Association between IL-6 and severe disease and mortality in COVID-19 disease: a systematic review and meta-analysis

Xiaohui Liu, Hongwei Wang, Si Shi, Jinling Xiao

ABSTRACT

Background: So far, SARS-CoV-2 is the seventh coronavirus found to infect humans and cause disease with quite a strong infectivity. Patients diagnosed as severe or critical cases are prone to multiple organ dysfunction syndrome, acute respiratory distress syndrome and even death. Proinflammatory cytokine IL-6 has been reported to be associated with the severity of disease and mortality in patients with COVID-19.

Objective: This systematic review and meta-analysis were carried out to evaluate the association between IL-6 and severe disease and mortality in COVID-19 disease.

Methods: A systematic literature search using China National Knowledge Infrastructure, Wanfang databases, China Science and Technology Journal Database, Chinese Biomedical Literature, Embase, PubMed and Cochrane Central Register of Controlled Trials was performed from inception until 16 January 2021.

Results: 12 studies reported the value of IL-6 for predicting the severe disease in patients with COVID-19. The pooled area under the curve (AUC) was 0.85 (95% CI 0.821 to 0.931). 5 studies elaborated the predictive value of IL-6 on mortality. The pooled sensitivity, specificity and AUC were 0.15 (95% CI 0.13 to 0.17, I²=98.9%), 0.73 (95% CI 0.65 to 0.79, I²=91.8%) and 0.531 (95% CI 0.451 to 0.612), respectively. Meta-regression analysis showed that country, technique used, cut-off, sample, study design and detection time did not contribute to the heterogeneity of mortality.

Conclusion: IL-6 is an adequate predictor of severe disease in patients infected with the COVID-19. The finding of current study may guide clinicians and healthcare providers in identifying potentially severe or critical patients with COVID-19 at the initial stage of the disease. Moreover, we found that only monitoring IL-6 levels does not seem to predict mortality and was not associated with COVID-19’s mortality.

INTRODUCTION

SARS-CoV-2, also referred to COVID-19, emerged from Wuhan, China in December 2019. So far, SARS-CoV-2 is the seventh of its kind found to infect humans and cause disease, with potentially powerful infectivity. It has been observed to spread extensively all across the world. Although most cases are mild to moderate, some critical patients have symptoms characterised by respiratory dysfunction and/or multiple organ failure. Though the disease fatality rate is not too high, the total count of infections is rather large and still a large number of patients are dying, particularly in the high-risk groups with poor prognosis at the time of hospitalisation. As more and more clinical data are being collected and released, it is evident that acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) are the primary reason for death in individuals experiencing the severe form of COVID-19. Early detection of severe or potentially critical cases, as well as timely treatment of target patients, is essential.

Systemic inflammatory response referred to as cytokine release syndrome (CRS) can be triggered by a variety of factors such as infection, toxin or special response to drugs, characterised by elevated amounts of proinflammatory cytokines (tumour necrosis factor (TNF), IL-6, IL-1 β, etc.). IL-6 contributes to host protection by inducing acute phase responses, haematopoiesis and immune reactions. It is developed rapidly and transiently in response to infections and tissue injuries. IL-6 has a pathological effect on systemic inflammation and autoimmunity although its expression is closely regulated by transcriptional and posttranscriptional pathways. IL-6 is the main cytokine whose development has been linked to several inflammatory diseases. High levels of IL-6 were seen in patients with SARS-CoV-2, and these levels were linked to pulmonary inflammation and severe lung injury.

Also, some investigations have revealed that CRS has an association with the severity and prognosis of the disease. It may have a pivotal role in severe respiratory failure and death caused by COVID-19. Previous reviews have shown that in severe COVID-19 disease, high levels of serum IL-6 are significantly related to the severity of COVID-19 and adverse clinical outcomes, which include admission to intensive care unit (ICU), ARDS and death. Several studies have depicted that IL-6 is a principle predictor of severe COVID-19. We carried out this systematic review and meta-analysis to evaluate the association between IL-6 and severe disease and mortality in COVID-19 disease and to furnish a reliable set of markers for early recognition of potentially severe or/critical cases.

