Elevated interleukin-6 and adverse outcomes in COVID-19 patients: a meta-analysis based on adjusted effect estimates

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Abstract
This study aimed to evaluate the association of interleukin-6 (IL-6) level with the poor outcomes in coronavirus disease 2019 (COVID-19) patients by utilizing a meta-analysis based on adjusted effect estimates. We searched the keywords from PubMed, Web of Science, and EMBASE on August 14, 2020. The pooled effects and 95% confidence interval (95% CI) were estimated by Stata 11.2. Subgroup analysis and meta-regression were performed to explore the source of heterogeneity. Sensitivity analysis was implemented to assess the stability of the results. Begg’s test and Egger’s test were conducted to assess the publication bias. Sixteen articles with 8752 COVID-19 patients were finally included in the meta-analysis. The results based on random-effects model indicated that elevated value of IL-6 was significantly associated with adverse outcomes in patients with COVID-19 (pooled effect = 1.21, 95% CI 1.13–1.31, I² = 90.7%). Subgroup analysis stratified by disease outcomes showed consistent results (severe: pooled effect = 1.18, 95% CI 1.05–1.31; ICU (intensive care unit) admission: pooled effect = 1.90, 95% CI 1.04–3.47; death: pooled effect = 3.57, 95% CI 2.10–6.07). Meta-regression indicated that study design was a source of heterogeneity. Publication bias was existent in our analysis (Begg’s test: P = 0.007; Egger’s test: P < 0.001). In conclusion, the elevated IL-6 level is an independent risk factor associated with adverse outcomes in patients with COVID-19.

Keywords COVID-19 · IL-6 · Adverse outcomes · Meta-analysis · Adjusted effect estimates

With the developing of the epidemic caused by coronavirus disease 2019 (COVID-19), biomarkers which might predict the adverse outcomes of COVID-19 patients gradually attract researchers’ attention. Interleukin-6 (IL-6) is one of the main pro-inflammatory factors in the formation of cytokine storm, which increases permeability to a great extent and damages organ function (Liu et al. 2020d). As a result, IL-6, as a possible indicator of the poor prognosis in patients with COVID-19, has been noticed, and many relevant articles have been published. Recently, a meta-analysis conducted by Zeng et al. aroused our interests, which reported the significant association between IL-6 levels and severe COVID-19 (weighted mean difference (WMD): − 21.32 ng/L, 95% confidence interval (CI) (− 28.34, − 14.31); P < 0.001, I² = 99.1%) (Zeng et al. 2020). However, this meta-analysis was based on unadjusted effect estimates. As we all know, there are several factors affecting the disease progression, such as gender, age, and comorbidities (Del Valle et al. 2020). Moreover, in the paper reported by Wang et al., the univariate logistic analysis suggested that the baseline levels of IL-6 were significantly associated with the disease progression of COVID-19 patients, while the multivariate logistic analysis indicated that only high levels of IL-6 were a risk factor for disease progression of COVID-19 patients (Wang et al. 2020). Therefore, it is necessary to evaluate the association of IL-6 level with the adverse outcomes of COVID-19 patients by utilizing a meta-analysis on the basis of adjusted effect estimates.

A scientific literature search of the electronic databases including PubMed, Web of Science, and EMBASE was carried out on August 14, 2020, to enroll all eligible

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publications which reported the association between elevated IL-6 levels and adverse outcomes in patients with COVID-19. The following terms were used as our search strategy: (“coronavirus disease 2019” OR “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV” OR “novel coronavirus”) AND (“IL-6” OR “interleukin-6”) AND (“mortality” OR “death” OR “fatality” OR “demise” OR “severe” OR “severity” OR “critical” OR “poor outcome” OR “poor prognosis” OR “adverse outcome” OR “progression”). We incorporated the articles that reported the correlation of IL-6 level with the poor outcomes of COVID-19 patients based on adjusted effect estimates. The meta-analysis was performed by the software Stata 11.2 to obtain the pooled effect and 95% CI. We used the $I^2$ test to evaluate the heterogeneity among the included articles. The fixed-effects model was chosen if $I^2 < 50\%$, while the random-effects model was used if $I^2 \geq 50\%$. Meta-regression and subgroup analysis were conducted to identify the source of heterogeneity. Sensitivity analysis was implemented by taking out one study each time to assess the stability of the results. Additionally, we used the Begg’s test and Egger’s test to assess the publication bias and conducted a trim and fill analysis to adjust the effect size.

