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,[5–9] the results across these studies are not entirely consistent. So far, it is unclear whether inflammatory markers are
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,
| 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 | ① | 7 |
| Wan SX[3]   | Apr 16                 | 123| Single              | Mild and severe COVID-19 patients in Chongqing Three Gorges Central Hospital | 43.1±13.1 | Jan 26 to Feb 4 | WHO interim guideline | ⑥⑦ | 8 |
| Qin CL[4]   | Mar 12                 | 452| Single              | Mild and severe COVID-19 patients in Tongji Hospital Affiliated to Huazhong University of Science and Technology | 61.2±15.6 | Jan 10 to Feb 12 | WHO interim guideline | ③④⑤⑥⑦⑧ | 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 | WHO interim guideline | ③ | 9 |
| Yuan J[6]   | Mar 06                 | 223| Single              | Mild and severe COVID-19 patients in Chongqing Public Medical Center | 46.5±16 | Jan 24 to Feb 23 | WHO interim guideline | ③ | 9 |
| Fang XW[7]  | Mar 25                 | 79 | Single              | Mild and severe COVID-19 patients in Anhui Provincial Hospital | 45±166 | Jan 22 to Feb 18 | WHO interim guideline | ③ | 6 |
| Wei WX[8]   | Mar 18                 | 95 | Single              | Mild, severe, and critically ill COVID-19 patients in Chengdu Public Health Clinical Medical Center | 45.5±66.7±39.8/6/3±28.2 | Jan 16 to Feb 18 | WHO interim guideline | ③ | 7 |
| Shi YL[9]   | Feb 27                 | 164| Single              | Mild, severe, and critically ill COVID-19 patients in Guangzhou Eighth People’s Hospital | 59.8/66.7±39.8/6/3±28.2 | Jan to Feb | WHO interim guideline | ③ | 8 |
| Liu et al[10] | Feb 28               | 79 | Multi               | Mild and severe COVID-19 patients in 3 tertiary hospitals in Wuhan | 38 (33-57) | Dec 30 to Jan 15 | WHO interim guideline | ①②③④ | 7 |
| Deng Y[11]  | 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 | WHO interim guideline | ①② | 8 |
| Zhou F[12]  | 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 | WHO interim guideline | ①②③④ | 8 |
| Chen T[13]  | 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 | WHO interim guideline | ①②③④ | 7 |
| Wang Y[14]  | 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[15] | Mar 12                | 463| Single              | Mild and severe COVID-19 patients in Wuhan Jinyintan Hospital | 15–90 | Dec 2019 to Feb 06, 2020 | WHO interim guideline | ① | 7 |
| Wang DP[16] | 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[17]   | Feb 17                 | 30 | Single              | Mild and severe COVID-19 patients in Jianghan University Affiliated Hospital | 36±8 | Jan 10 to Jan 31 | WHO interim guideline | ① | 6 |
| Zhong SH[18] | 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 | WHO interim guideline | ① | 6 |
| Guan WH[19] | Feb 06                 | 1099| Multi              | Mild and severe COVID-19 patients in 552 Hospitals in 31 provinces | 47.0 | NR | WHO interim guideline | ①② | 9 |
| Qian G[20]  | 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[21]   | 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 | ①②③ | 7 |
| Wan SX[22]  | Feb 29                 | 83 | Single              | Mild and severe COVID-19 patients in Hubei Province | 45.5±12.3 | Jan to Feb | WHO interim guideline | ①②③ | 8 |

