COMPARISON IN LEVELS OF INTERLEUKIN 6, FERRITINE, AND NEUTROPHIL-LYMPHOCYTE RATIO IN COVID-19 PATIENTS TREATED IN ICU AND NON-ICU

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ABSTRACT

Inflammation can occur due to infectious diseases, including COVID-19. A severe inflammatory response contributes to a weak adaptive immune response, resulting in an imbalanced immune response. Circulating biomarkers that can predict inflammation and immune status are potential predictors for the prognosis of COVID-19 patients. Ferritin and interleukin-6 can serve as significant biomarkers in the detection of cytokine storms, systemic inflammation, and the prognosis of COVID-19. The neutrophil-lymphocyte ratio is an independent prognostic biomarker for COVID-19 patients. The aim of this study is to determine different levels of IL-6, ferritin, and NLR in COVID-19 patients treated in ICU and non-ICU. This study was a comparative cross-sectional design of 62 COVID-19 patients. The research was conducted at the Laboratory and Medical Record of Dr. M. Djamil Padang hospital (May to September 2021). Interleukin-6 levels determined the ECLIA methods, ferritin with the ELFA methods, and NLR with calculation methods. Bivariate data were analyzed with the Mann-Whitney test. The characteristics of COVID-19 patients treated in ICU: 64.5% male, the average age was 53.52(10.71) years, 48.4% death, and non ICU: female 71.0%, average of 42.32 (12.22) years, and recovered 100%. The most common comorbid is hypertension. There were significant differences in IL-6, ferritin, and NLR levels in ICU and non-ICU patients with COVID-19 ($p<0.001$).

Keywords: Interleukin 6; Ferritin; Neutrophil-Lymphocyte Ratio; COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a progressive and potentially fatal infectious disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First discovered in China (Wuhan city, Hubei province) at the end of 2019, and was declared a pandemic by the World Health Organization in March 2020[1,2] Most patients with COVID-19 have mild symptoms and recover on their own; however, almost 10% develop life-threatening severe acute respiratory distress syndrome. It is necessary to identify patients at high risk of acute respiratory distress syndrome using systemic biomarkers.[3]

Patients infected with this disease have various clinical manifestations, ranging from mild symptoms without specific symptoms to severe pneumonia with impaired organ function.[2]

World Health Organization data for October 3, 2021, shows that the global number of confirmed cases of COVID-19 is 234,551,981 cases with a death rate of 4,796,171 (case fatality rate/CFR 2.0%). At the same time, in Indonesia, the number of confirmed cases of COVID-19 was 4,219,284, with a total of 142,173 deaths (CFR 3.4%). Data for West Sumatra as of October 3, 2021, there were 89,392 confirmed cases of COVID-19 with a death rate of 2128 cases.[4]

Coronavirus is a ribonucleic acid (RNA) virus, single strain positive, encapsulated, and not segmented.[5] The coronavirus genome consists of 30,000 nucleotides which encode four structural proteins, namely: N protein (nucleocapsid), M glycoprotein (membrane), S glycoprotein spike (spike), and E protein (envelope), and some non-structural.[6]

The main mechanism of SARS-CoV-2 infection is binding protein S on the viral envelope to a cell receptor, namely angiotensin-converting enzyme2 (ACE2), on SARS-CoV-2 target cells. Type 2 transmembrane serineprotease (TMPRSS2) in host cells will increase viral uptake by cleaving ACE2 and activating the SARS-CoV-2 protein. thereby facilitating the entry of the virus into the host cell. Angiotensin-converting enzymes two and TMPRSS2 are mainly expressed in the lung (pneumocyte type 2), small intestinal epithelium, esophagus, liver, large intestine, blood vessels, heart, and kidney.[7,8]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells expressing the surface receptors angiotensin-converting enzyme 2 (ACE2) and TMPRSS2. The active replication and release of the virus cause the host cell to undergo pyroptosis and release damage-associated molecular patterns, including ATP, nucleic acids, and ASC oligomers. These are recognized by neighboring epithelial cells, endothelial cells, and alveolar macrophages, triggering the generation of pro-inflammatory cytokines and chemokines (including IL-6, IP-10, macrophage inflammatory protein 1α (MIP1α), MIP1β and MCP1). These proteins attract monocytes, macrophages, and T cells to the site of infection, promoting further inflammation (with the addition of IFNγ produced by T cells) and establishing a pro-inflammatory feedback loop.[9]

