A Literature Review: Relationship between Interleukin-1 Beta and the Severity of COVID-19

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ABSTRACT

COVID-19 disease can cause dysregulation of the immune system, resulting in a cytokine storm. One of the cytokines released is IL-1β, a proinflammatory cytokine due to macrophage stimulation. This study aimed to provide a literature review of the value of Interleukin-1 beta (IL-1β) in patients with severity of COVID-19. This literature review was carried out using the search engines PubMed, Open Accessed Journal, Science Direct, and Google Scholar from December 2019 to December 2022. No studies suggested that IL-1β was associated with the severity of COVID-19. IL-1β is vital during the acute inflammatory response and helps T cells by linking innate and adaptive immunity as a lymphocyte activation factor. A gradual decrease in lymphocyte count was reported in severe COVID-19 diseases. The substantial reduction in lymphocyte count indicates that the SARS-CoV-2 virus increases immune cells and inhibits cellular immunity. This result might explain why IL-1β levels in mild COVID-19 were not significantly different from IL-1β levels in severe COVID-19. There was an increase in IL-1β levels in COVID-19 patients, but there was no relationship between IL-1β and the severity of COVID-19.

Keywords: COVID-19, interleukin-1β, severity

INTRODUCTION

Coronavirus Disease-19 (COVID-19) was first reported in Wuhan, China, in December 2019. This disease spreads very quickly in all countries, including Indonesia, and remains a world health problem, with the number of confirmed cases reaching 237,908,327 worldwide. The data from the World Health Organization (WHO) in October 2021 showed that the death toll from COVID-19 has reached 3,346,003 (1.4%). There are 4,228,552 confirmed cases of COVID-19 in Indonesia, and the death rate has reached 142,716 (3.4%).

COVID-19 is caused by a non-segmented single-stranded positive-sense RNA (ssRNA) virus, which has a capsule, round or elliptical particles, some pleomorphism, and a 60-140 nm diameter. This Coronavirus encodes five structural proteins in its genome, consisting of the spike (S), membrane (M), envelope (E), nucleocapsid (N), and helicase (HEX) glycoproteins. COVID-19 disease generally targets the respiratory tract and causes various clinical symptoms from mild to severe. Various immunological tests and inflammatory parameters have been carried out to detect the severity of COVID-19 disease, including Interleukin-1 beta (IL-1β).

IL-1β belongs to the subfamily of IL-1 located on chromosome 2. IL-1β is synthesized as a 31 kDa precursor peptide and cleaved to activate the mature form (mIL-1β) weighing 17 kDa. IL-1β is transcribed by monocytes, macrophages, and dendritic cells following Toll-Like Receptor (TLR) activation by Pathogen-Associated Molecular Patterns (PAMPs) or cytokine signaling. IL-1β is also transcribed by itself in an auto-inflammatory-induced manner. Inactive IL-1β precursors must be processed by caspase-1 cleavage, which requires activation of Damage Associated Molecular Patterns (DAMPs). Because of this, IL-1β is called a proinflammatory cytokine.

COVID-19 disease can cause dysregulation of the immune system, resulting in a cytokine storm. IL-1β is one of the proinflammatory cytokines released due to macrophage stimulation. On this basis, it is suspected that an increase in the IL-1β cytokine is related to the severity of COVID-19.

This literature review was carried out using the search engines PubMed, Open Accessed Journal, Science Direct, and Google Scholar from December 2019 to December 2022. The search was carried out in August 2022 with the keywords 'Interleukin-1 beta' and 'COVID-19' OR 'SARS-CoV-2', "Interleukin-1 beta and COVID-19". The titles, abstracts, and full texts of potential studies were then reviewed. Inclusion criteria were retrospective or prospective studies, case-control, and cohort studies involving patients confirmed with COVID-19 based on the IL-1β levels (with or without severity, mortality, and ICU) as the...
research subjects. Exclusion criteria were studies written in non-English language, comments, letters to the editor, or insufficient data. Pre-print studies that have not been peer-reviewed due to the emerging pandemic situation of COVID-19 were also included.