METHODS

The study was carried out following the preferred reporting items of systematic review and meta-analysis of the report checklist. It was prospectively registered in the PROSPERO database.
SEARCH STRATEGY
A systematic literature search using China National Knowledge Infrastructure, Wanfang databases, China Science and Technology Journal Database, Chinese Biomedical Literature, Embase, PubMed and Cochrane Central Register of Controlled Trials was performed from inception until 16 January, 2021. The search strategy was based on the following combination of keywords: ['coronavirus disease 2019' or 'COVID-19' or 'Wuhan coronavirus' or 'novel coronavirus' or '2019-nCoV' or 'coronavirus disease' or 'SARS-CoV-2' or 'SARS 2' or 'severe acute respiratory syndrome coronavirus 2' or 'Wuhan virus' or 'Chinese virus' or '2019 Coronavirus'] and ['severity' or 'cause' or 'complications'] and ['interleukin' or 'cytokines' or 'markers']. No language restrictions were imposed. The detail of search strategy of PubMed is shown in online supplemental additional file 1.

ELIGIBILITY CRITERIA
The title and abstracts were initially checked by two reviewers against the below-mentioned inclusion and exclusion criteria.

Inclusion criteria
(1) The study uses IL-6 to predict severe disease (including severe or/and critical cases) and mortality in patients who have been diagnosed with COVID-19, (2) the study provides sufficient data to determine the relevant indicators of diagnostic research, including false positive (FP), true positive (TP), true negative (TN), false negative (FN).

Exclusion criteria
(1) Case report, (2) review, (3) comment, (4) animal study, (5) conference abstract, (6) letter, (7) editorial, (8) lack of effective data information.

DATA EXTRACTION AND QUALITY ASSESSMENT
The data were extracted by two researchers independently from each literature that met the inclusion criteria. Any differences if encountered were sorted out through discussion or with the assistance of a third researcher: (1) an overview of the situation of the literature and related clinical information: first author, publication year, publication language, country, age, count of patients, IL-6 detection technique and so on and (2) diagnostic parameters in the literature; the detection cut-off value of IL-6 and its extracted diagnostic four-grid table parameters, including TP, FP, FN and TN. The sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and the area under the curve (AUC) were estimated by diagnostic four-grid data.

Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used for assessing the quality of the literature included. The evaluation tool included four parts: patient selection, reference standard, index test and flow and test timing.

STATISTICAL ANALYSES
Spearman’s correlation coefficient of logarithm SEN and (1-SPE) was used to determine the threshold effects. The SPE, SEN, NLR, PLR, diagnostic OR (DOR) and the corresponding 95% CI were determined using a bivariate random effects regression model, and the working characteristic curves of merged subjects were drawn. Sensitivity analysis was employed to ensure that the results are not affected by any single study. Deek funnel plot was conducted to evaluate publication bias. Meta-regression analysis is to investigate potential sources of heterogeneity among included studies. Stata V.15.0 and Meta-disc V.1.4 software were used to perform the meta-analysis.

RESULTS
Search strategy and characteristics of included studies
The process of including and excluding the research process is summarised in figure 1. A total of 35 clinical studies were singled out, through the initial literature search. Seventeen studies were excluded after a preliminary review, 3 studies did not report the predictive value of IL-6 on severe disease or mortality, whereas, in 13 studies, the researchers were unable to extract a four-grid table of results.19–31 1 study cohort included healthy people, and one study came from low-quality Chinese literature. The predefined inclusion criterion was met by the remaining 17 studies which were subjected to further analysis. The methodological quality of the included studies is presented in online supplemental additional file 2.

Two laboratory techniques were majorly used to determine the level of IL-6, namely, chemiluminescence immunoassay (29%) and ELISA (29%). Detection technology was not mentioned in seven of the studies (41%). Most of the samples were collected within the first day of admission, followed by within a week of admission. Nearly 80% of studies had been carried out in China. The patient sample size ranged from 41 to 901. All the included studies were cohort studies, 5 of them being prospective studies, whereas 11 were retrospective studies. Table 1 depicts the basic characteristics of each included study.

Quality assessment, sensitivity analyses and publication bias
The quality of the studies included in this work was not high and none of them met all the items in the QUADAS-2 checklist. Only three studies were made a part of the study, and the blind method was not mentioned. We only included the studies published in English in the sensitivity analysis. For predicting the severe disease and mortality, the combined AUC was 0.878 (95%
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<th>Language</th>
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<th>Male (%)</th>
<th>Age (mean±SD or range)</th>
<th>Technique used</th>
<th>Detection time</th>
<th>Cut-off</th>
<th>Study design</th>
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</table>

AUC, area under curve; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; FN, false negative; FP, false positive; NR, not reported; SEN, sensitivity; SPE, specificity; TN, true negative; TP, true positive.
CI 0.803 to 0.953) and 0.531 (95% CI 0.451 to 0.612), respectively. Deeks test was not statistically significant (p>0.05), thus, suggesting no direct evidence of publication bias. Deek funnel plot is shown in online supplemental additional file 3.