(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 | 47 (30–55) | Jan 23 to Feb 8 | WHO interim guideline | 1, 2, 3, 5 | 6            |
| Zhang J[29] | Mar 17                 | 135 | Single               | Mild and severe COVID-19 patients in Fuyang Second People’s Hospital | 45 ±7.7/43 ±14 | Jan 23 to Feb 2 | trial version 3–5 | 1, 2, 3, 0 | 7            |
| Chen W[30]  | Mar 17                 | 241 | Single               | Mild, severe, and critically ill COVID-19 patients | 41.6 ± 15.6 | Dec 2019 to Feb 21, 2020 | Trial seventh Edition | 1, 2, 3, 4 | 7            |
| Liu L[31]   | Mar 26                 | 90  | Single               | Mild and severe COVID-19 patients in tertiary hospitals in Zhuzhou | 47.8 ±19.5 | Jan 20 to Feb 27 | Trial fifth Edition | 1, 2, 3 | 7            |
| Li T[32]    | Apr 2                  | 120 | Single               | Mild, severe, and critically ill COVID-19 patients in Renmin Hospital of Wuhan University | 48 ±37/59±31 | Jan 31 to Feb 25 | Trial sixth Edition | 1, 2, 3, 0 | 6            |
| Xiong J[33] | Mar 03                 | 120 | 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 | 1, 2, 3, 7 | 7            |
| Chen W[34]  | Mar 27                 | 90  | Single               | Mild, severe, and critically ill COVID-19 patients in Wuhan Children’s Hospital | 51.7 ±8.6 | Jan to Feb | Trial fifth Edition | 1, 2, 4, 0 | 7            |
| Gao W[35]   | Mar 31                 | 90  | Single               | Mild, severe, and critically ill COVID-19 patients in Beijing Youan Hospital | 60 (48–66) | Feb 2 to Feb 23 | Trial sixth Edition | 1, 2, 3, 7 | 7            |
| Xie HS[36]  | Apr 2                  | 29  | Single               | Mild and severe COVID-19 patients in Wuhan Jinyintan Hospital | 43.9 ±15/65±1 | Dec 2019 to Feb 22, 2020 | Trial fifth Edition | 1, 2, 3, 4 | 7            |
| Zhang Y[37] | Feb 6                  | 29  | Single               | Mild, severe, and critically ill COVID-19 patients in Tongji Hospital Affiliated to Huashang University of Science and Technology | 26–79 | Jan | Trial fifth Edition | 1, 2, 3, 7 | 6            |
| Peng YD[38] | Mar 2                   | 112 | Single               | Mild and severe COVID-19 patients in western district of Union Hospital in Wuhan | 62 (53–76) | Jan 20 to Feb 15 | Trial sixth Edition | 1, 2, 3, 4 | 7            |
| Chen M[39]  | 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 | 1, 2, 4, 0 | 6            |
| Wan Q[40]   | Feb 24                 | 153 | Single               | Mild and severe COVID-19 patients in Zhongnan Hospital of Wuhan University | 43.4±15.7±6.1 | Dec 2019 to Feb 22, 2020 | Trial fifth Edition | 1, 2, 4, 7 | 7            |
| Liu J[41]   | 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, 2, 3, 0 | 6            |
| Ling Y[42]  | Mar 18                 | 292 | Single               | Mild and severe COVID-19 patients in Shanghai Public Health Clinical Center | 48.7±16/65±5.1 | Jan 20 to Feb 10 | Trial fifth Edition | 1, 2, 3, 4 | 9            |
| Bin Y[43]   | Feb 29                 | 55  | Single               | Mild and severe COVID-19 patients in Huaerqi District Chinese Medicine Hospital of Wuhan | 53.9±17.1 | Jan 29 to Feb 16 | Trial fifth Edition | 1, 2, 3, 0 | 6            |
| Xia XT[44]  | Apr 7                  | 63  | Single               | Mild and severe COVID-19 patients in Hubei Provincial Hospital of Integrated Chinese and Western Medicine | 62.3±15.6/14.6±14.9 | Jan 26 to Feb 20 | Trial fifth Edition | 1, 2, 3, 4 | 6            |
| Chen Q[45]  | Mar 6                  | 150 | Single               | Mild and severe COVID-19 patients in Tongji Hospital Affiliated to Huashang University of Science and Technology | 59±16 | Jan to Feb | Trial sixth Edition | 1, 2, 3, 4 | 7            |
| Liu SJ[46]  | Apr 2                  | 342 | Single               | NR | Jan 23 to Feb 12 | Trial sixth Edition | 1, 2, 3, 4, 7 | 7            |

