Meta-Analysis of Observational Studies in Epidemiology

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Association of elevated inflammatory markers and severe COVID-19

A meta-analysis

Pan Ji, MD, Jieyun Zhu, MD, Zhimei Zhong, MD, Hongyuan Li, MD, Jielong Pang, MD, Bocheng Li, MD, Jianfeng Zhang, MD, PhD*

Abstract

Our study aimed to assess the existing evidence on whether severe coronavirus disease 2019 (COVID-19) is associated with elevated inflammatory markers.

The PubMed, Embase, Web of Science, Scopus, Chinese National Knowledge Infrastructure, WanFang, and China Science and Technology Journal databases were searched to identify studies published between January 1 and April 21, 2020 that assayed inflammatory markers in COVID-19 patients. Three reviewers independently examined the literature, extracted relevant data, and assessed the risk of publication bias before including the meta-analysis studies.

Fifty-six studies involving 8719 COVID-19 patients were identified. Meta-analysis showed that patients with severe disease showed elevated levels of white blood cell count (WMD: 1.15, 95% CI: 0.78–1.52), C-reactive protein (WMD: 38.85, 95% CI: 31.19–46.52), procalcitonin (WMD: 0.08, 95% CI: 0.06–0.11), erythrocyte sedimentation rate (WMD: 10.15, 95% CI: 5.03–15.46), interleukin-6 (WMD: 23.87, 95% CI: 15.95–31.78), and interleukin-10 (WMD: 2.12, 95% CI: 1.97–2.28). Similarly, COVID-19 patients who died during follow-up showed significantly higher levels of white blood cell count (WMD: 4.11, 95% CI: 3.25–4.97), C-reactive protein (WMD: 74.18, 95% CI: 56.63–91.73), procalcitonin (WMD: 0.26, 95% CI: 0.11–0.42), erythrocyte sedimentation rate (WMD: 10.94, 95% CI: 4.79–17.09), and interleukin-6 (WMD: 59.88, 95% CI: 19.46–100.30) than survivors.

Severe COVID-19 is associated with higher levels of inflammatory markers than a mild disease, so tracking these markers may allow early identification or even prediction of disease progression.

Abbreviations: CI = confidence interval, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IL-10 = interleukin-10, IL-6 = interleukin-6, = not reported, PCT = procalcitonin, TNF-α = tumor necrosis factor-α, WBC count = white blood cell count, WMD = weighted mean difference.

Keywords: Coronavirus disease 2019, inflammatory marker, meta-analysis, severe disease

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) in December 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a severe threat to global public health. Data from the World Health Organization indicate that as of April 26, 2020, there were more than 2 million confirmed COVID-19 infections and nearly 200,000 COVID-19 deaths in 208 countries or territories.[1] The number of new cases continues to rise rapidly worldwide, which poses a significant challenge to public health.[1] While the disease is mild or even asymptomatic in most patients, and usually self-resolves without the need for hospitalization, it can rapidly and unpredictably progress to a severe form requiring hospitalization and intensive care.

Single-center studies suggest that numerous inflammation markers are elevated in patients in the intensive care unit[2] or patients with severe disease[3–5] relative to patients with milder conditions. These markers include leukocyte count, procalcitonin level (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-10 (IL-10). A meta-analysis also suggested that patients with increased PCT are nearly 5-fold more likely to have severe infection.[6]

Although several studies have suggested that severe disease may be associated with elevated WBC count, CRP, PCT, and IL-6,[5,7–9] the results across these studies are not entirely consistent. So far, it is unclear whether inflammatory markers are

Editor: Bernhard Schaller.

PJ and JZ contributed equally to this work.

This study was supported by grants from the National Natural Science Foundation of China (81960343), the Emergency Science and Technology Brainstorm Project for the Prevention and Control of COVID-19, which is part of the Guangxi Key Research and Development Plan (GuikeAB20058002), and the High-level Medical Expert Training Program of Guangxi "139" Plan Funding (G201903027).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, Zhang J. Association of elevated inflammatory markers and severe COVID-19: a meta-analysis. Medicine 2020;99:47(e23315).

Received: 7 June 2020 / Received in final form: 8 September 2020 / Accepted: 21 October 2020