Predictive value of IL-6 on severe disease
For predicting the severe disease, a total of 12 studies proceeded to report the values of IL-6 levels.\textsuperscript{33–44} Spearman’s correlation coefficient of logarithm SEN and (1-SPE) is 0.790 (p=0.002), which suggested the existence of a threshold effect. The forest plot of the DOR of IL-6 for predicting the severe disease in patients with COVID-19 is shown in \textbf{figure 2}. The pooled DOR was 13.05 (95% CI 8.25 to 20.64, I^2=28.0%), and there is no obvious heterogeneity among the studies. The summary receiver operating characteristic (SROC) curve is shown in \textbf{figure 3}. After eliminating the studies that may lead to heterogeneity one by one, the sensitivity analysis was carried out and the results depicted that the combined SEN, SPE and DOR had no significant change, suggesting that the stability of the results of this study was good. For predicting the severe disease, the AUC of IL-6 was 0.875 (95% CI 0.821 to 0.931), indicating a good diagnostic value.

Predictive value of IL-6 on mortality
The predictive value of IL-6 on mortality was reported by five studies involving 1387 patients.\textsuperscript{45–49} The results showed that the correlation coefficient of Spearman was 0.700 (p=0.118), which indicated that there was no diagnostic threshold effect. The forest plots of SEN, SPE, NLR, PLR, DOR, of IL-6 for predicting mortality in patients with COVID-19 are shown in \textbf{figure 4}. The respective values of pooled SEN and SPE were 0.15 (95% CI 0.13 to 0.17, I^2=98.9%) and 0.73 (95% CI 0.65 to 0.79, I^2=91.8%). The PLR was 1.16 (95% CI 0.72 to 1.88, I^2=19.5%) and the NLR was 0.93 (95% CI 0.82 to 1.05, I^2=56.9%). The DOR was 1.28 (95% CI 0.68 to 2.42, I^2=20.2%). As presented in \textbf{figure 5}, the SROC with pooled diagnostic accuracy was 0.531 (95% CI 0.451 to 0.612). Meta-regression analysis showed that country, technique used, cut-off, sample, study design and detection time did not contribute to the heterogeneity of mortality of the analyses.

\textbf{DISCUSSION}

Unlike any other pandemic in the past 50 years, COVID-19 has swept the world. Many reports have shown that patients with COVID-19 embrace death due to abnormal immune system response, that is to say, an abnormal release of circulating cytokines. The phenomenon of the release of many cytokines (including IL-6, TNF, etc) in patients infected with COVID-19 is known as ‘cytokine storm syndrome’.\textsuperscript{50–52} The advancement of COVID-19 disease from severe to critical is thought to be strongly associated with this cytokine storm. Cytokine storms cannot only lead to apoptosis of epithelial and endothelial cells but also causes vascular leakage, eventually leading to ARDS and other severe syndromes and ultimately even death.\textsuperscript{53} In critically ill COVID-19 patients, abnormal cytokine production and uncontrolled regulation were observed.\textsuperscript{34} This out-of-control cytokine storm is not only the core factor responsible for disease progression and symptom deterioration in patients with COVID-19 but also the main factor leading to COVID-19 death. In this sense, COVID-19 is a disease similar to other viral ailments, of the likes of; Middle East respiratory syndrome, 2020 SARS and avian influenza, all of which are characterised by...
the development of cytokine storms as a warning sign of disease escalation.

The excessive secretion of proinflammatory cytokines (TNF, IL-6 and IL-1β) in the early stage of the disease leads to an increased risk of high vascular permeability and multiple organ failure caused by CRS. When the high concentration of cytokines persists over time, it eventually leads to death. In patients with COVID-19, excessive production of cytokines may activate the coagulation pathway, induced disseminated intravascular coagulation and MODS or failure. IL-6 and TNF-α are the key mediators of CRS in COVID-19. IL-6 is the centre point of the current COVID-19 pandemic.

As early as the initial period of the upsurge of the COVID-19 epidemic, the levels of IL-6 are considered to be a reliable indicator of disease severity and prediction of ventilatory support. Pedersen’s study suggests that increased levels of IL-6 have a significant association with ICU admission and disease recovery. Prompetchara found that in comparison to the non-ICU patients, IL-6 levels in ICU patients were 52% higher. Another study of patients with severe symptoms described elevated serum IL-6 and C reactive protein (CRP) levels. Similar study of patients with severe symptoms described elevated serum IL-6 and CRP levels. Other studies have also shown that the high expression of IL-6 in patients with COVID-19 can accelerate the inflammatory process, lead to CRS, and worsen the prognosis. Several studies have shown that the serum IL-6 level in patients with COVID-19 increases, and its circulating level is significantly related to the severity of the disease as well as to the poor prognosis. In the animal model of SARS coronavirus infection, inhibition of IL-6 transcription factors and its production can reduced mortality. Previous studies have shown that a high mortality rate of COVID-19 infection has an association with raised IL-6 levels and IL-6 levels in patients who died of COVID-19 were notably high in comparison to those in recovered patients. However, there was no difference in plasma IL-6 levels between mild and severe or critical patients, or only slightly different in the early stages of disease progression. Similarly, there are also clinical data showing that plasma interferon-gamma-induced protein 10 (IP-10) and monocyte chemoattractant protein-3 (MCP-3) are closely related to the severity of the disease and fatal outcomes, rather than plasma IL-6. More interestingly, there was no significant difference in serum IL-6 levels between early nonsurvivors and survivors.