**RELATIONSHIP IL-1β WITH SEVERITY COVID-19**

A total of 5 studies that discussed the relationship between IL-1β and the severity of COVID-19 were found. From the results of this study, there was no

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<th>Authors</th>
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<tr>
<td>Xu Bo et al.</td>
<td>Retrospective, single centre observational study</td>
<td>187 adult patients in Hubei Provincial Hospital, Wuhan, China: mild 80, severe 45, critically 62</td>
<td>IL-1β (pg/mL) &lt;br&gt; Mild, median (IQR) 4.9 &lt;br&gt; Severe, median (IQR) 4.9 &lt;br&gt; Critically ill, median (IQR), 4.9 &lt;br&gt; p = 0.97</td>
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<td>Xu Xia et al.</td>
<td>Retrospective, single centre observational study</td>
<td>88 adult patients, in Tongji Hospital, Huazhong, China: moderate 47, severe 32, critically 9</td>
<td>IL-1β (pg/mL) = 5.0 n=52 &lt;br&gt; Moderate 3 &lt;br&gt; Severe 1 &lt;br&gt; Critically ill 1 &lt;br&gt; p &gt; 0.5</td>
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<td>Li Shaohua et al.</td>
<td>Retrospective cohort study</td>
<td>69, adult patients, Hubei: severe 26, non-severe 43</td>
<td>IL-1β (pg/mL) &lt;br&gt; Severe, median 5.0 &lt;br&gt; Non-severe, median 5.0 &lt;br&gt; p = 0.952</td>
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<td>Qin Chuan et al.</td>
<td>Retrospective study</td>
<td>452, adult patient, in Tongji Hospital, China: severe 286, non-severe 166</td>
<td>IL-1β (pg/mL) &lt;br&gt; Severe, median 5.0 &lt;br&gt; Non-severe, median 5.0 &lt;br&gt; p = 0.952</td>
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<td>Resti Y et al.</td>
<td>Cohort study</td>
<td>50, adult patient, in Dr. Soetomo Hospital Surabaya, Indonesia non-severe 20, severe 30</td>
<td>IL-1β (pg/mL) &lt;br&gt; Severe, 0 days, median 2.92 &lt;br&gt; Severe, 3 days, median 1.72 &lt;br&gt; Severe, 6 days, median 2.05 &lt;br&gt; Non-Severe &lt;br&gt; Non-severe, 0 days, median 2.94 &lt;br&gt; Non-severe, 3 days, median 2.10 &lt;br&gt; Non-severe, 6 days, median 3.31 &lt;br&gt; p IL-1β severe non-severe: 0 days, p 0.513 (p &gt; 0.05) &lt;br&gt; 3 days, p 0.646 (p &gt; 0.05) &lt;br&gt; 6 days, p 0.112 (p &gt; 0.05)</td>
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<td>Ke Chunjin et al.</td>
<td>Retrospective study</td>
<td>194, adult patients, in Institutional Ethics Board of Tongji Hospital, China (positive COVID-19 173, suspected COVID-19 21), (survivor 148, non-survivor 46)</td>
<td>IL-1β (pg/mL) &lt;br&gt; COVID-19, median (IQR) 2.20 &lt;br&gt; Non-COVID-19, median (IQR) 60.39 &lt;br&gt; p &gt; 0.1 &lt;br&gt; And &lt;br&gt; Survivor, median (IQR) 10.59 &lt;br&gt; Non-survivor, median (IQR) 2.89 &lt;br&gt; p &gt; 0.5</td>
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<td>Mikami Takahisa et al.</td>
<td>A multicenter retrospective cohort study</td>
<td>3708, adult patients, in New York City: survivor 2902, non-survivor 806</td>
<td>IL-1β (pg/mL) &lt;br&gt; Non-survivor, median 0.6 &lt;br&gt; Survivors, median 0.5 &lt;br&gt; p &gt; 0.5</td>
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<td>Mathilda Mandel et al.</td>
<td>Retrospective cohort study</td>
<td>71, adult patients, University of Israel alive 59, dead 12</td>
<td>IL-1β (pg/mL) &lt;br&gt; Recovered, median 0.31 &lt;br&gt; Death, median 0.41 &lt;br&gt; p 0.949</td>
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<td>Kaiyan Li et al.</td>
<td>Retrospective study</td>
<td>128, adult patients; 102 confirmed COVID-19, 26 non-COVID-19. In Tongji Hospital, Chinain 102 patients: non-survivor 15, survivor 87</td>
<td>IL-1β (pg/mL) &lt;br&gt; Non-survivor, median 4.9 &lt;br&gt; Survivor, median 4.9 &lt;br&gt; p = 0.388</td>
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relationship between increased IL-1β and the severity of COVID-19, with a p-value of >0.1. Another study also found no significant relationship between IL-1β levels and the severity of COVID-19.8-11