http://dx.doi.org/10.1097/MD.0000000000023315

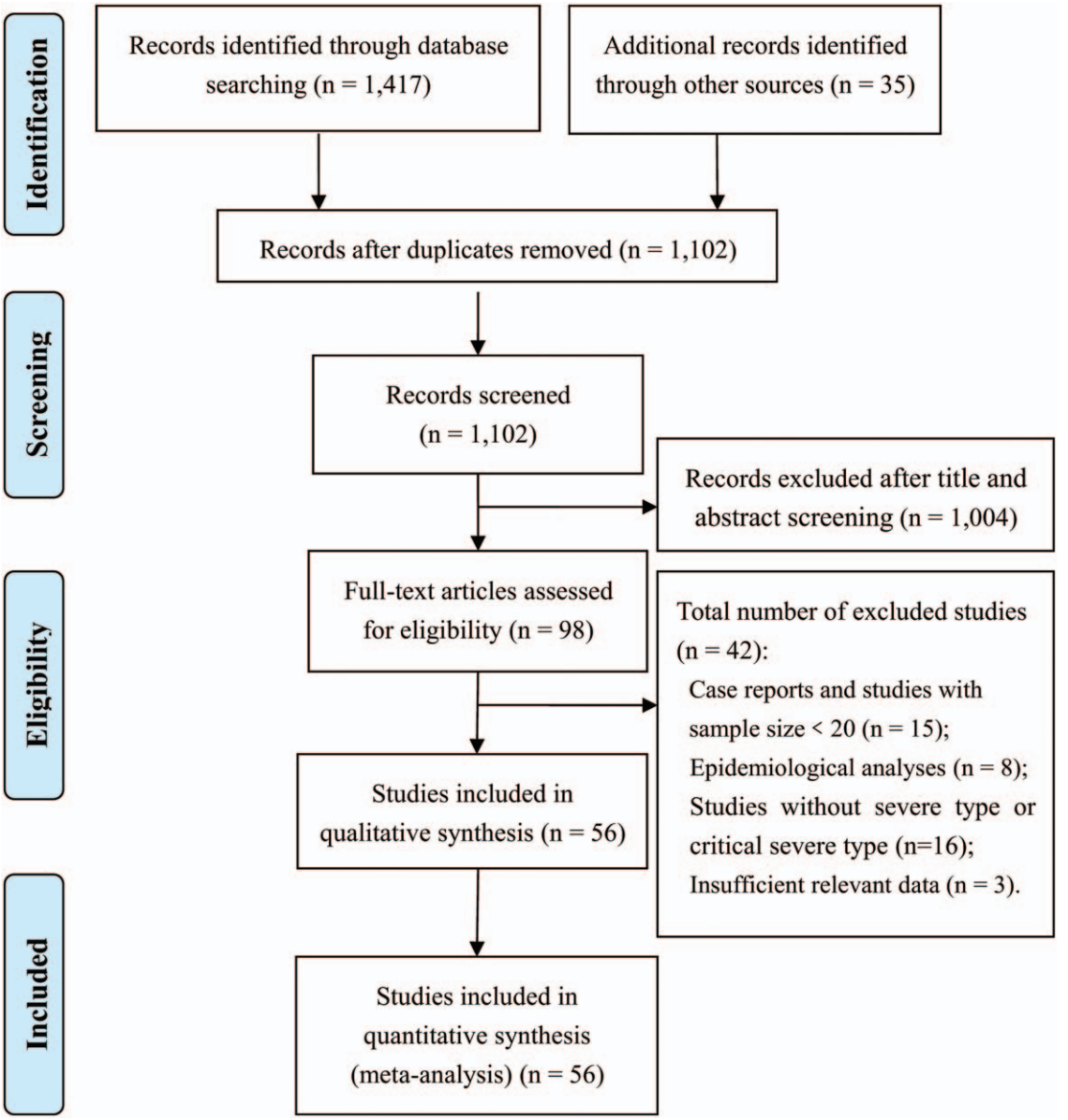

Figure 1. Flowchart of literature screening.

significantly higher in patients with severe COVID-19 than in those with mild disease. Therefore, to gain a clearer picture of the potential association between inflammatory markers and severe COVID-19, we meta-analyzed the relevant literature. The results may provide a basis for detecting or even predicting disease progression quickly enough to improve prognosis.

2. Data and methods

2.1. Search strategy

According to the Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology Statement,[10] our meta-analysis was carried out. We selected relevant studies published between January 1, 2020 and April 21, 2020. The literature was systematically searched using 7 databases: PubMed, Embase, Web of Science, Scopus, Chinese National Knowledge Infrastructure, WanFang, and the China Science and Technology Journal Database. Only literature available online was included, and no language restriction was imposed. The following keywords were used, both separately and in combination, when searching each database: "Coronavirus,""2019-nCoV," "COVID-19," "SARS-CoV-2," "IL-6," "IL-8," "IL-10," "tumor necrosis factor-alpha (TNF-α)," "erythrocyte sedimentation rate (ESR)," "procalcitonin," "C-reactive protein," "ESR," or "Laboratory finding."

2.2. Study eligibility

A study was included in the meta-analysis if it had a cohort, case-control, or case series design involving more than 20 patients with confirmed COVID-19; if it contained patients with the mild,

Table 1

Basic characteristics of included studies.

First author	Publication date in 2020	n	Single- or multicenter*	Patient population	Age†, yr	Follow-up	Diagnosis and severity criteria‡	Outcomes§	Quality score‖
Huang CL[2]	Feb 15	41	Single	Mild and severe COVID-19 patients in Hubei Province	49 (41–58)	Dec 2019 to Jan 2, 2020	WHO interim guideline	①⑥⑦	7
Wan SX[3]	Apr 16	123	Single	Mild and severe COVID-19 patients in Chongqing Three Gorges Central Hospital	43.1 ± 13.1/61.2 ± 15.6	Jan 26 to Feb 4	WHO interim guideline	①②③④⑤⑥⑦	8
Qin C[4]	Mar 12	452	Single	Mild and severe COVID-19 patients in Tongji Hospital Affiliated to Huazhong University of Science and Technology	52.1 ± 15.1/60.3 ± 13.4	Jan 10 to Feb 12	Trial fifth Edition	⑤	8
Xiao KH[5]	Feb 27	143	Single	Mild, severe, and critically ill COVID-19 patients in Chongqing Three Gorges Central Hospital	45.1 ± 1.0	Jan 23 to Feb 28	Trial fifth Edition	①③	9
Yuan J[8]	Mar 06	223	Single	Mild and severe COVID-19 patients in *Chongqing Public Medical Center*	46.5 ± 16	Jan 24 to Feb 23	Trial sixth Edition	①②	9
Fang XW[9]	Feb 25	79	Single	Mild and severe COVID-19 patients in Anhui Provincial Hospital	45 ± 16.6	Jan 22 to Feb 18	Trial sixth Edition	①③	6
Wei WX[13]	Mar 18	95	Single	Mild, severe, and critically ill COVID-19 patients in Chengdu Public Health Clinical Medical Center	45.5 ± 58.6/56.7 ± 39.8/66.3 ± 28.2	Jan 16 to Feb 18	Trial fifth Edition	①③	7
Shi YL[14]	Feb 27	164	Single	Mild, severe, and critically ill COVID-19 patients in Guangzhou Eighth Peoples Hospital	NR	Jan to Feb	Trial fifth Edition	①②③④	8
Liu et al[15]	Feb 28	79	Multi	Mild and severe COVID-19 patients in 3 tertiary hospitals in Wuhan	38 (33,57)	Dec 30 to Jan 15	Trial fourth Edition	①②	7
Deng Y[16]	Mar 20	225	Multi	Survival and non-survival COVID-19 patients in 2 tertiary hospitals in Wuhan	43 ± 18/68 ± 9	Jan 1 to Feb 21	Survival and non-survival	①③⑤	8
Zhou F[17]	Mar 11	191	Multi	Survival and nonsurvival COVID-19 patients in Wuhan Jinyintan Hospital and Wuhan Pulmonary Hospital	56 (46–67)	Dec 2019 to Jan 31, 2020	WHO interim guideline	①②③④⑤	8
Chen T[18]	Mar 26	274	Single	Survival and non-survival COVID-19 patients in Tongji Hospital Affiliated to Huazhong University of Science and Technology	62 (44–70)	Dec 2019 to Feb 28, 2020	Survival and non-survival	①②③⑤	7
Wang Y[19]	Apr 8	344	Single	Survival and non-survival COVID-19 patients in Tongji Hospital Affiliated to Huazhong University of Science and Technology	52–72	Jan 25 to Feb 25	WHO interim guideline	①②③④	7
Cheng KB[20]	Mar 12	463	Single	Mild and severe COVID-19 patients in Wuhan Jinyintan *Hospital*	15–90	Dec 2019 to Feb 06, 2020	Trial fifth Edition	①	7
Wang D[21]	Feb 08	138	Single	Mild and severe COVID-19 patients in Zhongnan Hospital of Wuhan University	56 (42–68)	Jan 1 to Jan 28	WHO interim guideline	①	7
Liu M[22]	Feb 17	30	Single	Mild and severe COVID-19 patients in Jianghan University Affiliated Hospital	35 ± 8	Jan 10 to Jan 31	Trial fifth Edition		6
Zhong SH[23]	Mar 26	62	Single	Mild, severe, and critically ill COVID-19 patients in Hainan General Hospital	51.8 ± 13.5	Jan 21 to Feb 10	Trial third Edition	①	6
Guan W[24]	Feb 06	1099	Multi	Mild and severe COVID-19 patients in 552 Hospitals in 31 provinces	47.0	NR	WHO interim guideline	①	9
Qian GQ[25]	Mar 17	88	Multi	Mild and severe COVID-19 patients in 5 hospitals in Zhejiang province	50 (36.5–57)	Jan 20 to Feb 11	WHO interim guideline	①②	9
LI KH[26]	Feb 15	41	Single	Mild and severe COVID-19 patients in Hubei Province	49 (41–58)	Dec 2019 to Jan 2, 2020	Trial fifth Edition	①②③	7
Wan SX[27]	Feb 29	83	Single		45.5 ± 12.3	Jan to Feb	WHO interim guideline	①②③	8

(*continued*)

Table 1

(continued).