Infectious diseases cause inflammation, and growing evidence supports its significant role in the progression of various viral pneumonia, including COVID-19. Severe inflammatory responses contribute to weak adaptive immune responses, resulting in an imbalanced immune response. Therefore, circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients.[10]

Viral and host factors play a role in SARS-CoV infection. The cytopathic effect of the virus and its ability to counteract the immune response determines the infection's severity. Dysregulation immune system then plays a role in tissue damage in SARS-CoV-2 infection. A weak immune response causes viral replication and tissue damage.[11]

Severe SARS-CoV-2 infection results from a cytokine storm caused by the activation of Th1 cells by CD^4 T cells, which will secrete Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) and stimulate monocyte production CD^{14+} and CD^{16+}. This will cause an increase in the pro-inflammatory cytokines IL-6 and IL-1β which accelerates the occurrence of inflammation. T cell activation CD^4 will also cause polarization Th to Th17, which will secrete the pro-inflammatory cytokine IL-17, attract immune cells such as monocytes/macrophages and neutrophils to the site of inflammation, and stimulate another inflammatory response cascade.[12] The classification of COVID-19 criteria must be carried out properly so that patients receive appropriate treatment, including intensive care for severe cases of COVID-19. Identification of laboratory markers is very important that plays a role in screening, clinical management, and prevention of disease complications. [8, 13] Inflammation plays an important role in the development of various pneumonia viruses, including COVID-19. Circulating biomarkers that can evaluate inflammation and immune status are potentially useful in the diagnosis and prognostic COVID-19 patients.[1] Interleukin-6 and ferritin are commonly examined inflammatory markers. Interleukin-6 is a pleiotropic cytokine that is produced in response to tissue damage and infection.[14] Several studies have found increased levels of IL-6 and ferritin in COVID-19 patients. This is based on the activation of macrophages due to infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). [15,16] Ferritin and IL-6 can be significant biomarkers to detect cytokine storms. Elevated levels of both can be considered a dangerous sign of systemic inflammation and a poor prognosis of COVID-19.[17] Ponti et al. concluded that IL-6 and ferritin could assess the severity and predict COVID-19 mortality.[8]

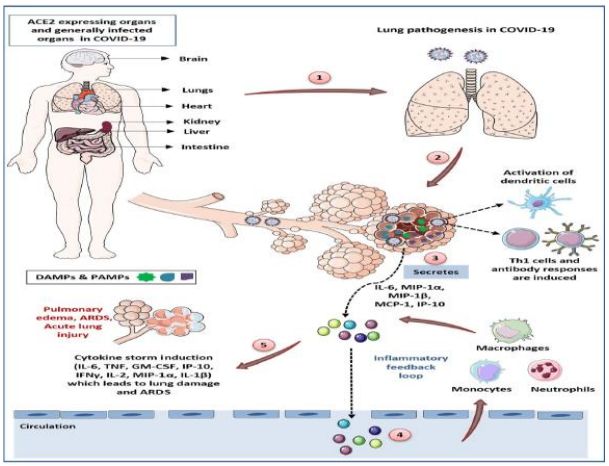

Figure 1. Immunopathogenesis COVID-19.[6]

Elevated NLR was an independent prognostic biomarker that affected pneumonia progression in COVID-19 patients.[10]

Infectious diseases are associated with inflammation, and existing data supports its significant role in the progression of various viral pneumonia, including COVID-19. Because of SARS-CoV-2 viral replication, cellular destruction leads to cytokines and chemokines from the activated macrophages. Therefore they activate immune responses, leading to cytokine storms and aggravations. The severity of the inflammatory response determines the adaptive immune response, resulting in an imbalance in the immune response. Serum ferritin and IL-6 have been associated with high risks for severe COVID-19 infection. The NLR is an indicator of the systematic inflammatory response.[1]

MATERIAL AND METHODS

This research is a cross-sectional comparative study. The research was conducted at the Laboratory Installation and Medical Record Installation at Dr. RSUP. M. Djamil Padang starting in May-November 2021. The population is all patients diagnosed with COVID-19 who are undergoing treatment in the ICU and non-ICU RSUP Dr. M. Djamil Padang. The research sample is part of the population that meets the inclusion and exclusion criteria, with a minimum sample of 26.