Figure S1 presents the process of study selection. The initial search produced 1044 articles with 603 excluded because of duplication. We excluded 198 articles after assessing the titles and abstracts, because some of the articles are reviews; some are correspondences, commentaries, or letters; and others are case reports, study protocols for clinical trial, or no-human studies. After assessing the full text, 176 were excluded because they did not report the association between IL-6 level and poor outcomes in COVID-19 patients, and 51 were excluded because original data were not reported or adjusted effect was not used. Finally, 16 articles consisting of 8752 COVID-19 patients were included in the meta-analysis (Ayanian et al. 2020; Bellmann-Weiler et al. 2020; Cummings et al. 2020; Del Valle et al. 2020; Li et al. 2020; Liu et al. 2020a, b, c, d, e; Phipps et al. 2020; Sardu et al. 2020; Song et al. 2020; Tian et al. 2020; Wang et al. 2020; Yan et al. 2020). The characteristics of the 16 eligible studies are shown in Table 1.

Our results indicated that elevated values of IL-6 were significantly associated with adverse outcomes in patients with COVID-19 (pooled effect = 1.21, 95% CI 1.13–1.31, $I^2 = 90.7\%$, random-effects model, Fig. 1a). Subgroup analysis stratified by countries, which also demonstrated consistent results (China: pooled effect = 1.12, 95% CI 1.04–1.20; USA: pooled effect = 1.78, 95% CI 1.15–2.77, Fig. S2a). The results of subgroup analysis only based on prospective studies showed that elevated IL-6 values were also significantly associated with adverse outcomes in COVID-19 patients (pooled effect = 1.07, 95% CI 1.01–1.14) (Fig. S2b). Meta-regressions revealed that different study designs (retrospective study or prospective study) contributed to the heterogeneity among studies ($P = 0.026$), while others had no contribution, such as effect estimate model (odds ratio (OR) and hazard ratio (HR)) ($P = 0.677$), disease outcomes ($P = 0.916$), country ($P = 0.458$), as well as adjusted factors and so on. In addition, sensitivity analysis indicated that there was few influence of individual study on pooled effects when we eliminated each of the included studies. However, publication bias was existent in our analysis (Begg’s test: $P = 0.013$; Egger’s test: $P < 0.001$, respectively). The trim and fill analysis revealed that after adjusting the asymmetry, the results were still stability (pooled effect = 1.116, 95% CI 1.022–1.220).

Based on our analysis taking the confounders into account, elevated IL-6 value was significantly associated with severe COVID-19 and can be regard as an independent risk factor for adverse outcomes in COVID-19 patients. IL-6, as a cytokine, has been previously verified elevating in inflammatory state for multiple conditions. The pathophysiological hallmark of COVID-19 is the severe inflammation and cytokine storm, which explains the elevation of IL-6 levels (Cai et al. 2020; Mo et al. 2020). Thus, IL-6 can be used as a significant indicator of adverse prognosis reminding the clinicians to pay more attention to the patients with COVID-19 who might have a poor outcome in the early stage.

However, there are still some limitations in our study. One of the main defects is that the adjusted factors were different among the selected studies. Additionally, the publication bias existed in our study. The generation of publication bias is probably owing to that studies with positive results are more likely to be published than negative ones and the number of relevant studies is still not enough. Thus, further well-designed studies with more available articles are required to verify our current findings in the future.