First author	Publication date in 2020	n	Single- or multicenter*	Patient population	Age†, yr	Follow-up	Diagnosis and severity criteria‡	Outcomes§	Quality score‖
Gao Y[28]	Mar 21	135	Single	Mild and severe COVID-19 patients in The Second Affiliated Hospital of Chongqing Medical University Mild and severe COVID-19 patients in Chongqing Three Gorges Central Hospital	47 (36–55)	Jan 23 to Feb 8	WHO interim guideline	①②③⑤	6
Zhang JJ[29]	Mar 17	43	Single	Mild and severe COVID-19 patients in Fuyang Second People's Hospital	45±7.7/43±14	Jan 23 to Feb 2	trail version 3–5	①②③⑧	7
Chen W[30]	Mar 17	91	Single	Mild, severe, and critically ill COVID-19 patients in Jingmen First People's Hospital	41.6±15.6	Dec 2019 to Feb 21, 2020	Trial seventh Edition	①	7
Li D[31]	Mar 26	80	Single	Mild and severe COVID-19 patients in tertiary hospitals in Zhuzhou	47.8±19.5	Jan 20 to Feb 27	Trial fifth Edition	①②③④	7
Li D[32]	Apr 2	62	Single	Mild, severe, and critically ill COVID-19 patients in Renmin Hospital of Wuhan University	49±37/59±31	Jan 31 to Feb 25	Trial sixth Edition	①②③	6
Xiong J[33]	Mar 03	89	Single	Mild, severe, and critically ill COVID-19 patients in Renmin Hospital of Wuhan University	53±16.9	Jan 17 to Feb 20	Trial sixth Edition	①②③	7
Liu J[34]	Mar 27	91	Single	Mild, severe, and critically ill COVID-19 patients in Wuhan Children's Hospital	NR	Jan 25 to Feb 18	Trial fifth Edition	①③	6
Gao W[35]	Mar 31	90	Single	Mild, severe, and critically ill COVID-19 patients in Beijing Youan Hospital	51.7±18.6	Jan to Feb	Trial sixth Edition	①②③	7
Xie HS[36]	Apr 2	79	Single	Mild and severe COVID-19 patients in Wuhan Jinyintan *Hospital*	60 (48–66)	Feb 2 to Feb 23	Trial sixth Edition	①②④	7
Zhang YF[37]	Apr 2	121	Single	Mild and severe COVID-19 patients in Zhongnan Hospital of Wuhan University	43.9±15/65±1	Dec 2019 to Feb 22, 2020	Trial fifth Edition	①	7
Chen L[38]	Feb 6	29	Single	Mild, severe, and critically ill COVID-19 patients in Tongji Hospital Affiliated to Huazhong University of Science and Technology	26–79	Jan	Trial fifth Edition	①⑤⑥⑦	6
Peng YD[39]	Mar 2	112	Single	Mild and severe COVID-19 patients in western district of Union Hospital in Wuhan	62 (5567)	Jan 20 to Feb 15	Trial sixth Edition	①③	7
Chen M[40]	Feb 27	54	Single	Mild, severe, and critically ill COVID-19 patients in Hubei No. 3 People's Hospital	43.8–69	Jan 24 to Feb 8	Trial fifth Edition	①②③④	6
Wan Q[41]	Feb 24	153	Single	Mild and severe COVID-19 patients in Chongqing Public Health Medical Center	43.4±15/57.7±13	Jan 26 to Feb 5	Trial fifth Edition	①	8
Li D[42]	Mar 5	30	Single	Mild and severe COVID-19 patients in Shenyang sixth people's hospital	21–72	Jan 22 to Feb 8	Trial fifth Edition	①	6
Ling Y[43]	Mar 18	292	Single	Mild and severe COVID-19 patients in Shanghai Public Health Clinical Center	48.7±16/65.5±16	Jan 20 to Feb 10	Trial fifth Edition	①②③④	9
Bin YF[44]	Feb 29	55	Single	Mild and severe COVID-19 patients in Huangpi District Chinese Medicine Hospital of Wuhan	53.9±17. 1	Jan 29 to Feb 16	Trial fifth Edition	①	6
Xia XT[45]	Apr 7	63	Single	Mild and severe COVID-19 patients in Hubei Provincial Hospital of Integrated Chinese and Western Medicine	62.3±15.1/64.6±14.9	Jan 26 to Feb 20	Trial fifth Edition	①	6
Chen C[46]	Mar 6	150	Single	Mild and severe COVID-19 patients in Tongji Hospital Affiliated to Huazhong University of Science and Technology	59±16	Jan to Feb	Trial sixth Edition	①	6
Liu SJ[47]	Apr 2	342	Single		NR	Jan 23 to Feb 12	Trial sixth Edition	①②③④	7

(*continued*)

Table 1

(continued).