The research data were analyzed using a computer program. Univariate analysis of categorical variables is presented in the form of frequency and percentage tables, while numerical variables are presented in the form of central tendency (mean ± SD) or median (minimum-maximum). The bivariate analysis begins with the data normality test, carried out with the Shapiro-Wilk test (n<50). Interleukin 6, ferritin, and NLR were not normally distributed to determine the difference using the Mann-Whitney test. If p<0.05, it is stated that there is a significant relationship.

RESULT

Subjects Characteristics

Subject characteristics of this study are shown in table 1.

Table 1. Subject Characteristics

Variable	ICU	Non ICU	p-value
Gender, f (%)			0,011*[a]
Male	20 (64,5)	9 (29,0)	
Female	11 (35,5)	22 (71,0)	
Age (years), mean (SD)	53,52 (10,71)	42,32 (12,22)	<0,001*[b]
Comorbidities, (%)			n/a
Hypertension	12 (38,7)	9 (29,0)	
Diabetes mellitus	5 (16,1)	1 (3,2)	
Kidney disease	1 (3,2)	2 (6,5)	
Heart disease	2 (6,5)	0	
Stroke	1 (3,2)	0	
There is not any	10 (32,3)	19 (61,3)	
Number of comorbidities, mean (SD)	1,10 (1,01)	0,45 (0,62)	0,004*[b]
Outcome, f(%)			n/a
Die	15 (48,4)	0	
Life	16 (51,6)	31 (100,0)	

* p<0,05 signifikan
n/a, *not account*
a, *uji chi-square*

b, *independent sample T test*

Based on table 1, it is known that there are differences in gender, age, and a number of comorbidities in ICU and non-ICU COVID-19 patients (p<0.05).

Most of the study for COVID-19 patients admitted to the ICU were male (64.5%) differs from COVID-19 patients treated in non-ICU, with most subjects female (71%).

Differences In Interleukin 6 Levels

Differences in IL-6 levels between COVID-19 patients admitted to the ICU and non-ICU can be seen in table 2.

Table2. Differences in IL-6 Levels Between COVID-19 Patients Admitted to the ICU and Non-ICU

Variable	ICU Median (min-max)	Non ICU Median (min-max)	p-value
IL -6 (pg/mL)	43,90 (8,3-434,7)	8,30 (1,5-74,6)	<0,001* [c]

* p<0,05 significant
c, Mann-Whitney test

The median level of IL-6 in COVID-19 patients treated in the ICU was higher at 43.90pg/mL compared to non ICU which is 8.30 pg/mL. A statistically significant difference was found in IL-6 levels between COVID-19 patients admitted to the ICU and non-ICU (p<0.05)

Differences in Ferritin Levels

Differences in ferritin levels between ICU and non-ICU COVID-19 patients can be seen in table 3.

Table 3. Differences in Ferritin Levels Between COVID-19 Patients Admitted to the ICU and Non-ICU

Variable	ICU Median (min-max)	Non ICU Median (min-max)	p-value
Ferritin (ng/mL)	1.007,67 (151,87-6.526,28)	213,00 (14,55-1.133,00)	<0,001*[c]

* p<0,05 significant
[c] Mann-Whitney test

The median ferritin level in COVID-19 patients admitted to the ICU was higher at 1.007.67 ng/mL, compared to non ICU which is 213.00 ng/mL. A statistically significant difference was found in ferritin levels between COVID-19 patients admitted to the ICU and non-ICU (p<0.05).

Differences in NLR

Differences in NLR between ICU and non-ICU COVID-19 patients can be seen in table 4.

