.00001)
4.1.2 Mortality
Cheng YC 2020 17 40 80 1281 10.8% 11.10 [5.70, 21.61]
Du RH 2020 7 21 20 158 7.6% 3.45 [1.24, 9.58]
Li Y 2020 4 5 9 20 2.3% 4.89 [0.46, 51.87]
Zhang J 2020 10 25 70 638 9.1% 5.41 [2.34, 12.50]
Zhou F 2020 25 54 15 137 9.9% 7.01 [3.29, 14.95]
Subtotal (95% CI) 145 2234 39.6% 6.87 [4.59, 10.29]
Total events 63 194
Heterogeneity: Tau² = 0.01; Chi² = 4.20, df = 4 (P = 0.38); I² = 5%
Test for overall effect: Z = 9.36 (P < 0.00001)
Total (95% CI) 1173 4079 100.0% 4.22 [2.85, 6.23]
Total events 241 301
Heterogeneity: Tau² = 0.25; Chi² = 28.03, df = 12 (P = 0.005); I² = 57%
Test for overall effect: Z = 7.23 (P < 0.00001)
Test for subgroup differences: Chi² = 5.88, df = 1 (P = 0.02), I² = 83.0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
B WBC decreased
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.2.1 severity
Feng Y 2020 24 124 67 351 12.9% 1.02 [0.61, 1.71]
Guan W 2020 102 167 228 811 13.2% 4.01 [2.84, 5.68]
Huang CL 2020 1 13 9 27 6.9% 0.17 [0.02, 1.49]
Li KH 2020 4 25 6 58 9.9% 1.65 [0.42, 6.45]
Li XC 2020 48 267 84 275 13.1% 0.47 [0.31, 0.71]
Li Y 2020 1 9 5 16 6.5% 0.28 [0.03, 2.83]
Wang ZL 2020 3 14 33 53 9.8% 0.17 [0.04, 0.67]
Subtotal (95% CI) 619 1591 72.3% 0.70 [0.26, 1.92]
Total events 181 432
Heterogeneity: Tau² = 1.42; Chi² = 78.71, df = 6 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.69 (P = 0.49)
4.2.2 mortality
Du RH 2020 3 21 43 158 10.2% 0.45 [0.12, 1.59]
Li Y 2020 1 5 5 20 6.3% 0.75 [0.07, 8.38]
Zhou F 2020 5 54 27 137 11.2% 0.42 [0.15, 1.14]
Subtotal (95% CI) 80 315 27.7% 0.45 [0.21, 0.96]
Total events 9 75
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Total (95% CI) 699 1906 100.0% 0.64 [0.28, 1.46]
Total events 190 507
Heterogeneity: Tau² = 1.30; Chi² = 86.45, df = 9 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%
0.02 0.1 1 10 50
Favours [experimental] Favours [control]
C Neutrophil elevated
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.3.1 severity
Li KH 2020 7 25 10 58 10.2% 1.87 [0.62, 5.65]
Li XC 2020 96 267 22 275 27.7% 6.46 [3.91, 10.67]
Zhang J 2020 154 409 35 254 32.5% 3.78 [2.51, 5.69]
Subtotal (95% CI) 701 587 70.4% 4.12 [2.38, 7.14]
Total events 257 67
Heterogeneity: Tau² = 0.14; Chi² = 5.08, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 5.06 (P < 0.00001)
4.3.2 mortality
Du RH 2020 12 21 39 158 13.2% 4.07 [1.59, 10.38]
Zhang J 2020 12 25 177 638 16.4% 2.40 [1.08, 5.37]
Subtotal (95% CI) 46 796 29.6% 3.00 [1.63, 5.53]
Total events 24 216
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.54 (P = 0.0004)
Total (95% CI) 747 1383 100.0% 3.82 [2.57, 5.69]
Total events 281 283
Heterogeneity: Tau² = 0.08; Chi² = 6.95, df = 4 (P = 0.14); I² = 42%
Test for overall effect: Z = 6.62 (P < 0.00001)
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours [experimental] Favours [control]
D Neutrophil decreased
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.4.1 severity
Li KH 2020 2 25 3 58 14.4% 1.59 [0.25, 10.18]
Li XC 2020 17 267 50 275 48.7% 0.31 [0.17, 0.55]
Li Y 2020 2 14 24 53 18.1% 0.20 [0.04, 0.99]
Subtotal (95% CI) 306 386 81.1% 0.38 [0.15, 0.92]
Total events 21 77
Heterogeneity: Tau² = 0.27; Chi² = 3.21, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 2.14 (P = 0.03)
4.4.2 mortality
Du RH 2020 2 21 16 158 18.9% 0.93 [0.20, 4.38]
Subtotal (95% CI) 21 158 18.9% 0.93 [0.20, 4.38]
Total events 2 16
Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)
Total (95% CI) 327 544 100.0% 0.44 [0.20, 0.98]
Total events 23 93
Heterogeneity: Tau² = 0.25; Chi² = 4.74, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 2.00 (P = 0.05)
Test for subgroup differences: Chi² = 1.00, df = 1 (P = 0.32), I² = 0.1%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
E Platelet decreased
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.5.1 severity
Guan W 2020 90 156 225 713 22.6% 2.96 [2.07, 4.22]
Huang CL 2020 1 13 1 27 4.8% 2.17 [0.12, 37.64]
Li XC 2020 89 265 68 274 22.5% 1.53 [1.05, 2.23]
Subtotal (95% CI) 434 1014 49.9% 2.14 [1.20, 3.79]
Total events 180 294
Heterogeneity: Tau² = 0.14; Chi² = 6.25, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 2.59 (P = 0.010)
4.5.2 mortality
Chen RC 2020 13 38 401 1116 19.6% 0.93 [0.47, 1.83]
Liu Y 2020 21 49 28 334 19.5% 8.20 [4.13, 16.27]
Zhou F 2020 11 54 2 137 11.1% 17.27 [3.88, 80.97]
Subtotal (95% CI) 141 1587 50.1% 4.70 [0.80, 27.57]
Total events 45 431
Heterogeneity: Tau² = 2.18; Chi² = 24.69, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.72 (P = 0.09)
Total (95% CI) 575 2601 100.0% 2.97 [1.48, 5.98]
Total events 225 725
Heterogeneity: Tau² = 0.53; Chi² = 32.99, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.05 (P = 0.002)
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
F Lymphocyte decreased
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.6.1 severity
Feng Y 2020 89 124 136 352 9.3% 4.04 [2.59, 6.31]
Guan W 2020 147 153 584 726 7.8% 5.96 [2.58, 13.75]
Huang CL 2020 11 13 15 28 4.7% 4.77 [0.89, 25.57]
Ji D 2020 30 40 48 168 8.0% 7.50 [3.40, 16.53]
Li KH 2020 22 25 22 58 5.9% 12.00 [3.21, 44.82]
Li XC 2020 255 267 234 275 8.5% 3.72 [1.91, 7.26]
Li Y 2020 8 9 14 16 2.8% 1.14 [0.09, 14.68]
Wang ZL 2020 11 14 17 53 5.6% 7.76 [1.91, 31.51]
Zhang J 2020 261 409 77 254 9.6% 4.05 [2.90, 5.67]
Subtotal (95% CI) 1054 1930 62.4% 4.49 [3.61, 5.60]
Total events 834 1147
Heterogeneity: Tau² = 0.00; Chi² = 6.80, df = 8 (P = 0.56); I² = 0%
Test for overall effect: Z = 13.43 (P < 0.00001)
4.6.2 mortality
Chen RC 2020 40 41 949 1161 3.9% 8.94 [1.22, 65.36]
Du RH 2020 19 21 114 158 5.3% 3.67 [0.82, 16.40]
Li Y 2020 4 5 18 20 2.7% 0.44 [0.03, 6.19]
Yang XB 2020 173 238 133 1238 9.6% 22.11 [15.78, 30.98]
Zhang J 2020 16 25 322 638 7.9% 1.74 [0.76, 4.01]
Zhou F 2020 41 54 36 137 8.3% 8.85 [4.26, 18.37]
Subtotal (95% CI) 384 3352 37.6% 5.06 [1.63, 15.71]
Total events 293 1572
Heterogeneity: Tau² = 1.53; Chi² = 43.41, df = 5 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.80 (P = 0.005)
Total (95% CI) 1438 5282 100.0% 5.33 [3.23, 8.79]
Total events 1127 2719
Heterogeneity: Tau² = 0.65; Chi² = 83.59, df = 14 (P < 0.00001); I² = 83%
Test for overall effect: Z = 6.55 (P < 0.00001)
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%
0.02 0.1 1 10 50
Favours [experimental] Favours [control]