(continued)
| First author | Publication date in 2020 | n | Single- or multicenter* | Patient population | Age†, yr | Follow-up | Diagnosis and severity criteria‡ | Outcomes§ | Quality score |
|-------------|-------------------------|---|------------------------|--------------------|---------|----------|-------------------------------|-----------|-------------|
| An W[48]   | Apr 16                  | 110 | Single                | Survival and nonsurvival COVID-19 patients in Ezhou Central Hospital | NR | Jan 24 to Feb 19 | Current trial version | ①③④ | 7 |
| Feng Y[49] | Apr 10                  | 476 | Multi                 | Mild and severely ill COVID-19 patients from 3 hospitals in Wuhan, Shanghai, and Anhui | NR | Jan 1 to Feb 15 | Trial fifth Edition | ①②③④ | 8 |
| Cai G[50]  | Apr 2                   | 298 | Single                | Mild and severely ill 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 | ① | 6 |
| Zheng J[51] | Mar                    | 161 | Single                | Mild and severely ill COVID-19 patients in Changsha First Hospital | 40.7± 15.0/56.8± 15.2 | Jan 17 to Feb 7 | Trial fifth Edition | ①③ | 7 |
| Tang J[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 | ①③④ | 8 |
| Zheng H[53] | Apr 10                  | 99  | Single                | Mild and severely ill COVID-19 patients in the 9th People’s Hospital of DongGuan | 42.5± 15.6/63.8± 16.5 | Jan 16 to Feb 20 | Trial fifth Edition | ① | 6 |
| Wang L[54] | Mar 10                  | 339 | Single                | Survival and non-survival COVID-19 patients in Renmin Hospital of Wuhan University | 68.7± 7.3/86.3± 9.3 | Jan 1 to Feb 6 | Trial sixth Edition | ①③④ | 7 |
| Zheng Y[55] | Apr 12                  | 150 | Multi                 | Mild and severely ill 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 | ①②③ | 8 |
| Tu W[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 nonsurvival | ① | 8 |
| Chen X[57] | Apr 17                  | 48  | Single                | Mild and severely ill COVID-19 patients in General Hospital of Central Theater Command | 52.8± 14.2/63.7± 12.6 | Jan 1 to Feb 19 | Trial sixth Edition | ①③④ | 9 |
| Ma J[58]   | Apr 13                  | 37  | Single                | Mild and severely ill 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 | ① | 7 |
| Wang Z[59] | Mar 16                  | 69  | Single                | Mild and severely ill 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 | ①②③④⑤⑥⑦ | 7 |
| Zou Q[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 | ① | 6 |
| He X[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 | ① | 8 |
| Zuo F[62]  | Apr 14                  | 50  | Single                | Mild and severely ill COVID-19 patients in Nanyang Central Hospital | 46.6± 16.3/53.7± 10.1 | Jan 19 to Mar 20 | Trial fifth Edition | ①②③ | 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. ①WBC = white blood cell count, ②CRP = C-reactive protein, ③PCT = procalcitonin, ④ESR = erythrocyte sedimentation rate, ⑤IL-6 = interleukin-6, ⑥IL-10 = interleukin-10, ⑦TNF-α = tumor necrosis factor-α.
8Score based on the Newcastle-Ottawa Scale guidelines.[11]
severe, or critical disease, or if 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.
The quality of included studies was assessed based on the Newcastle-Ottawa Scale guidelines. 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. 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 $\chi^2$ 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
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 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 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 I² ranging from 60.1% to 98.5%. Therefore we repeated each meta-analysis after excluding 1 study at a time. We found that the
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. 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. 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).” 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 in severe disease, yet other studies found the same marker to be higher in severe disease. 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 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, 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...
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,\(^\text{[38]}\) with levels in critically ill patients exceeding those with the milder disease by up to 10 times.\(^\text{[38]}\) Our results are also consistent with a positive correlation between IL-6 levels and the risk of mortality.\(^\text{[57]}\) IL-6 has strong pro-inflammatory effects.\(^\text{[66–68]}\) Increases in IL-6 also trigger increases in PCT, which may explain why both are significantly higher in severe COVID-19.\(^\text{[69]}\) The reason for there is no significant difference in TNF-\(\alpha\) levels between mild and severe groups is unclear, but it may be related to the inhibition of