First author	Publication date in 2020	n	Single- or multicenter*	Patient population	Age†, yr	Follow-up	Diagnosis and severity criteria‡	Outcomes§	Quality score‖
				Mild, severe, and critically ill COVID-19 patients in Ezhou Central Hospital				①③④	
An W[48]	Apr 16	110	Single	Survival and nonsurvival COVID-19 patients in Hubei No.3 People' s Hospital of Jianghan University	NR	Jan 24 to Feb 19	Current trail version	①②③④	7
Feng Y[49]	Apr 10	476	Multi	Mild, severe, and critically ill COVID-19 patients from 3 hospitals in Wuhan, Shanghai and Anhui	NR	Jan 1 to Feb 15	Trial fifth Edition	①②③④⑤	8
Cai QX[50]	Apr 2	298	Single	Mild and severe COVID-19 patients in The Third People's Hospital of Shenzhen	42.7±18.7/61.5±7.6	Jan 11 to Feb 6	WHO interim guideline	①②	6
Zheng F[51]	Mar	161	Single	Mild and severe COVID-19 patients in Changsha First Hospital	40.7±15.0/56.5±15.2	Jan 17 to Feb 7	Trial fifth Edition	①③⑤	7
Tang JS[52]	Apr 13	40	Single	Mild, severe, and critically ill COVID-19 patients in The Ninth People's hospital of DongGuan	NR	Jan to Feb	Trial sixth Edition	①②	8
Zheng YL[53]	Apr 10	99	Single	Mild and severe COVID-19 patients in Chengdu Public Health Clinical Medical Center	42.5±15.1/63.8±16.5	Jan 16 to Feb 20	Trial fifth Edition	①③⑤	6
Wang L[54]	Mar 30	339	Single	Survival and non-survival COVID-19 patients in Renmin Hospital of Wuhan University	68.7±7.5/76.3±9.9	Jan 1 to Feb 6	Trial sixth Edition	①②⑤	7
Ruan QR[55]	Apr 6	150	Multi	Mild and severe COVID-19 patients in Wuhan Jinyintan Hospital and Tongji Hospital Affiliated to Huazhong University of Science and Technology	58.3±27.9/54.3±50.0	NR	Survival and nonsurvival	①⑤	8
Tu WJ[56]	Apr 6	174	Single	Survival and non-survival COVID-19 patients in Zhongnan Hospital of Wuhan University	50.0±18.7/71.3±21.6	Jan 3 to Feb 24	Survival and non-survival	①③⑤	8
Chen XH[57]	Apr 17	48	Single	Mild and severe COVID-19 patients in General Hospital of Central Theater Command	52.8±14.2/63.7±15.2/79.6±12.6	Jan 1 to Feb 19	Trial sixth Edition	①⑤	9
Ma J[58]	Apr 13	37	Single	Mild and severe COVID-19 patients in Renmin Hospital of Wuhan University	61.0±4.9/66.5±9.6	Jan 1 to Mar 30	Trial seventh Edition	①②③④⑤⑥⑦	7
Wang ZL[59]	Mar 16	69	Single	Mild and severe COVID-19 patients in western district of Union Hospital in Wuhan	40.0±14.5/69.8±12.4	Jan 16 to Jan 29	Trial third Edition	①⑦	7
Zou QX[60]	Apr 21	50	Single	Mild, severe, and critically ill COVID-19 patients in Sino-French New City Campus of Tongji Hospital Affiliated to Huazhong University of Science and Technology	62.3±10.6/65.8±11.1/72.4±8.5	Feb to Mar	Trial sixth Edition	①④	6
He XW[61]	Apr 21	56	Single	Survival and non-survival COVID-19 patients in Sino-French New City Campus of Tongji Hospital Affiliated to Huazhong University of Science and Technology	64.8±12.3/69.7±13.0	Feb 3 to Feb 24	Trial seventh Edition	①②③	8
Zuo FT[62]	Apr 14	50	Single	Mild and severe COVID-19 patients in Nanyang Central Hospital	46.6±16.3/53.7±10.1	Jan 19 to Mar 20	Trial fifth Edition		8

* All studies were retrospective.

† Reported as range, mean ± SD, or median (interquartile range).

‡ Version of New Coronavirus Pneumonia Prevention and Control Program in China, or WHO interim guideline.

§ NR = not reported. ① WBC = white blood cell count, ② CRP = C-reactive protein, ③ PCT = procalcitonin, ④ ESR = erythrocyte sedimentation rate, ⑤ IL-6 = interleukin-6, ⑥ IL-10 = interleukin-10, ⑦ TNF-α = tumor necrosis factor-α.

‖ Score based on the Newcastle-Ottawa Scale guidelines.[11]

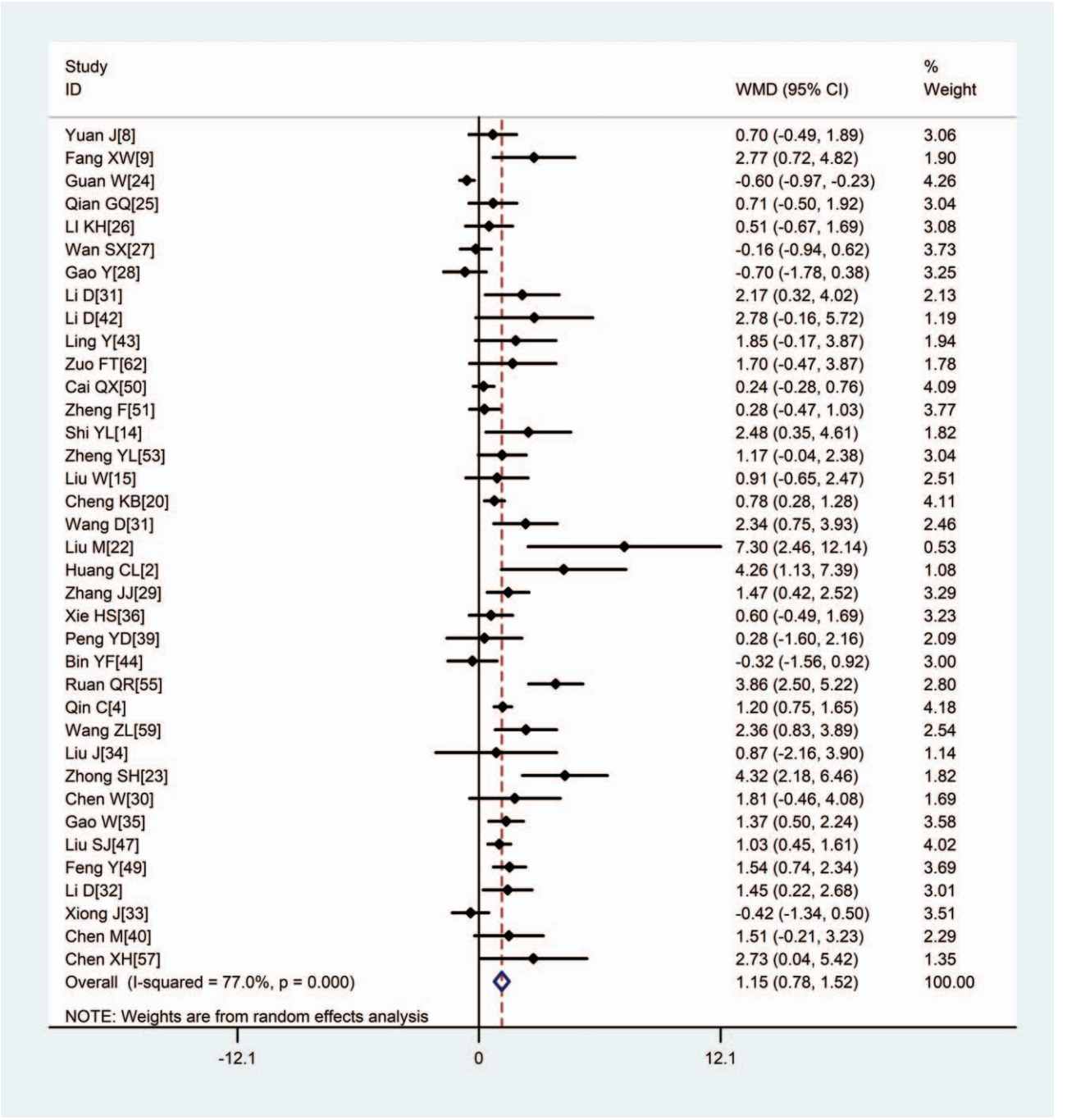

Figure 2. Meta-analysis of the difference in white blood cell count (×1012/L) between patients with mild or severe COVID-19. WMD = weighted mean difference, COVID-19 = coronavirus disease 2019.