A elevated CRP
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
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 KH 2020 23 25 27 58 1.5% 13.20 [2.85, 61.24]
Li XC 2020 255 268 205 272 11.5% 6.41 [3.44, 11.94]
Li Y 2020 7 9 9 16 1.7% 2.72 [0.43, 17.42]
Zhang J 2020 324 409 94 254 28.1% 6.49 [4.58, 9.20]
Subtotal (95% CI) 954 1565 80.6% 5.57 [4.41, 7.04]
Total events 816 875
Heterogeneity: Chi² = 7.68, df = 5 (P = 0.17); I² = 35%
Test for overall effect: Z = 14.37 (P < 0.00001)
4.7.2 mortality
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, 4.50]
Total events 70 1180
Heterogeneity: Chi² = 11.08, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 2.99 (P = 0.003)
Total (95% CI) 1038 3420 100.0% 4.97 [4.00, 6.19]
Total events 886 2055
Heterogeneity: Chi² = 31.48, df = 9 (P = 0.0002); I² = 71%
Test for overall effect: Z = 14.39 (P < 0.00001)
Test for subgroup differences: Chi² = 6.15, df = 1 (P = 0.01), I² = 83.7%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
B elevated PCT
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.8.1 severity
Guan W 2020 16 117 19 516 17.0% 4.14 [2.06, 8.33]
Huang CL 2020 3 12 0 27 3.7% 20.26 [0.96, 429.41]
Li KH 2020 21 25 23 58 12.4% 7.99 [2.43, 26.30]
Li XC 2020 43 237 3 249 12.4% 18.18 [5.55, 59.47]
Wang DW 2020 27 36 22 102 15.2% 10.91 [4.48, 26.56]
Wang ZL 2020 0 12 4 50 3.9% 0.41 [0.02, 8.20]
Subtotal (95% CI) 439 1002 64.6% 7.53 [3.66, 15.47]
Total events 110 71
Heterogeneity: Tau² = 0.35; Chi² = 9.80, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 5.49 (P < 0.00001)
4.8.2 mortality
Chen RC 2020 14 34 34 838 16.4% 16.55 [7.71, 35.55]
Du RH 2020 4 21 16 158 12.3% 2.09 [0.63, 6.97]
Zhou F 2020 13 51 1 113 6.7% 38.32 [4.85, 302.73]
Subtotal (95% CI) 106 1109 35.4% 9.92 [1.99, 49.32]
Total events 31 51
Heterogeneity: Tau² = 1.54; Chi² = 9.79, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 2.80 (P = 0.005)
Total (95% CI) 545 2111 100.0% 8.14 [4.25, 15.57]
Total events 141 122
Heterogeneity: Tau² = 0.52; Chi² = 20.34, df = 8 (P = 0.009); I² = 61%
Test for overall effect: Z = 6.33 (P < 0.00001)
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%
0.002 0.1 1 10 500
Favours [experimental] Favours [control]
C IL-6
Severe/Deceased
Non-severe/Survival
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.9.1 severity
Chen XH 2020 42.44 58.06 27 10.4 20.15 21 24.3% 0.69 [0.10, 1.28]
Wang RR 2020 44.64 27.3 25 61.61 17.89 100 25.0% -0.84 [-1.29, -0.39]
Wu CM 2020 12.12 3.9 84 6.82 1.83 117 25.4% 1.83 [1.50, 2.17]
Subtotal (95% CI) 136 238 74.7% 0.57 [-1.14, 2.27]
Heterogeneity: Tau² = 2.22; Chi² = 87.62, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.65 (P = 0.52)
4.9.2 mortality
Zhou F 2020 11 5.11 54 6.3 2.15 137 25.3% 1.43 [1.09, 1.78]
Subtotal (95% CI) 54 137 25.3% 1.43 [1.09, 1.78]
Heterogeneity: Not applicable
Test for overall effect: Z = 8.11 (P < 0.00001)
Total (95% CI) 190 375 100.0% 0.79 [-0.37, 1.94]
Heterogeneity: Tau² = 1.34; Chi² = 94.84, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%
-2 -1 0 1 2
Favours [experimental] Favours [control]
D Co-infection
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
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) 121 285 63.5% 7.63 [1.29, 45.22]
Total events 6 1
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.24 (P = 0.03)
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 36.5% 16.00 [1.87, 136.95]
Total events 12 1
Heterogeneity: Not applicable
Test for overall effect: Z = 2.53 (P = 0.01)
Total (95% CI) 242 570 100.0% 10.68 [2.73, 41.81]
Total events 18 2
Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 3.40 (P = 0.0007)
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