### Table 2

| Marker | No. studies | No. patients | P | \(I^2\) | Model | Meta-analysis |
|--------|-------------|--------------|---|---------|-------|---------------|
|        |             |              |   |         |       | WMD (95%CI)   |              |
| Mild versus severe disease |            |              |   |         |       |               |              |
| WBC, \(x 10^9/L\) | 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 | <.001 | 0.0% | F | 2.12 (1.97,2.28) | <.001 |
| TNF-\(\alpha\), pg/mL | 5 | 723 | <.001 | 91.1% | R | 0.20 (−0.60,1.01) | .622 |
| Nonsurvivors versus survivors |            |              |   |         |       |               |              |
| WBC, \(x 10^9/L\) | 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 | <.001 | 98.0% | R | 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-\(\alpha\) = tumor necrosis factor-\(\alpha\), WBC = white blood cell count, WMD = weighted mean difference.

\(R\) means random model; \(F\) means fixed model.

![Figure 6. Sensitivity analysis of white blood cell count between patients with mild or severe COVID-19.](https://example.com/figure6.png)
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.\(^{[3]}\) 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.

- **Conceptualization:** Pan Ji, Jielong Pang, Bocheng Li.
- **Data curation:** Zhimei Zhong, Hongyuan Li, Jielong Pang.
- **Formal analysis:** Pan Ji, Zhimei Zhong.
- **Funding acquisition:** Jianfeng Zhang.
- **Investigation:** Zhimei Zhong.
- **Methodology:** Pan Ji, Jielong Pang, Bocheng Li, Jianfeng Zhang.
- **Resources:** Jianfeng Zhang.
- **Software:** Jieyun Zhu, Hongyuan Li, Bocheng Li.
- **Supervision:** Jianfeng Zhang.
- **Validation:** Jianfeng Zhang.

### Writing – original draft: Pan Ji, Jieyun Zhu.

### Writing – review & editing: Jianfeng Zhang.

### References

1. WHO. Coronavirus disease 2019 (COVID-19) Situation Dashboard [Internet]. Available at: https://covid19.who.int/ [Accessed April 27, 2020].
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
3. Wan S, Yi Q, Fan S, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. Br J Haematol 2020;189:428–37.
4. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;ciaa248.
5. Xiao KH, Shui LL, Pang XH, et al. Clinical features of coronavirus disease 2019 in Northeast area of Chongqing: analysis of 143 cases. J Third Mil Med Univ 2020;42:549–54.
6. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta 2020;505:190–1.

7. Ullaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect 2020;50:382–3.
8. Yuan J, Sun YL, Zuo YJ, et al. Clinical characteristics of 223 novel coronavirus pneumonia cases in Chongqing. J Southwest Univ (Natural Science Ed) 2020;42:17–24.
9. Fang XW, Mei Q, Yang TJ, et al. Clinical characteristics and treatment analysis of 79 cases of COVID-19. Chin Pharmacol Bull 2020;36:453–9.
10. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:208–12.
11. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
12. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
13. Wei WX, He XP, Ying BW, et al. The correlation between acute phase protein combined biochemical indicators and clinical classification of COVID-19. Int J Lab Med 2020;41:1602–7.
14. Shi YL, Qu JY, Chen X, et al. Expressions of multiple inflammation markers in the patients with 2019 novel coronavirus pneumonia and their clinical values. Chin J Lab Med 2020;43:E013–13.
15. Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020;133:1032–8.
16. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl) 2020;133:1261–7.
17. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
18. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
19. Wang Y, Lu X, Chen H, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020;201:1430–4.
20. Cheng KB, Wei M, Shen H, et al. Clinical characteristics of 463 patients with common and severe type coronavirus disease 2019. Shanghai Med J 2020;1–5.
21. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
22. Liu M, He P, Liu HG, et al. Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia. Chin J Tuberculosis Respir Dis 2020;209–14.
23. Zhong SH, Lin F, Shi L. The clinical characteristics and outcome of 62 patients with COVID-19. Medical J Chin People’s Liberation Army 2020;1–9.
24. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of 2019 novel corona virus infection in China. N Engl J Med 2020;382:1708–20.
25. Qian QG, Yang NB, Ding F, et al. Epidemiologic and clinical characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang,
China: a retrospective, multi-centre case series. QJM 2020;92:806.