severe, or critical disease, or it contained survivor and non-survivor groups; and if it reported sufficient details about inflammatory markers. The diagnosis and severity classification was based on the New Coronavirus Pneumonia Prevention and Control Program in China or WHO interim guideline, and patients were grouped into different types such as mild, moderate, severe, and critical diseases. The mild and moderate diseases were defined as "mild," while severe and critical patients were categorized as "severe" in this study. All analyses were based on previously published studies. Thus no ethical approval and patient consent are required.

2.3. Data extraction and quality assessment

Three reviewers independently screened the articles' titles and abstract to assess whether they were eligible for inclusion. The following data were extracted from included studies into an Excel database: the first author's surname, the publication date of the article, study design, sample size, age, outcome indicators, and assessment of bias risk. A fourth reviewer resolved disagreements. When necessary, authors of the original studies were contacted to obtain further information or clarification.

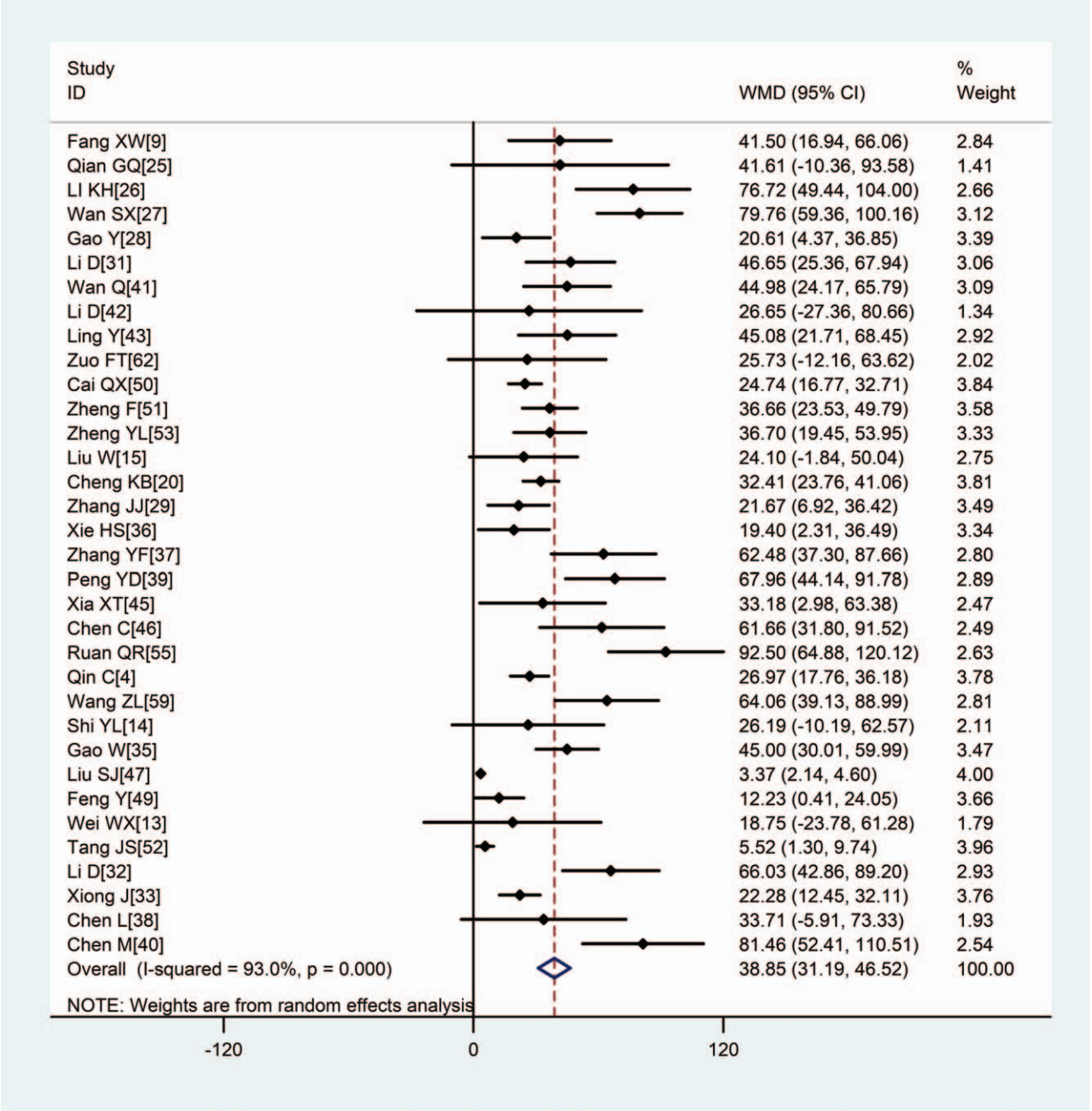

Figure 3. Meta-analysis of the difference in CRP (mg/L) between COVID-19 patients with mild or severe disease. WMD = weighted mean difference, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein.

The quality of included studies was assessed based on the Newcastle-Ottawa Scale guidelines.[11] Three reviewers assessed study quality, and differences were resolved through discussion. Studies scoring more than 6 out of the total possible 9 points were considered high quality.