IL-6, a chemokine that is released by macrophages and T-cells for stimulating an immune response, is a key biomarker of inflammation. It is also made up of multiple cell types that respond to a multitude of pathological conditions, which include inflammation, infection and cancer. IL-6 may promote CRS by inducing cytolytic dysfunction. It has been observed that high levels of IL-6 exposure inhibit the cytotoxicity of natural killer (NK) cells while downregulating the expression of granulocyte B and perforin in severe COVID-19. These events result in the development of cytokine storms as a warning sign of disease escalation.
in the inability of cytotoxic NK cells or T lymphocytes to kill target cells through perforin or granulase-induced apoptosis, thereby causing an increase in the survival time of target cells and enhancement of antigen stimulation. Overall, it results in an excessive generation of proinflammatory cytokines, leading to ARDS and MODS eventually taking place.81–85

This is the first assessment-based study to the best of our knowledge that focused on evaluating the association between IL-6 and severe disease and mortality in COVID-19 affected individuals. In predicting the severe disease, because of the existence of the threshold effect, we only combined DOR and evaluated its diagnostic value by drawing the SROC curve and calculating AUC. The results demonstrated that the pooled DOR of IL-6 was 13.05 (95% CI 8.25 to 20.64, I²=28%), and AUC was 0.875 (95% CI 0.821 to 0.931), thereby indicating that IL-6 has a good diagnostic value in predicting the severe disease. At present, the criteria for the classification of mild and severe cases are based primarily based on respiration, PaO2/FiO2, and blood oxygen saturation. While these indicators are very important in COVID-19, there is a definite lack of specificity. Currently, the clinical measurement of IL-6 is not extensive, but for many clinical laboratories, it is a relatively simple and inexpensive method to detect potentially severe or critically ill subjects.

Although the pathological and clinical findings of deceased patients with COVID-19 suggest that CRS play a key role in their mortality, the critical stroma that leads to death remains uncertain. The results of this work showed that the AUC of IL-6 for predicting mortality was 0.531 (95% CI 0.451 to 0.612). The mortality prediction is not supported by the statistics, and IL-6 levels do not seem to correlate with the COVID-19 mortality. In addition, a number of studies have shown that the clinical effect of using the anti-IL-6R monoclonal antibodies tocilizumab to prevent the death of COVID-19 patients is not good.86–88 And in these studies, almost all patients were treated with antiviral, antibacterial or fungal drugs at the same time, and some patients were treated with glucocorticoids. Therefore, the clinical efficacy of patients with improved prognosis may come from a combination of these treatments. In two of the large-scale studies, most critically ill patients (82% and 57%)89 90 died after being treated with tocilizumab.

However, given the limitations of meta-analysis, the results should be interpreted rather carefully. IL-6 has been observed to be a key driver of inflammation associated with COVID-19 infection.3 Despite the high concentrations of IL-6 in the blood, isolated IL-6 measurements may not be sufficient to be used as a tool for predicting mortality in COVID-19 due to a variety of elements. First, on any given day, IL-6 levels in the same individual vary greatly, with the morning trough being the most obvious effect.91 Second, in an absolute sense, there are differences among different patients with respect to the intensity of IL-6 response to infection.92 In addition, the existence of immune metabolic complications such as obesity can also affect the concentration of circulating IL-6.93–95 The body’s response to IL-6 is not reflected by the absolute level of IL-6, which majorly relies on several other elements. For example, blood buffers formed by the level of A Disintegrin and Metalloproteinase 17 activity and the circulating levels of aforementioned soluble IL-6 receptor and soluble gp130, which function against the proinflammatory effects of IL-6.91,96

To sum up this study, it was found out that IL-6 is an adequate predictor of severe disease in patients infected with the COVID-19 virus. It is a multifunctional cytokine that regulates metabolism to inflammation, autoimmunity and acute-phase reaction. The cytokine storm, which is caused by COVID-19 infection, is characterised by an active inflammatory reaction involving a large number of proinflammatory cytokines. The cytokine storm is caused by an abrupt rise in circulating levels of proinflammatory cytokines such as IL-6, IL-1, TNF and interferon. IL-6 is a key driver of inflammation associated with COVID-19 infection. High levels of IL-6 were observed in patients with COVID-19, which were related to pulmonary inflammation and severe lung injury. However, isolated IL-6 measurements may not be sufficient to be used as a tool for predicting mortality in COVID-19 due to a variety of elements.