◂**Fig. 5** 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.

group than in the non-severe/survival group (pooled results: AST: OR = 2.78, 95% CI 2.24 to 3.46, $P < 0.00001$; ALT: OR = 1.74, 95% CI 1.43 to 2.13, $P < 0.00001$; CK: OR = 2.03, 95% CI 1.40 to 2.96, $P = 0.0002$; sCr: OR = 3.80, 95% CI 2.32 to 6.20, $P < 0.00001$) (Fig. 6A, B, E, and F). In addition, lactate dehydrogenase (LDH) and total bilirubin (TBIL) levels were assessed. The results suggest that increased LDH is associated with a higher risk of progression (OR = 4.12, 95% CI 2.88 to 5.90, $P < 0.00001$) but not mortality; however, increased TBIL is associated with a higher risk of mortality (OR = 2.58, 95% CI 1.14 to 5.83, $P < 0.00001$) but not progression (Fig. 6C and D).

Other results

The proportion of elevated N-terminal pronatriuretic peptide (NT-proBNP) or D-dimer was significantly higher in the severe/deceased group than in the non-severe/survival group (pooled OR = 4.57, 95% CI 2.68 to 7.81, $P < 0.00001$; OR = 3.19, 95% CI 2.53 to 4.02, $P < 0.00001$, respectively) without significant heterogeneity ($I^2 = 0\%$ and $I^2 = 49\%$, respectively) (Fig. 7B and C). We found that increased high-sensitivity cardiac troponin I (Hs-cTnI) is associated with a higher risk of mortality (OR = 14.40, 95% CI 2.45 to 84.54, $P = 0.003$) but not severity (Fig. 7A); however, bilateral pneumonia in CT/X-ray is associated with a higher risk of severity (OR = 2.27, 95% CI 1.13 to 4.58, $P = 0.02$) but not mortality, with statistical significance despite some degree of heterogeneity ($I^2 = 62\%$ and $I^2 = 86\%$, respectively) (Fig. 7D).