Another study that discussed IL-1β parameters with the severity of COVID-19 was conducted by Xu et al. They also divided the severity of COVID-19 into three categories: moderate (47 patients), severe (32 patients), and critically ill (9 patients). However, out of a total of 88 patients, only 52 patients were tested for IL-1β. Of the 52 patients, the relationship with the degree of severity was analyzed. The results showed no significant relationship between IL-1β levels and the severity of COVID-19.10

Research conducted by Li et al. only divided the severity of disease into two categories, namely severe with 26 patients and non-severe with 43 patients. This research also tried to analyze the relationship between IL-1β and the severity of COVID-19, but no significant relationship was found between IL-1β and the severity of COVID-19.11

A study by Resti et al. carried out time-series examinations on days 0, 3, and 6 for IL-1β and IL-10 parameters in 50 COVID-19 patients from May to October 2020 in Indonesia. The subjects were divided into two groups, namely, 20 non-severe and 30 severe groups. The results found no significant differences on days 0, 3, and 6 in both groups (p>0.05). The median values of the IL-1β/IL-10 ratio on days 3 and 6 decreased in the severe and non-severe groups. The minimum and maximum values range became tighter on day 6. The median of the non-severe group was higher than the severe group on days 0 and 3 but lower on days 6. Statistical analysis showed no significant difference in the IL-1β/IL-10 ratio between the non-severe and non-severe groups on days 0, 3, and 6 (p>0.05). This finding also suggested no correlation between the IL-1β/IL-10 ratio and the severity of COVID-19 in patients on days 0, 3, and 6. However, the ratio of serum IL-1β and IL-10 levels in the non-severe group was lower compared to the severe group on day 6 (p>0.05).12

**RELATIONSHIP IL-1β WITH MORTALITY COVID-19**

In addition to the relationship between IL-1β and mortality in COVID-19, four studies discussed the relationship between IL-1β and mortality in COVID-19 patients by dividing COVID-19 patients into two categories, survivor and non-survivor subjects. These three studies also found no significant relationship between IL-1β and mortality in COVID-19 patients.13-16

In a retrospective cohort study by Mikami et al., there was a subject of 3708 adult patients hospitalized in New York City; 2902 patients were in the survivor category, and 806 were in the non-survivor category. Statistical analysis showed no significant difference in the IL-1β between survivors and non-survivors of COVID-19 (p>0.5).12

The increase in the proinflammatory cytokine IL-1β serum levels was found in mild degrees; however, there was no significant difference in moderate and severe degrees. The four studies also found that IL-1β levels increased in mild, moderate, and severe degrees. However, the differences in levels of the proinflammatory cytokine IL-1β based on the severity of COVID-19 were not significant.8-11

The cytokine IL-1β is generally the primary regulator of inflammation by controlling various processes of innate immunity. Monocytes, macrophages, Dendritic Cells (Dcs), and neutrophils are immune cells capable of producing large amounts of IL-1β. IL-1β is vital during acute inflammatory responses and helps T cells by linking innate and adaptive immunity as a lymphocyte activation factor. A gradual decrease in the lymphocyte count was reported in severe COVID-19 diseases. A substantial reduction in the lymphocyte count indicates that the SARS-CoV-2 virus produces immune cells and inhibits cellular immunity. This finding might explain why IL-1β levels in mild COVID-19 were not significantly different from IL-1β levels in severe cases.17-19

**CONCLUSION**

There was an increase in IL-1β levels in COVID-19 patients, but there was no relationship between IL-1β and the severity of COVID-19 or between IL-1β and mortality.

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