In conclusion, elevated IL-6 was an independent risk factor associated with the adverse outcomes in patients with COVID-19. Thus, COVID-19 patients with high levels of IL-6 were worth noticing and needed more clinical attention. Furthermore, the biomarkers indicating poor prognosis in patients with COVID-19 should be further researched in order to help clinicians reasonably arrange the medical resource.
| Author          | Country | Cases (n) | Age (years) | Male, n (%) | Study design | Cutoff value | Outcomes | Adjusted effect estimate (95% CI) | Confounders                                                                 |
|----------------|---------|-----------|-------------|-------------|--------------|--------------|----------|-----------------------------------|----------------------------------------------------------------------------|
| Cummings MJ (PMID: 32442528) | USA     | 257       | 62 (51, 72) | 171 (67)    | P            | Per decile increase | Death    | HR 1.11 (1.02, 1.20)              | Age, gender, symptom duration before hospital presentation, hypertension, chronic cardiac disease, COPD or interstitial lung disease, diabetes, D-dimer |
| Liu X (PMID: 32475880)          | China   | 88        | 60.45 ± 11.51 | 51 (58)     | P            | 7 pg/ml       | Severe   | OR 1.31 (1.032, 1.687)            | Lymphocyte count, LDH level, erythrocyte count, albumin level, A/G ratio, blood glucose level |
| Phipps MM (PMID: 32473607)      | USA     | 3381      | 65 (52, 76) | 1297 (57)   | R            | NR           | Death    | OR 1.45 (1.1, 1.93)              | Age, gender, BMI, peak ferritin, peak D-dimer, peak CRP, peak PCT, peak creatinine kinase, peak high sensitivity troponin |
| Del Valle DM (PMID: 32511562)   | USA     | 1268      | 63 (53, 72) | 787 (60.1)  | P            | 70 pg/ml     | Death    | HR 2.06 (1.33, 3.18)             | Age, gender, race/ethnicity, BMI, smoking status, TNF-a, IL-8, IL-1b, CRP, D-dimer, ferritin, diabetes, hypertension, CKD, asthma, CHF, COPD, sleep apnea, atrial fibrillation, cancer, severity scores |
| Tian J (PMID: 32479790)         | China   | 232       | 64 (58, 69) | 119 (51)    | R            | NR           | Severe   | OR 1.03 (1, 1.05)               | Age, ECOG performance status, tumor stage, antitumor treatments, TNF-a, IL-6, IL-2R, procalcitonin, CRP, lymphocytes, leukocyte count, neutrophils, monocytes, LDH, albumin, A/G ratio, NT-proBNP, myoglobin, hs-cTnI, platelet count, activated partial thromboplastin time, prothrombin time, D-dimer |
| Author                  | Country | Cases (n) | Age (years) | Male, n (%) | Study design | Cutoff value | Outcomes                      | Adjusted effect estimate (95% CI) | Confounders                                                                 |
|------------------------|---------|-----------|-------------|-------------|--------------|--------------|-------------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Wang F (PMID: 32620125) | China   | 323       | 46 (33, 59) | 154 (47.7)  | P            | 7 pg/ml       | Progressive                  | OR 1.03 (1, 1.05)                  | NLR, T lymphocyte, CRP, IL-6, ESR |
| Liu J (PMID: 32622796)  | China   | 107       | 68 (61, 76) | 52 (49)     | R            | 10 pg/ml      | Poor outcomes                | OR 7.228 (2.222, 23.514)          | Age, calcium, CRP, PCT, IL-6, D-dimer |
| Sardu C (PMID: 3263594) | Italy   | 62        | 58 ± 18     | 41 (66.1)   | P            | NR           | ICU admission                | HR 1.617 (1.094, 2.389)           | Demographic variables that were significantly different amongst the groups and values of left ventricle ejection fraction |