2.4. Statistical analyses

For studies that reported continuous data as ranges or as medians and interquartile ranges, the means and standard deviation were calculated as described.[12] All meta-analyses were performed using STATA 12 (StataCorp, TX) and a significance definition of 2-tailed $P < .05$. We calculated the weighted mean difference (WMD) and 95% confidence interval (CI) for differences in continuous variables between patients with severe or mild COVID-19 and between all COVID-19 patients who survived or died follow-up. Heterogeneity between studies was analyzed using the χ^2 test with significance set at $P < .10$ and was quantified using the I^2 statistic. The fixed-effect model was utilized when there was no significant heterogeneity in the pooled data. Otherwise, a sensitivity analysis was used to identify the study or studies explaining most of the heterogeneity, then these studies were removed, and the remaining ones were meta-analyzed using a random-effects model. Publication bias was

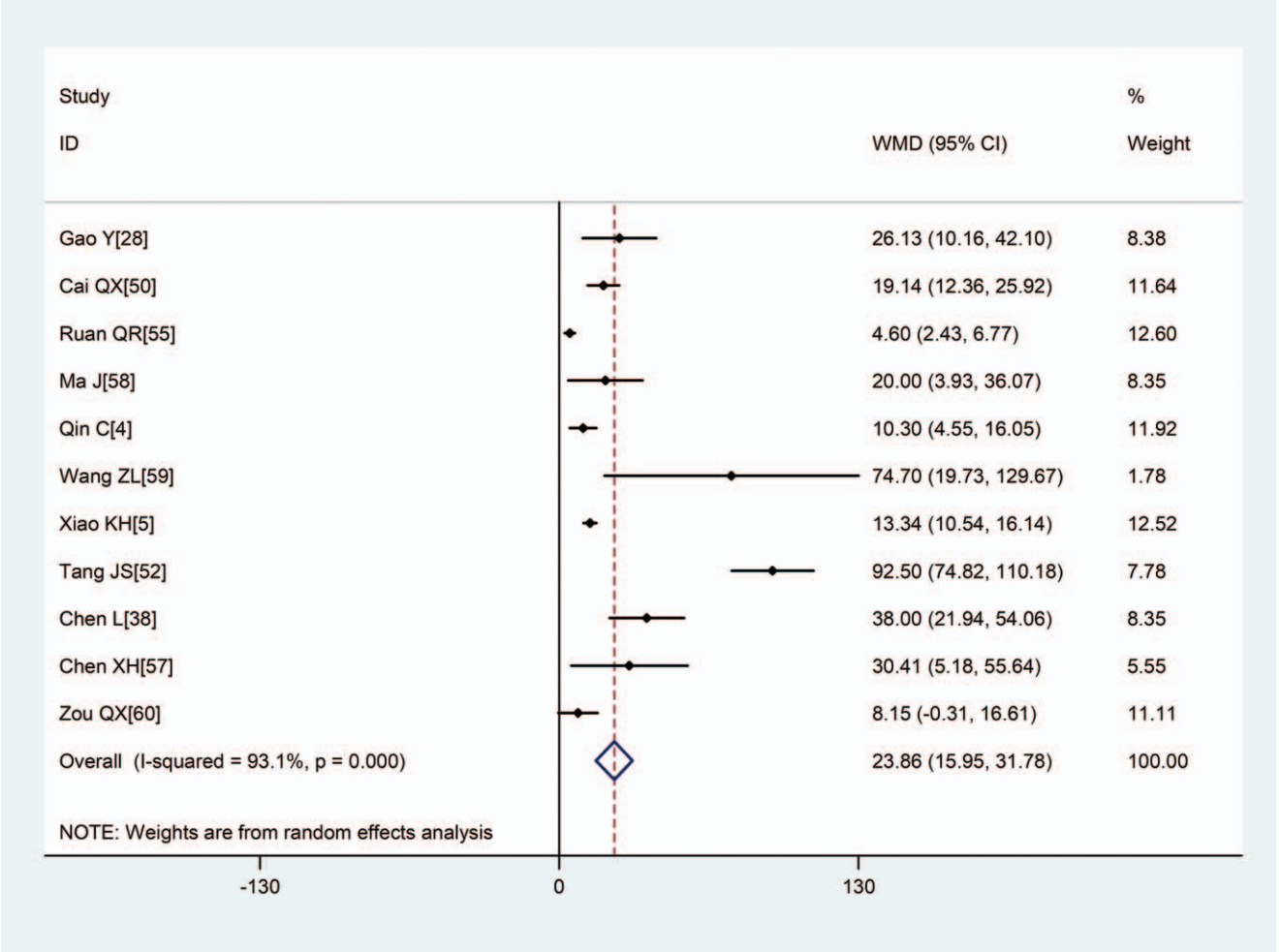

Figure 4. Meta-analysis of the difference in IL-6 (pg/mL) between COVID-19 patients with mild or severe disease. WMD = weighted mean difference, COVID-19 = coronavirus disease 2019, L-6 = interleukin-6.

assessed using funnel plots, Egger regression asymmetry test, and Begg test.

3. Results

3.1. Literature screening and assessment

A total of 1417 records were identified from the various databases examined, and 35 additional records were identified from the Chinese Medical Journal Network. After a detailed assessment based on the inclusion criteria, 56 studies[2–5,8,9,13–62] involving 8719 COVID-19 patients were included in the meta-analysis (Fig. 1).

3.2. Characteristics of included studies

All studies included in the meta-analysis were conducted in China and published between February 6, 2020 and April 21, 2020. These retrospective studies examined Chinese patients distributed across 31 provinces. Follow-up data were reported for most patients. All studies received quality scores varying from 6 to 9 points, indicating high quality (Table 1).

3.3. Meta-analysis

3.3.1. Inflammatory markers. Pooled results revealed that patients with severe disease showed significantly higher (WMD: 1.15, 95% CI: 0.78–1.52), CRP (WMD: 38.85, 95% CI: 31.19–46.52), PCT (WMD: 0.08, 95% CI: 0.06–0.11), erythrocyte sedimentation rate (WMD: 10.15, 95% CI: 5.03–15.46), IL-6 (WMD: 23.87, 95% CI: 15.95–31.78), and IL-10 (WMD: 2.12, 95% CI: 1.97–2.28) (Figs. 2–5, Table 2). In contrast, the 2 groups showed similar TNF-α levels.

Eight studies[16–19,48,54,56,61] comparing 543 COVID-19 patients who died during follow-up with 1713 who remained alive during the same period found that on admission, patients who subsequently died showed significantly higher white blood cell count (WMD: 4.11, 95% CI: 3.25–4.97), CRP (WMD: 74.18, 95% CI: 56.63–91.73), PCT (WMD: 0.26, 95% CI: 0.11–0.42), erythrocyte sedimentation rate (WMD: 10.94, 95% CI: 4.79–17.09), and IL-6 (WMD: 59.88, 95% CI: 19.46–100.30) (Table 2).