Only five studies included in our study used IL-6’s level for the prediction of mortality. In our final analysis, 4 studies were published in Chinese, whereas 13 studies were in English. Since researches published in English potentially have an extensive readership and are presumably peer-reviewed from various countries, we only conducted a sensitivity analysis of the 13 articles published in English, meanwhile omitting the works that were not published in English. The sensitivity analysis results were found to be consistent with the primary analysis results, indicating that the language of publication is not a confounding factor.

Our meta-analysis, however, suffers from some definite limitations. (1) The most important element is the significant heterogeneity of the results, (2) the degree of variability of laboratory tests in evaluating serum IL-6 is another important limitation, as local laboratories have varying values for normal ranges in the light of locally generated/available data, (3) the number of publications that we included in the meta-analysis is limited, and there are some defects in robustness, (4) of the 17 studies, 2 were from Belgium, 1 from Turkey, 1 from Israel and 13 from China. The languages involved, that is, English and Chinese may be selectively biased towards specific populations or languages, (5) the sample size of the study additionally affects the overall outcomes of this study to a certain extent.

CONCLUSIONS

IL-6 is an adequate predictor of severe disease in patients infected with the COVID-19 virus. The finding of current study mtry guide clinicians and healthcare providers in identifying potentially severe or critical patients with COVID-19.
at the initial stage of the disease. Moreover, we found that only monitoring IL-6 levels do not seem to predict mortality and was not associated with COVID-19’s mortality. This may indicate the need for combination therapy to reduce COVID-19’s mortality.

References


Self assessment questions

1. The progressive increase in peripheral blood lymphocyte count is a clinical early warning index of severe and critical COVID-19 in adults
   a. True
   b. False

2. COVID-19’s clinical types are mild, moderate, severe and critical type
   a. True
   b. False

3. At present, the main clinical manifestations of COVID-19 are fever, fatigue and dry cough. Some patients gradually develop dyspnea. Severe cases are acute respiratory distress syndrome, septic shock, metabolic acidosis that is difficult to correct and coagulation dysfunction
   a. True
   b. False

4. SARS-CoV-2 transmission routes include droplet transmission and contact transmission
   a. True
   b. False

5. About half of the patients with COVID-19 will have dyspnea after 1 week, and severe ones may have symptoms such as acute respiratory distress syndrome, septic shock, metabolic acidosis that is difficult to correct and coagulation dysfunction
   a. True
   b. False

Acknowledgements

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Contributors

XL and HW contributed equally. XL and HW completed the conception and design of the manuscript. XL acquired data, extracted data and interpreted the data. HW examined the data critically. XL and HW drafted the manuscript. SS and JX reviewed and revised the manuscript. All the authors approved the final version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Provenance and peer review

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REFERENCES


The review focuses on the role of cytokines in COVID-19 disease. The study assesses the severity and prognosis of coronavirus disease 2019 (COVID-19) and the involvement of the chemokine/chemokine-receptor system in the disease. The review highlights the importance of cytokines in understanding the pathogenesis and clinical implications of COVID-19. It emphasizes the role of cytokine storm syndromes and the complex cytokine network in disease severity and predicts the progression of COVID-19.

Key findings include:

- Increased levels of inflammatory cytokines (e.g., interleukin-6, interferon-γ) are associated with disease severity and predict the progression of COVID-19.
- Dysregulation of immune response in patients with COVID-19 is linked to hypercytokinemia.
- Cytokine release syndrome in severe COVID-19 may be the key to reduce mortality.

The review underscores the importance of cytokine analysis in the diagnosis and management of COVID-19 patients, highlighting the need for further research to develop targeted therapies for cytokine-driven inflammation.

Answers
1. True
2. True
3. True
4. True
5. True
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Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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- **Unclear**
- **Low**
Deek funnel plot of Predictive value of IL-6 on disease severity

Deeks’ Funnel Plot Asymmetry Test
pvalue = 0.24

1/root(ESS)

Diagnostic Odds Ratio

Study
Regression Line
Deek funnel plot of Predictive value of IL-6 on mortality