Publication bias

Egger's regression analysis and Begg's rank correlation analysis were performed to assess publication bias (Table S2). With the exception of dyspnea and smoking, the *P*-values for all factors were greater than 0.05, indicating the absence of publication bias. To confirm the publication bias for dyspnea, we adopted the trim-and-fill method (Fig. 8). After assessing five studies, the *P*-value was less than 0.0001, which is the same as the previous result; however, the OR (95% CI) changed from -1.809 (-2.251, -1.366) to 0.260 (0.160, 0.422), suggesting publication bias. Similarly, we did funnel plot analysis for smoking, showing asymmetry, indicating publication bias (Fig. 3).

Sensitivity analysis

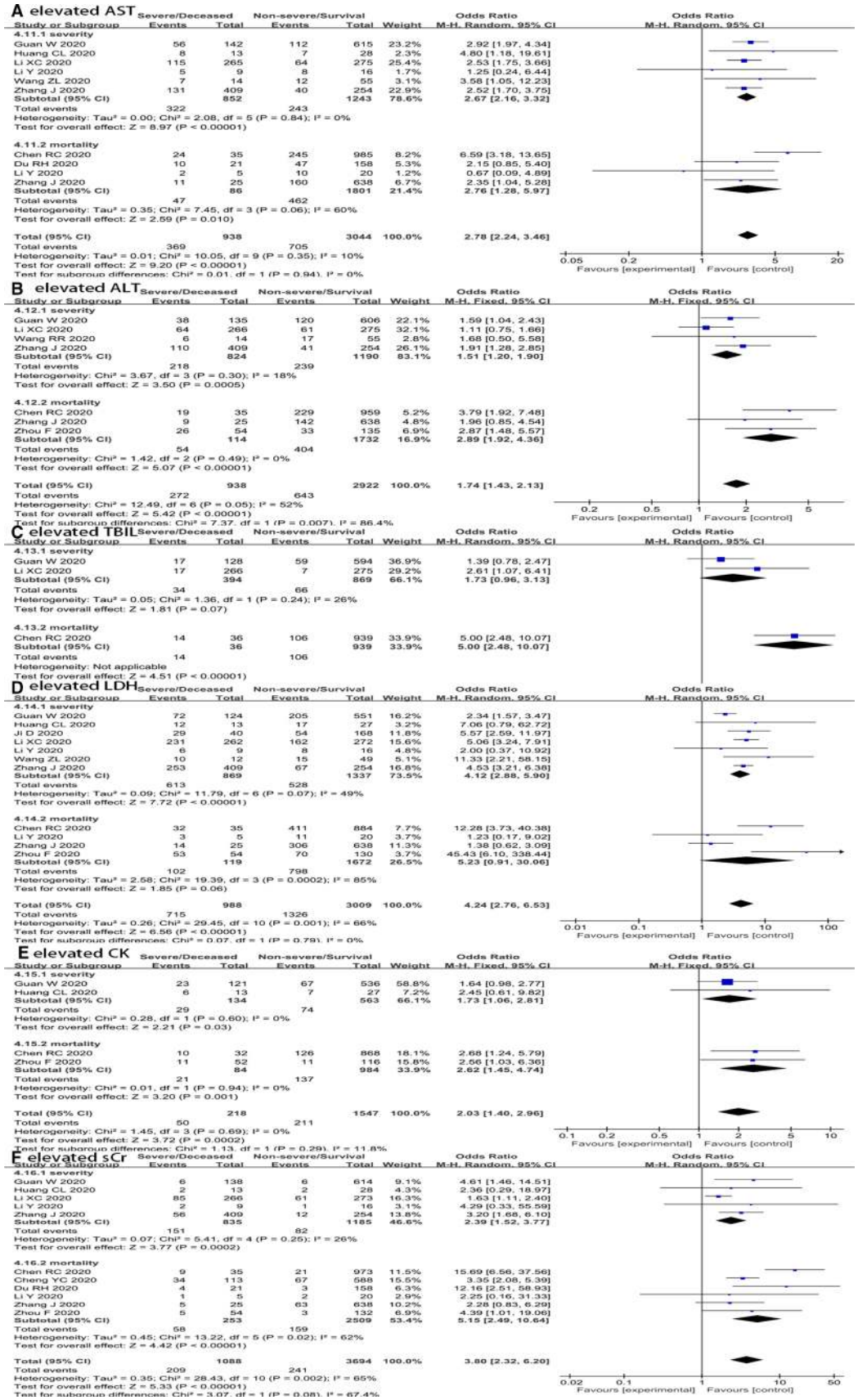
Although subgroup analysis was used in this study, heterogeneity was still noted for some factors. We performed leave-one-out sensitivity analysis to identify possible explanations for heterogeneity (Table S3). High heterogeneity with an $I^2 > 50\%$ and $P < 0.05$ was found in the analysis of some risk 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
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.11.1 severity
Guan W 2020 56 142 112 615 23.2% 2.92 [1.97, 4.34]
Huang CL 2020 8 13 7 28 2.3% 4.80 [1.18, 19.61]
Li XC 2020 115 265 64 275 25.4% 2.53 [1.75, 3.66]
Li Y 2020 5 9 8 16 1.7% 1.25 [0.24, 6.44]
Wang ZL 2020 7 14 12 55 3.1% 3.58 [1.05, 12.23]
Zhang J 2020 131 409 40 254 22.9% 2.52 [1.70, 3.75]
Subtotal (95% CI) 852 1243 78.6% 2.67 [2.16, 3.32]
Total events 322 243
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 5 (P = 0.84); I² = 0%
Test for overall effect: Z = 8.97 (P < 0.00001)
4.11.2 mortality
Chen RC 2020 24 35 245 985 8.2% 6.59 [3.18, 13.65]
Du RH 2020 10 21 47 158 5.3% 2.15 [0.85, 5.40]
Li Y 2020 2 5 10 20 1.2% 0.67 [0.09, 4.89]
Zhang J 2020 11 25 160 638 6.7% 2.35 [1.04, 5.28]
Subtotal (95% CI) 86 1801 21.4% 2.76 [1.28, 5.97]
Total events 47 462
Heterogeneity: Tau² = 0.35; Chi² = 7.45, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 2.59 (P = 0.010)
Total (95% CI) 938 3044 100.0% 2.78 [2.24, 3.46]
Total events 369 705
Heterogeneity: Tau² = 0.01; Chi² = 10.05, df = 9 (P = 0.35); I² = 10%
Test for overall effect: Z = 9.20 (P < 0.00001)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%
0.05 0.2 1 5 20
Favours [experimental] Favours [control]
B elevated ALT
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
4.12.1 severity
Guan W 2020 38 135 120 606 22.1% 1.59 [1.04, 2.43]