3.3.2. Sensitivity analysis. For most of the outcomes described in Section 3.3.1, there was heterogeneity in the pooled data, with I^2 ranging from 60.1% to 98.5%. Therefore we repeated each meta-analysis after excluding 1 study at a time. We found that the

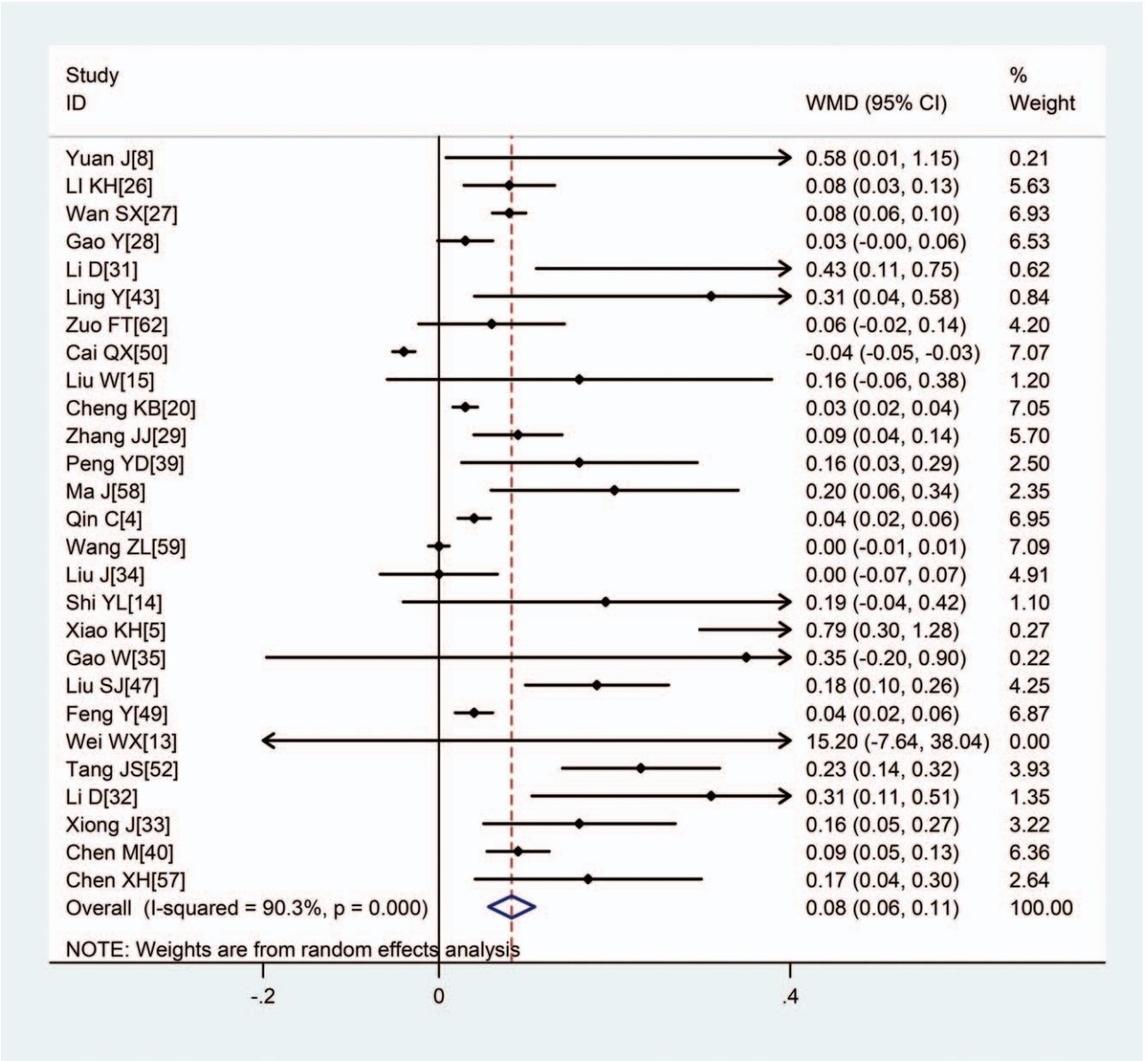

Figure 5. Meta-analysis of the difference in PCT (ng/mL) between COVID-19 patients with mild or severe disease. WMD = weighted mean difference. COVID-19 = coronavirus disease 2019, PCT = procalcitonin.

results did not change substantially (Fig. 6), suggesting our original meta-analyses' reliability.

4. Discussion

Inflammation markers can appear elevated in infected individuals, including those infected with SARS-CoV-2.[54] Previous work suggested that the magnitude of the elevation WBC count, CRP, PCT, and IL-6 may relate to the severity of the resulting COVID-19.[17,59] The National Health Commission of the People's Republic of China included elevated inflammatory factors such as IL-6 and CRP as potential early warning indicators of severe disease in its widely used "COVID-19 diagnosis and treatment plan (for version 7)."[63] While these considerations imply that monitoring levels of inflammatory markers may help identify progression to severe disease, the literature has not been entirely consistent on which markers may be useful in this regard. For example, at least 2 studies found white blood cell count is similar or even lower in severe disease than in mild disease[23,44] in severe disease, yet other studies found the same marker to be higher in severe disease.[32,35] To help clarify the inflammatory markers whose elevation may signal severe COVID-19, we meta-analyzed the relevant literature from January 1, 2020, at the beginning of what would quickly become a global pandemic. Our analysis of 56 studies[2–5,8,9,13–62] involving 8719 patients with confirmed COVID-19 suggests that WBC, CRP, PCT, ESR, and IL-6 are significantly higher with mild disease, and higher in those who die during follow-up than in those who survive. It is also noteworthy that our results are also in keeping with those of previous studies,[6,64,65] but our study included larger sample size and the analyzed inflammation markers that are more comprehensive. However, there is no insufficient evidence that shows a ranking

Table 2

Meta-analysis of inflammatory marker levels in Chinese COVID-19 patients.

Marker	No. studies	No. patients	Heterogeneity		Model*	Meta-analysis	
			P	I^2		WMD (95%CI)	*P*
Mild versus severe disease							
WBC, $\times 10^9$/L	37	8973	<.001	77.0%	R	1.15 (0.78,1.52)	<.001
CRP, mg/L	34	4910	<.001	93.0%	R	38.85 (31.19,46.52)	<.001
PCT, ng/mL	27	4250	<.001	90.3%	R	0.08 (0.06,0.11)	<.001
ESR, mm/h	11	2684	<.001	75.7%	R	10.25 (5.03,15.46)	<.001
IL-6, pg/mL	11	1359	<.001	93.1%	R	23.87 (15.95,31.78)	<.001
IL-10, pg/mL	4	673	.791	0.0%	F	2.12 (1.97,2.28)	<.001
TNF-α, pg/mL	5	723	<.001	91.1%	R	0.20 (−0.60,1.01)	.622
Nonsurvivors versus survivors							
WBC, $\times 10^{12}$/L	4	1034	.057	60.1%	R	4.11 (3.25,4.97)	<.001
CRP, mg/L	7	1522	<.001	76.4%	R	74.18 (56.63,91.73)	<.001
PCT, ng/mL	4	1067	<.001	93.2%	R	0.26 (0.11,0.42)	.001
ESR, mm/h	3	440	.902	0.0%	F	10.94 (4.79,17.09)	<.001
IL-6, pg/mL	5	1322	<.001	98.0%	R	59.88 (19.46,100.30)	.004

CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IL-10 = interleukin-10, IL-6 = interleukin-6, PCT = procalcitonin, TNF-α = tumor necrosis factor-α, WBC = white blood cell count, WMD = weighted mean difference.

