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## Letter to the editor

### Interleukin-6 as a potential biomarker of COVID-19 progression

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), also known as the 2019 novel Coronavirus (2019-nCoV), has caused a recent outbreak of Coronavirus Disease (COVID-19) [1,2]. To date, COVID-19 has already affected 372,757 people globally, with a 4.35% mortality rate. In Indonesia, the first case of COVID-19 was reported on March 2, 2020. Since then, the number of positive cases has risen significantly to 686 cases, according to government data on March 23, 2020.

Although most cases were mild to moderate, some patients developed severe symptoms characterized by respiratory dysfunction and/or multiple organ failure [3]. In the current situation, identification of COVID-19 disease progression mainly relies on the clinical manifestation, while no effective biomarker has been proposed. It has been suggested that one of the possible mechanisms underlying rapid disease progression is a cytokine storm [1,2]. Previous retrospective studies indicated that an elevated level of interleukin-6 (IL-6) was associated with a high case fatality of COVID-19 infection [1]. Thus, a meta-analysis of the current scientific literature was performed to investigate whether the measurement of serum IL-6 may predict progression of COVID-19 patients.

A comprehensive literature search was conducted from PubMed, Scopus, Web of Science, and Google Scholar. Keywords such as "IL-6", "coronavirus 2019/COVID-19", "2019-nCoV", "SARS-CoV-2" were used on their own or in combination without applying language restriction and dated up to March 25, 2020. Selection criteria were case-control or cohort studies evaluating serum IL-6 levels in COVID-19 patients with or without severe condition (*i.e.*, the period of infection, CT score, ICU admission, troponin levels, those needing mechanical ventilation, or those who died). A meta-analysis was performed using a random-effect model to allow for heterogeneity in individual studies. Hedge's standardized mean difference (SMD) with 95% confidence interval (CI) was used to assess the IL-6 level in non-severe and severe patients. Heterogeneity

was evaluated with Q-test and $I^2$ statistics. Begg's funnel plot and Egger's regression test were applied to determine publication bias if the pooled effect size consisted of 10 or more studies. A sensitivity test was performed by sequentially omitting one study each time to evaluate the stability of the results. Data that was not expressed as mean and standard deviation was extrapolated from the sample size, median, and interquartile range (IQR). The meta-analysis was performed using RevMan version 5.3 and the value of 0.05 was indicative of statistical significance.

We initially identified 73 articles based on our search strategy, 64 of which were excluded after title, abstract, or full-text reading, because they were review articles, did not report IL-6 levels, or did not classify the condition of COVID-19 patients as non-severe and severe. Finally, only nine studies were included in this meta-analysis [1–9]. Although the heterogeneity was considerably high ($I^2 = 89\%$; $P < 0.00001$), we observed that IL-6 levels were significantly increased in COVID-19-infected patients with severe condition compared with those with non-severe condition (SMD = 0.71, 95%CI −0.31–1.12, $P = 0.0005$) (Fig. 1). Begg's funnel plot (data not shown) and Egger's test were performed, and no publication bias was observed (P Egger's test = 0.117). A sensitivity analysis was conducted by eliminating one individual study each time (Fig. 2). However, the results remained unchanged, suggesting that the findings were statistically stable and robust.