Li XC 2020 64 266 61 275 32.1% 1.11 [0.75, 1.66]
Wang RR 2020 6 14 17 55 2.8% 1.68 [0.50, 5.58]
Zhang J 2020 110 409 41 254 26.1% 1.91 [1.28, 2.85]
Subtotal (95% CI) 824 1190 83.1% 1.51 [1.20, 1.90]
Total events 218 239
Heterogeneity: Chi² = 3.67, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 3.50 (P = 0.0005)
4.12.2 mortality
Chen RC 2020 19 35 229 959 5.2% 3.79 [1.92, 7.48]
Zhang J 2020 9 25 142 638 4.8% 1.96 [0.85, 4.54]
Zhou F 2020 26 54 33 135 6.9% 2.87 [1.48, 5.57]
Subtotal (95% CI) 114 1732 16.9% 2.89 [1.92, 4.36]
Total events 54 404
Heterogeneity: Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 5.07 (P < 0.00001)
Total (95% CI) 938 2922 100.0% 1.74 [1.43, 2.13]
Total events 272 643
Heterogeneity: Chi² = 12.49, df = 6 (P = 0.05); I² = 52%
Test for overall effect: Z = 5.42 (P < 0.00001)
Test for subgroup differences: Chi² = 7.37, df = 1 (P = 0.007), I² = 86.4%
0.2 0.5 1 2 5
Favours [experimental] Favours [control]
C elevated TBIL
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.13.1 severity
Guan W 2020 17 128 59 594 36.9% 1.39 [0.78, 2.47]
Li XC 2020 17 266 7 275 29.2% 2.61 [1.07, 6.41]
Subtotal (95% CI) 394 869 66.1% 1.73 [0.96, 3.13]
Total events 34 66
Heterogeneity: Tau² = 0.05; Chi² = 1.36, df = 1 (P = 0.24); I² = 26%
Test for overall effect: Z = 1.81 (P = 0.07)
4.13.2 mortality
Chen RC 2020 14 36 106 939 33.9% 5.00 [2.48, 10.07]
Subtotal (95% CI) 36 939 33.9% 5.00 [2.48, 10.07]
Total events 14 106
Heterogeneity: Not applicable
Test for overall effect: Z = 4.51 (P < 0.00001)
D elevated LDH
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.14.1 severity
Guan W 2020 72 124 205 551 16.2% 2.34 [1.57, 3.47]
Huang CL 2020 12 13 17 27 3.2% 7.06 [0.79, 62.72]
Ji D 2020 29 40 54 168 11.8% 5.57 [2.59, 11.97]
Li XC 2020 231 262 162 272 15.6% 5.06 [3.24, 7.91]
Li Y 2020 6 9 8 16 4.8% 2.00 [0.37, 10.92]
Wang ZL 2020 10 12 15 49 5.1% 11.33 [2.21, 58.15]
Zhang J 2020 253 409 67 254 16.8% 4.53 [3.21, 6.38]
Subtotal (95% CI) 869 1337 73.5% 4.12 [2.88, 5.90]
Total events 613 528
Heterogeneity: Tau² = 0.09; Chi² = 11.79, df = 6 (P = 0.07); I² = 49%
Test for overall effect: Z = 7.72 (P < 0.00001)
4.14.2 mortality
Chen RC 2020 32 35 411 884 7.7% 12.28 [3.73, 40.38]
Li Y 2020 3 5 11 20 3.7% 1.23 [0.17, 9.02]
Zhang J 2020 14 25 306 638 11.3% 1.38 [0.62, 3.09]
Zhou F 2020 53 54 70 130 3.7% 45.43 [6.10, 338.44]
Subtotal (95% CI) 119 1672 26.5% 5.23 [0.91, 30.06]
Total events 102 798
Heterogeneity: Tau² = 2.58; Chi² = 19.39, df = 3 (P = 0.0002); I² = 85%