| Ayanian S (PMID: 32677844) | USA     | 299       | NR          | 161 (54)    | R            | 50 pg/ml      | ICU admission                | OR 5.9 (2.7, 13.1)                | D-dimer, ferritin, CRP, LDH |
| Li T (PMID: 32688107)   | China   | 312       | 69.2 ± 7.3  | 187 (59.9)  | R            | NR           | Intubation                    | OR 4.6 (1.7, 12.4)                | Age, SOFA score, APACHE II score, platelet count, D-dimer, creatinine, lung consolidation |
| Liu D (PMID: 32696591)  | China   | 115       | 62.0 (51.0, 70.0) | 115 (100) | R            | 14 pg/ml      | Fatal outcome                | OR 5.21 (2.65, 10.27)             | Hypertension, age, WBC count, lymphocyte count, D-dimer, procalcitonin, CRP |
|                        |         | 120       | 0 (0)       |             |              |              |                               | OR 12.89 (4.71, 35.3)            | IL-2R, IL-8, WBC count, lymphocyte count, high-sensitivity cardiac troponin I |
| Liu SP (PMID: 32712122) | China   | 255       | 64 (24, 92) | 136 (53.3)  | P            | NR           | ICU admission                | OR 1.01 (1.002, 1.018)           | Diabetes, high FPG at admission, high IL-6, D-dimer |
| Song Y (PMID: 32733921) | China   | 64        | 64.8 ± 12.2 | 42 (65.6)   | R            | 703.9 pg/ml   | Myocardial injury            | OR 13.63 (3.33, 55.71)           | hs-CRP, IL-2R, IL-8, TNF-α |
| Bellmann-Weiler (PMID: 32751400) | USA | 259     | NR          | 156 (60.6)  | R            | NR           | ICU admission                | OR 1.961 (1.088, 3.535)          | Gender, temperature, SpO2, DM, COPD, ferritin, transferrin, leukocytes |
| Author | Country | Cases (n) | Age (years) | Male, n (%) | Study design | Cutoff value | Outcomes | Adjusted effect estimate (95% CI) | Confounders |
|--------|---------|-----------|-------------|-------------|--------------|--------------|----------|-----------------------------------|-------------|
| Yan Q (PMID: 32766817) | China | 882 | 71 (68, 77) | 440 (49.9) | R | 6 pg/l | Death | HR 25.53 (3.5, 186.04) | Age, gender, cardiovascular diseases, chronic respiratory disease, CKD, cerebrovascular disease, diabetes, malignancy, lymphocytes, D-dimer, LDH, cardiac injury, liver injury, AKI |
| Liu Z (PMID: 32765283) | China | 728 | 58 (49, 68) | 342 (46.98) | R | 7 pg/ml | Death | HR 10.39 (1.09, 99.23) | Age, cardiovascular disease, lymphocyte count, D-dimer, LDH |
| | | | | | | | Severe | OR 3.56 (2.06, 6.19) | Age, cardiovascular disease, lymphocyte count, D-dimer, LDH |

The values of age are mean ± standard deviation (SD) or median (interquartile range, IQR). The values of male are n (%). P prospective study, R retrospective study, CI confidence interval, ICU intensive care unit, HR hazard ratio, OR odds ratio, LDH lactate dehydrogenase, A/G ratio albumin-globulin ratio, BMI body mass index, CRP C-reactive protein, PCT procalcitonin, TNF tumor necrosis factor, IL interleukin, CKD chronic kidney disease, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, ECOG Eastern Cooperative Oncology Group, IL-2R IL-2 receptor, NT-proBNP N-terminal pro-B-type natriuretic peptide, hs-cTnl high-sensitivity cardiac troponin I, NLR neutrophil to lymphocyte ratio, ESR erythrocyte sedimentation rate, SOFA sequential organ failure assessment, APACHE acute physiologic and chronic health evaluation, WBC white blood cell, FPG fasting plasma glucose, hs-CRP high-sensitivity C-reactive protein, DM diabetes mellitus, AKI acute kidney injury, SpO2 peripheral capillary oxygen saturation, NR not reported.
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