

Elevated interleukin-6 is associated with severity of COVID-19: A meta-analysis

Coronavirus disease 2019 (COVID-19) has spread rapidly around the world since its emergence in humans last December. Previous studies suggested that numerous markers of inflammation were elevated in patients with severe disease relative to patients with milder conditions,^{1,2} and an elevated level of interleukin-6 (IL-6) was associated with a high case fatality of COVID-19 infection.³ Two recent meta-analyses also suggested that IL-6 levels were significantly increased in COVID-19 patients with severe diseases.^{4,5} Yet several large related clinical studies have been conducted since then. Therefore, to gain a clearer picture of the potential association between IL-6 levels 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.

This meta-analysis was carried out according to the Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology (MOOSE) Statement.⁶ The databases PubMed, Embase, Web of Science, Scopus, and Chinese National Knowledge Infrastructure were systematically searched for studies published from January 1, 2020, to May 1, 2020, without language limits (Supporting Information File 1). We also manually searched the reference lists of included studies to identify additional eligible studies. Studies were included in the meta-analysis if they had cohort, case-control, or case series designs involving more than 20 patients with confirmed COVID-19; if they contained patients with mild and severe disease, or survivor and death groups; and if they reported sufficient details about IL-6. We considered the disease to be "mild" in those patients described in the studies as having mild or moderate disease, "severe" in those patients described as having severe disease, and "critically ill" in those patients described as having critically ill disease, as being admitted to the intensive care unit or as requiring mechanical ventilation.

The quality of the included studies was evaluated based on the Newcastle-Ottawa Scale guidelines.⁷ Data from studies reporting continuous data as ranges or as median and interquartile ranges were converted to mean \pm SD.⁸ The weighted mean differences (WMDs) in continuous variables between patient groups were calculated, together with the associated 95% confidence intervals (CIs). All meta-analyses were performed using STATA 12 (Stata-Corp). A fixed-effects model was used when the I^2 statistic was below 50% and the associated $p > .10$; otherwise, a random-effects

model was used. The sensitivity analysis was employed to explore the source of heterogeneity. Funnel plot, together with Egger's regression asymmetry test and Begg's test, was used to evaluate publication bias. A two-tailed $p < .05$ was regarded as statistically significant.

In the end, we meta-analyzed 23 studies involving 3400 COVID-19 patients (Supporting Information File 2). Although the heterogeneity was considerably high, the pooled results revealed that compared with the severe group, the IL-6 levels were lower in the mild group (WMD: -24.49, 95% CI: -34.64 to -14.34, $p < .001$) but significantly increased in the critically ill group (WMD: 30.66, 95% CI: 7.53 to 53.78, $p = .009$) (Figure 1). A subgroup analysis comparing patients by survival found an even higher IL-6 level observed in patients who died (WMD: 41.32, 95% CI: 28.15 to 54.49, $p < .001$) (Figure 1).

The meta-analyses of IL-6 levels from all included studies were repeated after omitting each study in turn, and the results were similar to those obtained with the entire data set. Nonsignificant p values were obtained when all studies were analyzed using Egger's test (.108) and Begg's test (.540), suggesting no significant risk of publication bias (Supporting Information File 3).

Compared to the nine studies involving 1426 patients in the most recent relevant meta-analysis,⁵ the present study includes 23 studies published up to May 1, 2020, and a total pooled population of 3400 COVID-19 patients. Our results indicate that elevated IL-6 levels occur more often in severe and critically ill than mild COVID-19, and they occur more often in patients who die from the disease than in those who survive. Our results are consistent with the idea that IL-6 levels positively correlate with COVID-19 severity and risk of fatality.^{3,9}

IL-6 has strong proinflammatory effects, an increase in levels of IL-6 has previously been observed in patients with respiratory dysfunction,¹⁰ indicating a possible shared mechanism of cytokine-mediated lung damage caused by SARS-CoV-2 infection.⁴ In addition, it seems that the highly pathogenic SARS-CoV-2 is associated with rapid virus replication and resulting in an elevated response of IL-6-induced severe respiratory distress.⁴

In summary, elevated levels of IL-6 are associated with severity of COVID-19. And thus, monitoring IL-6 levels in COVID-19 patients may aid in the early detection of severe disease. But further research is needed to verify and extend our results, especially as all the included studies were retrospective, and most did not control for