Table 4. Differences in NLR between COVID-19 Patients Treated in ICU and Non-ICU

Varia	ICU Median (min-max)	Non ICU Median (min-max)	p-value
Netrof Limfo Rasio	11,00 (2,17-47,42)	2,61 (0,71-12,85)	<0,001[c*]

* p<0,05 significant
c Mann-Whitney test

The median NLR in COVID-19 patients treated in the ICU was higher at 11.00 (2.17-47.42), while the non-ICU was 2.61 (0.71-12.85) with a p-value < 0.001. A statistically significant difference was found in NLR between COVID-19 patients treated in ICU and non-ICU (p<0.05).

DISCUSSION

We assessed differences in IL-6, ferritin, and NLR levels in 62 confirmed COVID-19 patients in the ICU (31 people) and non-ICU (31 people). In this study, the most subjects

for COVID-19 patients treated in the ICU were men (64.5%) in contrast to COVID-19 patients treated in non-ICU, with the most subjects being women (71%).

Mohammedsaeed et al. reported 57.8% of male patients with severe COVID-19. [18] Metaanalysis study by Ortolan et al. was performed on cases of COVID-19 between Male to female, and the ratio was 1:0.9. Male is more susceptible to infection SARS-CoV2, present with a more severe disease condition and has a better prognosis worse. This study found a significant relationship between the male sex and mortality.[19]

This might be because behavioral factors and roles which increase the risk of acquiring COVID-19 tend to be more common among men. Men are more involved in various risky behaviors, such as alcohol consumption, being involved in key activities during burial rites, and working in basic sectors and occupations that require them to continue being active, to work outside their homes, and to interact with other people even during the containment phase. Therefore, more men are outside the house, sitting with other people and taking off their masks to drink and smoke. This increased exposure rate puts men at high risk of contracting COVID-19. [20]

From this study, the mean age of patients admitted to the ICU was 53.52 (10.71) years, while the mean of non-ICU care patients was 42.32 (12.22) years. This study is similar to a study by Fan et al., where the average age of ICU patients was 54 years, while the mean age of non-ICU patients was 42 years ($p = 0.02$).[21]

The study by Mohammedsaeed et al. indicated that 57.2% of COVID-19 patients are severe cases have high mean age (78±13.8), whereas 42.8% are non-severe patients with low mean age (54±12.01, $P<0.05$).[18] Susceptibility to COVID-19 is related to age, sex, and underlying disease. Most cases of COVID-19 have mild symptoms and get better on their own. Serious illness requires hospitalization because it has the potential to become a critical illness characterized by respiratory failure, shock, sepsis, and multi-organ failure, which ultimately requires intensive care.[20]

Older patients, especially those aged 65 and over with comorbidities and who are infected, have a higher chance of admission to the intensive care unit (ICU) and death from COVID-19. Patients with comorbidities should take all necessary precautions to avoid infection with SARS-CoV-2, as they usually have the worst prognosis. Age-related changes in the geriatric population may be due to changes in lung anatomy and muscle atrophy resulting in changes in physiological function, reduced lung reserve, reduced airway clearance, and reduced barrier function. [22]

Male patients with COVID-19 have a significant risk of death compared to women. Comorbidities are also associated with an increased risk of significant mortality. Significantly increased mortality in men is associated with higher expression of ACE-2, which can be regulated by male sex hormones, putting them at greater risk of SARS-CoV-2 infection and poor clinical outcome. [23]

A cross-sectional multicentric study on COVID-19 patients in Wuhan, China, demonstrated that premenopausal women had a milder severity and better outcome of COVID-19 in contrast to men of the same age. Estrogen has also been shown to dampen the production of pro-inflammatory cytokines IL-12 from activated macrophages

and IL-6 by directly altering CD16. This could indicate a possible role of estrogen in preventing COVID-19-associated cytokine storm syndrome.[24]

Testosterone has a general immunosuppressive role, which may explain males' greater susceptibility to the development of more severe SARS-CoV-2 infectious disease. Testosterone also plays a positive regulatory role in TMPRSS2 expression, which facilitates entry of the SARS-CoV-2 virus. [24,25]