Cytokines are vital in regulating immunological and inflammatory responses. Among them, IL-6 is of major importance because of its pleiotropic effects [1]. Here, we presented the evidence that circulating IL-6 levels are closely linked to the severity of COVID-19 infection. An increase in IL-6 levels has previously been observed in patients with respiratory dysfunction [2], implying a possible shared mechanism of cytokine-mediated lung damage caused by COVID-9 infection. Furthermore, it seems that the highly pathogenic SARS-CoV-2 is associated with rapid virus replication and a tendency to infect the lower respiratory tract, resulting in an elevated response of IL-6-induced severe respiratory distress. Thus, our results suggest that serial measurement of circulating IL-6 levels may be important in identifying disease progression among COVID-19-infected patients. In line with our findings, an elevated level of IL-6 has been proven to be a good biomarker for severity of hepatitis B virus (HBV) infection [10]. Therefore, it is reasonable that immediate initial evaluation of IL-6 level be performed upon hospital admission of COVID-19 patients, due to its potential benefits to assess worsening clinical features and disease progression in COVID-19.
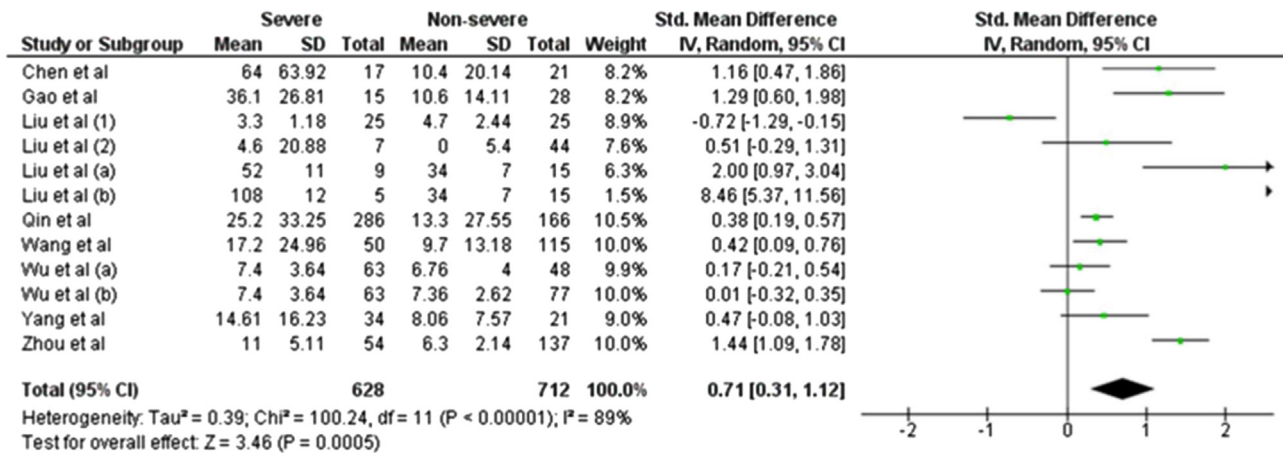
**Fig. 1.** Forest plot for pooled standardized mean difference (SMD) and 95% confidence interval (95% CI) of circulating IL-6 levels in COVID-19-infected patients with severe and non-severe condition.
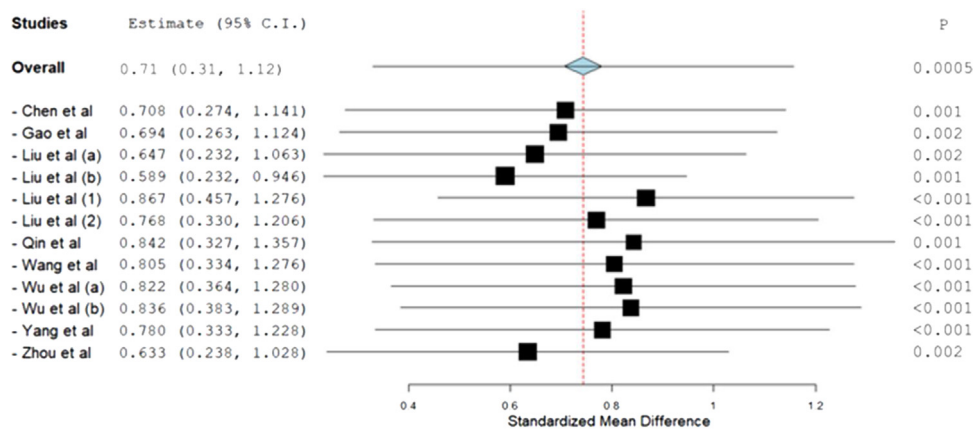


**Fig. 2.** Sensitivity analysis of changes in IL-6 levels of COVID-19-infected patients.

## Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

## Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

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## Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

## Disclosure of interest

The authors declare that they have no competing interest.

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