Test for overall effect: Z = 1.85 (P = 0.06)
Total (95% CI) 988 3009 100.0% 4.24 [2.76, 6.53]
Total events 715 1326
Heterogeneity: Tau² = 0.26; Chi² = 29.45, df = 10 (P = 0.001); I² = 66%
Test for overall effect: Z = 6.56 (P < 0.00001)
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
E elevated CK
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
4.15.1 severity
Guan W 2020 23 121 67 536 58.8% 1.64 [0.98, 2.77]
Huang CL 2020 6 13 7 27 7.2% 2.45 [0.61, 9.82]
Subtotal (95% CI) 134 563 66.1% 1.73 [1.06, 2.81]
Total events 29 74
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)
4.15.2 mortality
Chen RC 2020 10 32 126 868 18.1% 2.68 [1.24, 5.79]
Zhou F 2020 11 52 11 116 15.8% 2.56 [1.03, 6.36]
Subtotal (95% CI) 84 984 33.9% 2.62 [1.45, 4.74]
Total events 21 137
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.20 (P = 0.001)
Total (95% CI) 218 1547 100.0% 2.03 [1.40, 2.96]
Total events 50 211
Heterogeneity: Chi² = 1.45, df = 3 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.72 (P = 0.0002)
Test for subgroup differences: Chi² = 1.13, df = 1 (P = 0.29), I² = 11.8%
0.1 0.2 0.5 1 2 5 10
Favours [experimental] Favours [control]
F elevated sCr
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.16.1 severity
Guan W 2020 6 138 6 614 9.1% 4.61 [1.46, 14.51]
Huang CL 2020 2 13 2 28 4.3% 2.36 [0.29, 18.97]
Li XC 2020 85 266 61 273 16.3% 1.63 [1.11, 2.40]
Li Y 2020 2 9 1 16 3.1% 4.29 [0.33, 55.59]
Zhang J 2020 56 409 12 254 13.8% 3.20 [1.68, 6.10]
Subtotal (95% CI) 835 1185 46.6% 2.39 [1.52, 3.77]
Total events 151 82
Heterogeneity: Tau² = 0.07; Chi² = 5.41, df = 4 (P = 0.25); I² = 26%
Test for overall effect: Z = 3.77 (P = 0.0002)
4.16.2 mortality
Chen RC 2020 9 35 21 973 11.5% 15.69 [6.56, 37.56]
Cheng YC 2020 34 113 67 588 15.5% 3.35 [2.08, 5.39]
Du RH 2020 4 21 3 158 6.3% 12.16 [2.51, 58.93]
Li Y 2020 1 5 2 20 2.9% 2.25 [0.16, 31.33]
Zhang J 2020 5 25 63 638 10.2% 2.28 [0.83, 6.29]
Zhou F 2020 5 54 3 132 6.9% 4.39 [1.01, 19.06]
Subtotal (95% CI) 253 2509 53.4% 5.15 [2.49, 10.64]
Total events 58 159
Heterogeneity: Tau² = 0.45; Chi² = 13.22, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 4.42 (P < 0.00001)
Total (95% CI) 1088 3694 100.0% 3.80 [2.32, 6.20]
Total events 209 241
Heterogeneity: Tau² = 0.35; Chi² = 28.43, df = 10 (P = 0.002); I² = 65%
Test for overall effect: Z = 5.33 (P < 0.00001)
Test for subgroup differences: Chi² = 3.07, df = 1 (P = 0.08), I² = 67.4%
0.02 0.1 1 10 50
Favours [experimental] Favours [control]