The most comorbid disease in this study was hypertension, both in COVID-19 patients treated in the ICU and non-ICU. The study by Sanyaolu et al. found that the most common comorbidities found in COVID-19 patients were hypertension (15.8%), cardiovascular

and cerebrovascular disease (11.7%), and diabetes (9.4%). [22]

In this study, the average number of comorbidities of COVID-19 patients treated in ICU was 1.10 (1.01), while in non-ICU, 0.45 (0.62), there is a statistically significant difference ($p<0.05$). A metaanalysis study by Cheng et al. supports the finding that chronic comorbidities may contribute to severe outcomes in patients with COVID-19. According to the present study's findings, old age and two or more comorbidities significantly impact COVID-19 outcomes in hospitalized patients in China.[26]

Median IL-6 levels in this study showed COVID-19 patients admitted to the ICU higher than non-ICU, which is 43.90 pg/mL vs. 8.30 pg/mL. Kazancioglu et al. found the median level of IL-6 in severe COVID-19 patients was 28.6 (2.69-118) pg/mL and not severe 3 (2-19) pg/mL with $p = 0.001$.[27]

Many reports indicate that patients with COVID-19 die result of an abnormal immune system response characterized by the release of excess cytokines (cytokine storm). High levels of IL-6 were significantly associated with levels of COVID-19 severity and adverse clinical outcomes, which increased the risk of ICU admission, ARDS, and death. [28,29]

A study performed by Herold et al. showed IL-6 levels > 35 pg/mL and CRP levels greater than 32.5 mg/L at the start of treatment indicates a high sensitivity for detecting patients at risk of respiratory failure (84% and 95%) with specificity (63% for both parameters). This study concluded that IL-6 and CRP levels function as a predictor of patients requiring ventilatory support.[30]

Kazancioglu et al. study got median ferritin levels in severe COVID-19 patients 330 (30.8-1580) ng/mL and not severe 84.9 (5.2-823) ng/mL with $p < 0.001$.[27]

Deng et al., in their study, obtained ferritin level was significantly higher in a critical group compared with moderate and severe groups. The median ferritin concentration was about three times higher in the death group than in the survival group (1722.25 g/L vs. 501.90 g/L, $p < 0.01$). The ferritin measured at admission may serve as an independent factor for predicting in-hospital mortality in patients with COVID-19 in ICU.[31]

Ferritin is an iron storage protein widely measured as a status indicator of iron and inflammatory markers. Serum ferritin levels may increase significantly in response to inflammation and various diseases. Circulating ferritin levels increase during viral infection and can be a marker of viral replication [32,33]

Elevated ferritin levels due to cytokine storm have been reported in COVID-19 patients heavy one. The mechanism responsible for the relationship between hyperferritinemia and disease severity in patients with COVID-19 is unclear, but there are several possibilities for this phenomenon: 1) During the cytokine storm in COVID-19, pro-inflammatory cytokine production is very rapid, including IL-6, TNF -, IL-1, IL-12, and IFN, which stimulate hepatocytes, Kupffer cells, and macrophages to secrete ferritin. 2) Cell damage due to inflammation can increase intracellular leakage of ferritin, thereby increasing serum ferritin. 3) Acidotic conditions of the microvascular environment and increased ROS production can liberate iron from ferritin. This free iron can participate in the Haber-Weiss and Fenton reactions, creating hydroxy radicals which will cause further cell damage. [32,33]

A metaanalysis study conducted by Shang et al., 2020 showed that higher NLR values at admission are associated with a higher risk of severity and death in COVID-19 patients, so they can be used to predict the prognosis of COVID-19 patients. The neutrophil-lymphocyte ratio is an indicator of systemic inflammation that has been widely used for various conditions, such as predicting death in septic patients, cardiovascular disease outcomes, and poor prognosis in ICU inpatients. The biological mechanism underlying this association is that a high NLR indicates an imbalance in the inflammatory response due to an increase in neutrophils and a decrease in the number of lymphocytes. [34]

CONCLUSION

There are differences in IL-6 levels, ferritin levels, and NLR of COVID-19 patients treated in the ICU and non-ICU.

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