[26] Li K, Wu J, Wu F, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol 2020;1–29. doi:10.1097/IRJ.0000000000001167.

[27] Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020;92:797–806.

[28] Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020;92:791–6.

[29] Zheng Y, Xu H, Yang M, et al. Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu. J Clin Virol 2020;127:104366.

[30] Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect 2020;80:39–45.

[31] Ruan Q, Yang K, Wang W, et al. Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;1–4. doi:10.1007/s00134-020-06028-z.

[32] Tu WJ, Gao J, Yu L, et al. Clinical laboratory study of 25 fatal cases of COVID-19 in Wuhan. Intensive Care Med 2020;46:1137–20.

[33] Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clin Infect Dis 2020;doi:10.1093/cid/ciaa272.

[34] Ma J, Yin J, Qian Y, et al. Clinical characteristics and prognosis in cancer patients with COVID-19: a single-center retrospective study. J Infect 2020;81:318–56.

[35] Wang Z, Yang B, Li Q, et al. Clinical features of 69 cases with Coronavirus Disease 2019 in Wuhan. Chin Clin Dis 2020;43:2095–103.

[36] Zuo FT, Li CL, Dong ZG, et al. Analysis of the correlation between laboratory indexes and clinical classification of 153 patients with novel coronavirus pneumonia. Tianjin Med J 2020;5:455–59.

[37] Xie H, Zhao J, Lian N, et al. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: a retrospective study. Liver Int 2020;40:1321–6.

[38] Zhang Y, Zheng L, Liu L, et al. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int 2020;40:2095–103.

[39] Chen L, Liu HG, Liu W, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Chin J Tuberc Respir Dis 2020;43:203–8.

[40] Peng YD, Meng K, Guan HQ, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Chin J Cardiol 2020;48:00004–14.

[41] Chen M, An W, Xia F, et al. Retrospective analysis of COVID-19 patients with different clinical subtypes. Herald Med 2020;39:459–64.

[42] Sun Q, Shi AQ, He T, et al. Analysis of clinical features of 153 patients with novel coronavirus pneumonia in Shangqiu, China. J Clin Dis 2020;16:20.

[43] Li D, Liu HY, Wang Y, et al. Clinical features of 30 cases with novel coronavirus pneumonia. Chin J Clin Dis 2020;38:E018–118.

[44] Liu Y, Lin YX, Qian ZP, et al. Clinical analysis of risk factors for severe patients with novel coronavirus pneumonia. Chinese J Clin Dis 2020;1–0. http://rs.xygle.com/yufabiao/1185115.htm.

[45] Bin YF, Ji P, Liang XD, et al. Clinical characteristics of 55 hospitalized patients with COVID-19 in Wuhan, China. J Guangxi Med Univ 2020;37:338–42.

[46] Xia XT, Wen MY, Zhan SF, et al. An increased neutrophil/lymphocyte ratio is an early warning signal of severe COVID-19. J South Med Univ 2020;40:33–6.

[47] Chen C, Chen T, Yan JT, et al. Analysis of myocardial injury in patients with COVID-19 and association between comitant cardiovascular diseases and severity of COVID-19. Chinese J Cardiol 2020;48:567–71.

[48] Liu SJ, Cheng F, Yang XY, et al. A study of laboratory confirmed cases between laboratory indexes and clinical classification of 342 cases with Corona Virus Disease 2019 in Ezhou. Lab Med 2020;1–2.

[49] An W, Xia F, Chen M, et al. Analysis of clinical features of 11 death cases caused by COVID-19. J Pract Med 2020;1–6.

[50] Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020;75:1742–52.

[51] Zheng F, Tang W, Li H, et al. Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha. Eur Rev Med Pharmacol Sci 2020;24:3404–10.

[52] Tang JS, Xuan C, Lin JT, et al. Clinical significance of detecting c-reactive protein, interleukin-6 and procalcitonin in COVID-19. J Pract Med 2020;36:839–41.

[53] Zhang J, Wu J, Han M, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol 2020;1–29. doi:10.1097/IRJ.0000000000001167.

[54] Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020;52:836–62.

[55] Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91–5.

[56] Zhang C, Wu Z, Li J, et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020;105954.