◂**Fig. 6** Blood biochemistry test risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated AST, (B) elevated ALT, (C) elevated TBIL, (D) elevated LDH, (E) elevated CK, and (F) elevated sCr.

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].

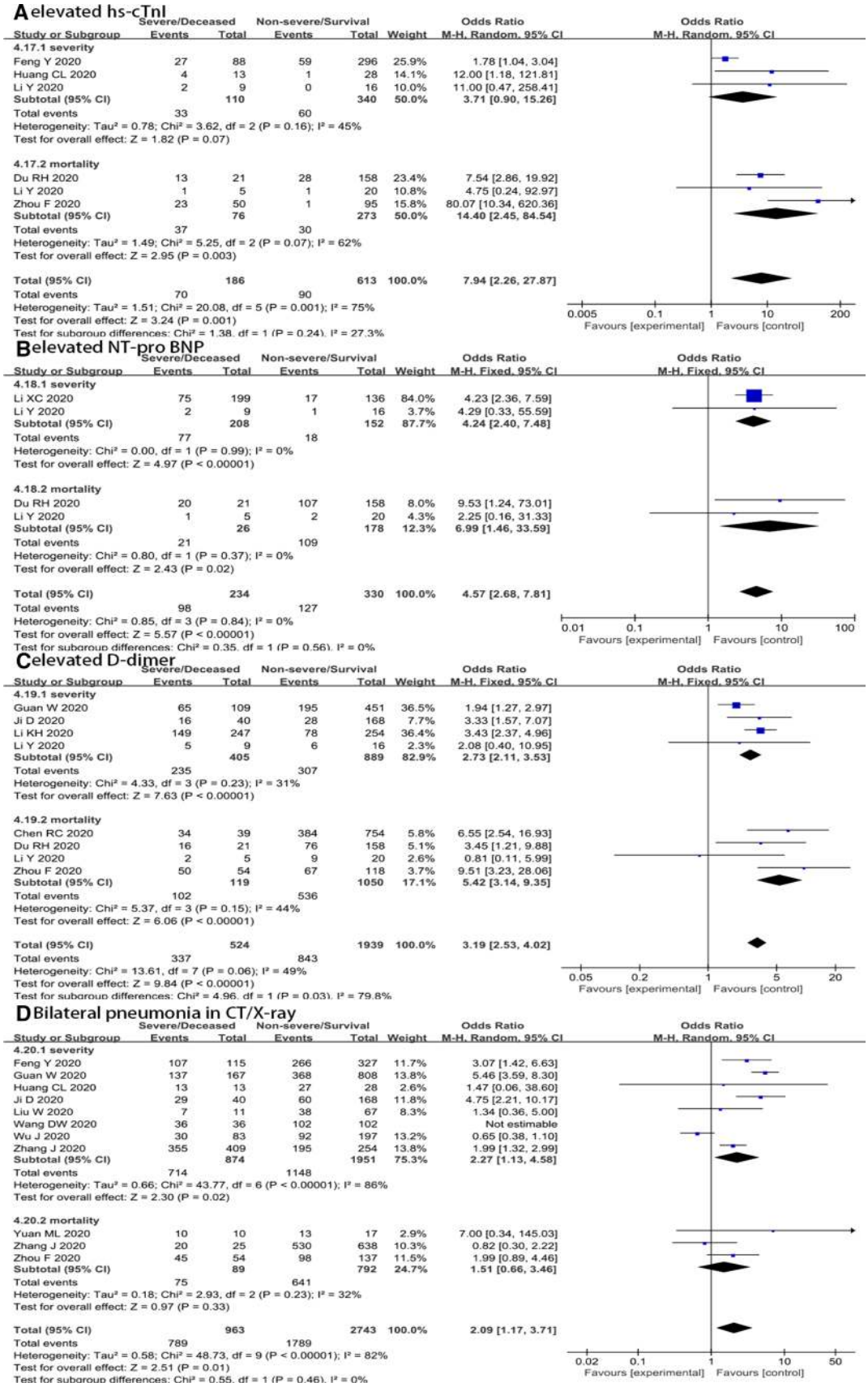
Regarding clinical manifestations, sputum production was associated with a dramatically increased risk of progression and mortality. Exudation is a clinical manifestation of inflammation [69], and the volume of exudate is positively correlated with the severity of inflammation. We also found that the 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