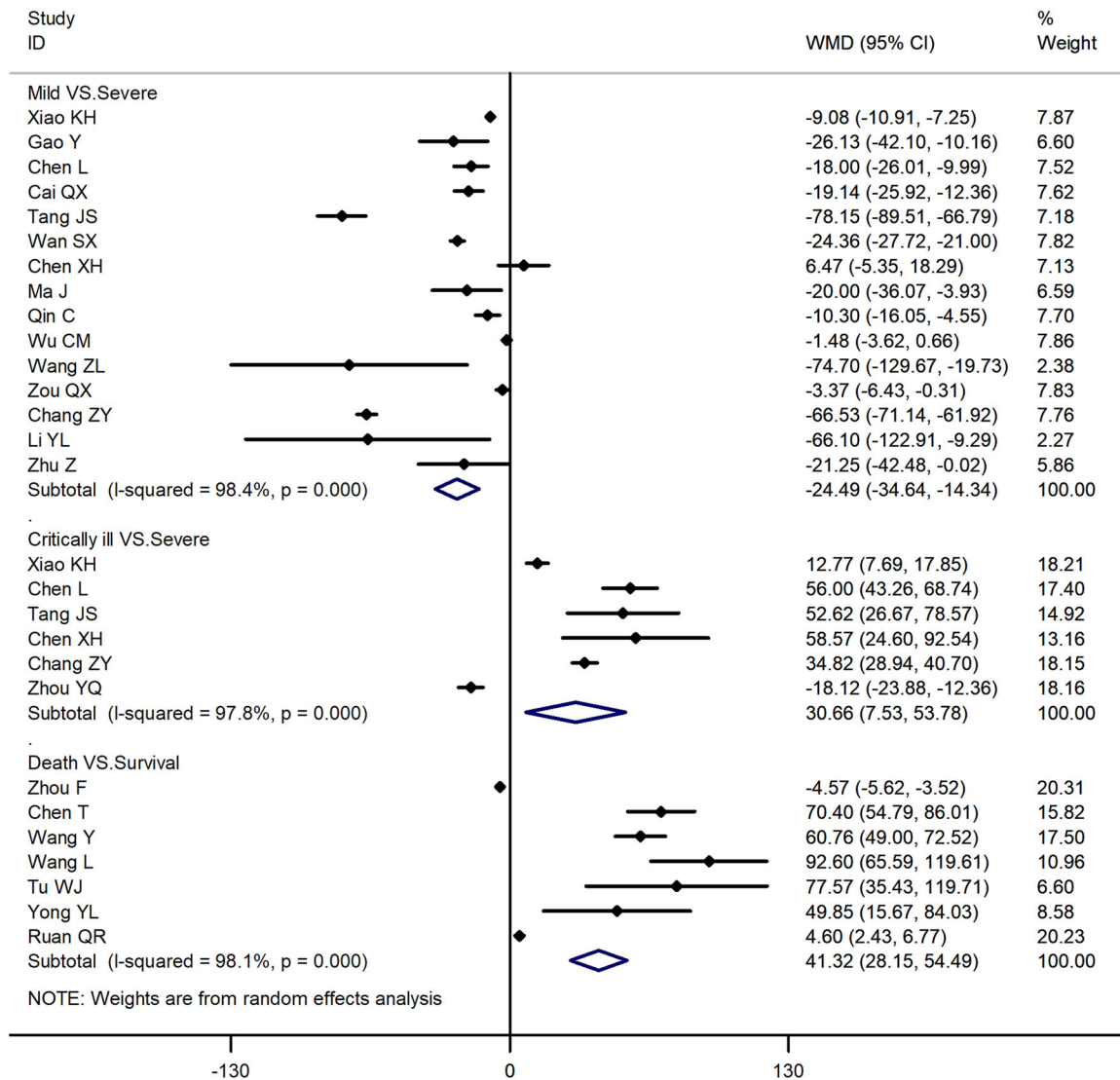


FIGURE 1 Forest plot of weighted mean difference (WMD) and 95% confidence interval (95% CI) in interleukin-6 levels between COVID-19 patients

potential effects of confounding factors such as age, as well as differences in disease severity and course.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

KEYWORDS

2019 coronavirus disease, critically ill, interleukin-6, meta-analysis, severe disease

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.