* R means random model; F means fixed model.

for inflammatory markers in terms of correlation with the severity of COVID-19. These findings justify the monitoring of inflammatory markers to detect COVID-19 progression as early as possible for timely intervention.

Our results are consistent with the idea that IL-6 levels positively correlate with COVID-19 severity,[38] with levels in critically ill patients exceeding those with the milder disease by up to 10 times.[38] Our results are also consistent with a positive correlation between IL-6 levels and the risk of mortality.[57] IL-6 has strong pro-inflammatory effects.[66–68] Increases in IL-6 also trigger increases in PCT, which may explain why both are significantly higher in severe COVID-19.[69] The reason for there is no significant difference in TNF-α levels between mild and severe groups is unclear, but it may be related to the inhibition of

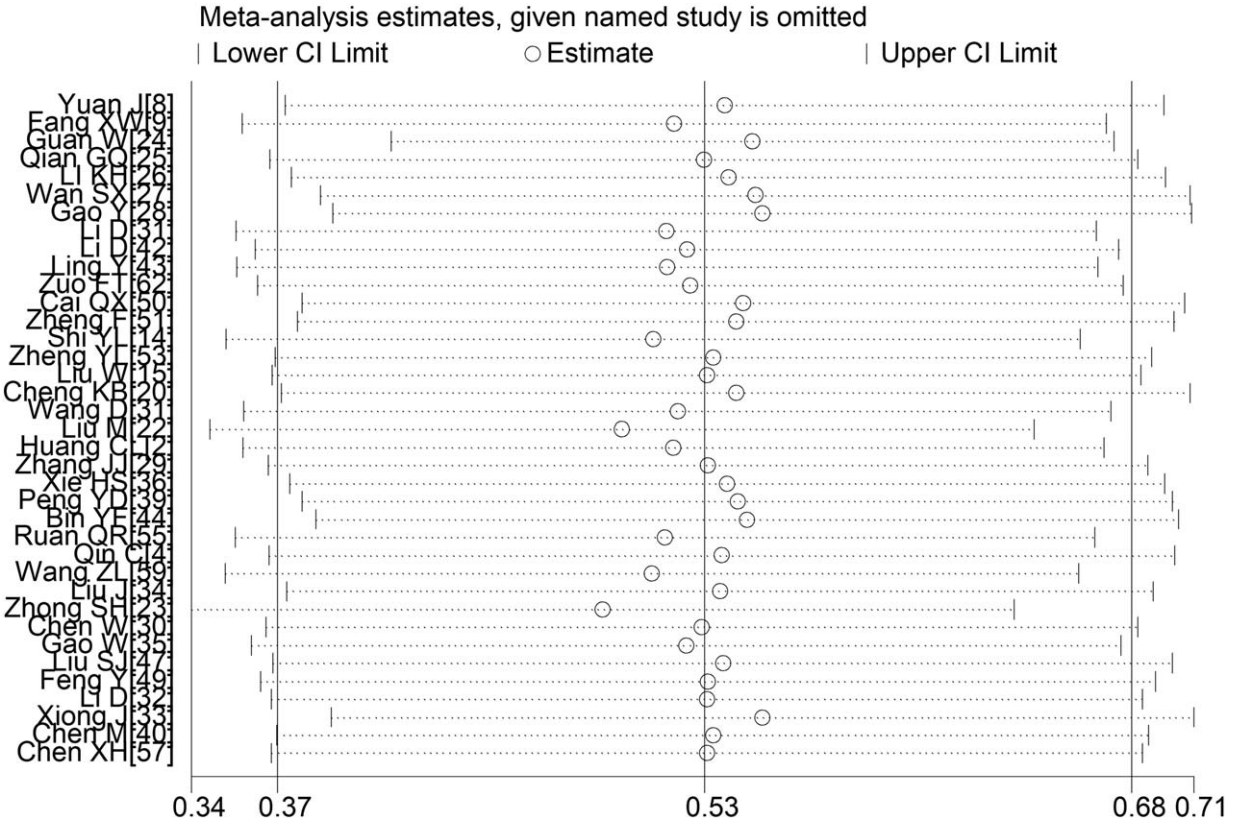

Figure 6. Sensitivity analysis of white blood cell count between patients with mild or severe COVID-19. COVID-19 = coronavirus disease 2019.

Th2 cells involved in humoral immunity in the early stage of infection[3] or the sample size is small, and the results are not representative.

The increase in inflammatory markers seen with severe COVID-19 is reminiscent of increases in similar markers during infection. For example, upon bacterial infection, PCT is released into the circulation, and elevated levels in peripheral blood correlate with infection severity.[5] Tan et al[70] found that CRP increased significantly in the initial stage of severe COVID-19 infection, while there was no significant difference in CT imaging between the severe group and the mild group. Research is needed to clarify to what extent the increases in inflammatory markers are caused directly by SARS-CoV-2 or reflect comorbidities such as hypertension, diabetes mellitus, and other chronic diseases that, like infectious diseases, trigger a chronic proinflammatory state. Patients with such comorbidities are more likely to develop severe COVID-19 than patients who are otherwise healthy,[71] at least partly because such conditions weaken the innate immune response, increasing the risk of SARS-CoV-2 infection.[70]

Our results suggest that monitoring inflammatory markers may serve as an early warning system for progression to severe COVID-19. Simultaneously, monitoring levels of IL-6, CRP, and PCT can allow early detection of bacterial infections, which may reduce overprescription of antibiotics for patients who do not need them and trigger early antibiotic therapy to prevent sepsis and other severe conditions.[72]

Although our meta-analysis rigorously analyzed data from a large sample of COVID-19 patients, our results are limited by the heterogeneity observed across studies, such as in the disease course and severity, reflecting the difficulties of standardizing methods during an emerging epidemic. We could not control for these and other potential confounders because all studies in our meta-analysis were retrospective. Due to the nature of reporting in the emerging outbreak, we did not perform a risk of bias assessment and presume it to be high across studies, which should be considered when interpreting results.

5. Conclusion

In summary, current evidence showed that higher levels of inflammatory markers such as WBC, CRP, PCT, ESR, IL-6, and IL-10 are associated with the severity of COVID-19 and thus could be used as significant prognostic factors of the disease.

Author contributions

Zhimei Zhong, Hongyuan Li, Jielong Pang, and Bocheng Li collected and analyzed the data. Jianfeng Zhang acquired the funding. Pan Ji and Jieyun Zhu designed the study and wrote the first draft of the manuscript. Jianfeng Zhang designed and supervised the study, and finalized the manuscript, which all authors read and approved.

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