A elevated hs-cTnI
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.17.1 severity
Feng Y 2020 27 88 59 296 25.9% 1.78 [1.04, 3.04]
Huang CL 2020 4 13 1 28 14.1% 12.00 [1.18, 121.81]
Li Y 2020 2 9 0 16 10.0% 11.00 [0.47, 258.41]
Subtotal (95% CI) 110 340 50.0% 3.71 [0.90, 15.26]
Total events 33 60
Heterogeneity: Tau² = 0.78; Chi² = 3.62, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 1.82 (P = 0.07)
4.17.2 mortality
Du RH 2020 13 21 28 158 23.4% 7.54 [2.86, 19.92]
Li Y 2020 1 5 1 20 10.8% 4.75 [0.24, 92.97]
Zhou F 2020 23 50 1 95 15.8% 80.07 [10.34, 620.36]
Subtotal (95% CI) 76 273 50.0% 14.40 [2.45, 84.54]
Total events 37 30
Heterogeneity: Tau² = 1.49; Chi² = 5.25, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 2.95 (P = 0.003)
Total (95% CI) 186 613 100.0% 7.94 [2.26, 27.87]
Total events 70 90
Heterogeneity: Tau² = 1.51; Chi² = 20.08, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 3.24 (P = 0.001)
Test for subgroup differences: Chi² = 1.38, df = 1 (P = 0.24), I² = 27.3%
0.005 0.1 1 10 200
Favours [experimental] Favours [control]
B elevated NT-pro BNP
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
4.18.1 severity
Li XC 2020 75 199 17 136 84.0% 4.23 [2.36, 7.59]
Li Y 2020 2 9 1 16 3.7% 4.29 [0.33, 55.59]
Subtotal (95% CI) 208 152 87.7% 4.24 [2.40, 7.48]
Total events 77 18
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 4.97 (P < 0.00001)
4.18.2 mortality
Du RH 2020 20 21 107 158 8.0% 9.53 [1.24, 73.01]
Li Y 2020 1 5 2 20 4.3% 2.25 [0.16, 31.33]
Subtotal (95% CI) 26 178 12.3% 6.99 [1.46, 33.59]
Total events 21 109
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.02)
Total (95% CI) 234 330 100.0% 4.57 [2.68, 7.81]
Total events 98 127
Heterogeneity: Chi² = 0.85, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 5.57 (P < 0.00001)
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
C elevated D-dimer
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
4.19.1 severity
Guan W 2020 65 109 195 451 36.5% 1.94 [1.27, 2.97]
Ji D 2020 16 40 28 168 7.7% 3.33 [1.57, 7.07]
Li KH 2020 149 247 78 254 36.4% 3.43 [2.37, 4.96]
Li Y 2020 5 9 6 16 2.3% 2.08 [0.40, 10.95]
Subtotal (95% CI) 405 889 82.9% 2.73 [2.11, 3.53]
Total events 235 307
Heterogeneity: Chi² = 4.33, df = 3 (P = 0.23); I² = 31%
Test for overall effect: Z = 7.63 (P < 0.00001)
4.19.2 mortality
Chen RC 2020 34 39 384 754 5.8% 6.55 [2.54, 16.93]
Du RH 2020 16 21 76 158 5.1% 3.45 [1.21, 9.88]
Li Y 2020 2 5 9 20 2.6% 0.81 [0.11, 5.99]
Zhou F 2020 50 54 67 118 3.7% 9.51 [3.23, 28.06]
Subtotal (95% CI) 119 1050 17.1% 5.42 [3.14, 9.35]
Total events 102 536
Heterogeneity: Chi² = 5.37, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 6.06 (P < 0.00001)
Total (95% CI) 524 1939 100.0% 3.19 [2.53, 4.02]
Total events 337 843
Heterogeneity: Chi² = 13.61, df = 7 (P = 0.06); I² = 49%
Test for overall effect: Z = 9.84 (P < 0.00001)
Test for subgroup differences: Chi² = 4.96, df = 1 (P = 0.03), I² = 79.8%
0.05 0.2 1 5 20
Favours [experimental] Favours [control]
D Bilateral pneumonia in CT/X-ray
Severe/Deceased
Non-severe/Survival
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.20.1 severity
Feng Y 2020 107 115 266 327 11.7% 3.07 [1.42, 6.63]
Guan W 2020 137 167 368 808 13.8% 5.46 [3.59, 8.30]
Huang CL 2020 13 13 27 28 2.6% 1.47 [0.06, 38.60]
Ji D 2020 29 40 60 168 11.8% 4.75 [2.21, 10.17]
Liu W 2020 7 11 38 67 8.3% 1.34 [0.36, 5.00]
Wang DW 2020 36 36 102 102 Not estimable
Wu J 2020 30 83 92 197 13.2% 0.65 [0.38, 1.10]
Zhang J 2020 355 409 195 254 13.8% 1.99 [1.32, 2.99]
Subtotal (95% CI) 874 1951 75.3% 2.27 [1.13, 4.58]
Total events 714 1148
Heterogeneity: Tau² = 0.66; Chi² = 43.77, df = 6 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.30 (P = 0.02)
4.20.2 mortality
Yuan ML 2020 10 10 13 17 2.9% 7.00 [0.34, 145.03]
Zhang J 2020 20 25 530 638 10.3% 0.82 [0.30, 2.22]
Zhou F 2020 45 54 98 137 11.5% 1.99 [0.89, 4.46]
Subtotal (95% CI) 89 792 24.7% 1.51 [0.66, 3.46]
Total events 75 641
Heterogeneity: Tau² = 0.18; Chi² = 2.93, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 0.97 (P = 0.33)
Total (95% CI) 963 2743 100.0% 2.09 [1.17, 3.71]
Total events 789 1789
Heterogeneity: Tau² = 0.58; Chi² = 48.73, df = 9 (P < 0.00001); I² = 82%
Test for overall effect: Z = 2.51 (P = 0.01)
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%
0.02 0.1 1 10 50
Favours [experimental] Favours [control]

◂**Fig. 7** Other lab examination risk factors for progression and mortality in COVID-19. Forest plots are shown for the effects of (A) elevated hs-cTnl, (B) elevated NT-pro BNP, (C) elevated D-dimer, and (D) bilateral pneumonia in CT/X-ray.

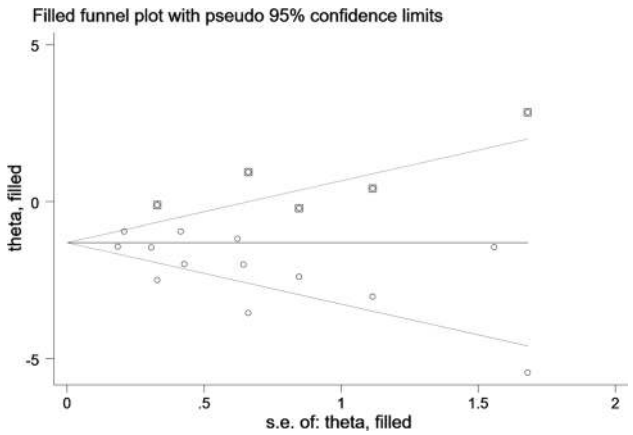


Fig. 8 Trim-and-fill analysis for the publication bias for dyspnea

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.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00705-021-05012-2.

Author contributions All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Funding No funding or sponsorship was received for this study or publication of this article.

Declarations

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

Compliance with ethics guidelines This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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