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Interleukin-6 and Ferritine Levels as Predictors of Severity of Covid-19 Patients Treated in Adam Malik General Hospital

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Abstract: ***Background: COVID-19 is a new type of disease that has never been previously identified in humans. The virus that causes COVID-19 is called Sars-CoV-2. Cytokine Release Syndrome or cytokine storm as the underlying pathological development of severe COVID-19 disease. Circulating levels of IL-6 are closely related to the severity of COVID-19 infection. Ferritin is a key mediator of immune dysregulation in COVID-19 patients through its immune-suppressing effects and production of pro-inflammatory cytokines that directly contribute to cytokine storm. Methods: This research is an observational study with cross sectional design. This study took blood samples from COVID-19 patients who were treated at RSUP.H. Adam Malik, Medan, research subjects there are 34 patients. Samples were checked for IL-6 and Ferritin. The research was conducted after obtaining ethical approval and informed consent. Result and Discussion: There were 22 male subjects (64.7%) with an average age of 55 years, with the youngest 31 years old and the oldest 73 years old. 23 patients (67.6%) were severe and 11 patients (32.4%) were moderate. Using a ventilator there were 19 patients (55.9%), 17 patients died (50%). Ferritin levels showed a median of 1245.65 ng/mL with the lowest value of 154.69 ng/mL and the highest level of 2000 ng/mL. The median level of IL-6 was 31.35 pg/mL with the lowest level of 1.5 pg/mL and the highest level of 614.20 pg/mL. The Mann Whitney test showed that there was no significant relationship between IL-6 and the severity of COVID-19 (p = 0.204). The Mann Whitney test showed that there was a significant relationship between ferritin and the severity of COVID-19 (p = 0.002). Conclusion: There is no significant relationship between IL-6 and the severity of COVID-19. There is a significant relationship between ferritin and the severity of COVID-19.***

Keywords: COVID-19, IL-6, Ferritin

1. Introduction

On December 31 2019, WHO China Country Office reported a case of pneumonia of unknown etiology in Wuhan City, Hubei Province, China. On January 7 2020, China identified the pneumonia of unknown etiology as coronavirus disease (COVID-19). After infection, patients with COVID-19 may experience simptoms mild, moderate, or severe symptoms. [1, 2, 3]

The immunological profile of critically ill patients with COVID-19 demonstrates hyperactivation of humoral immune pathways including interleukin (IL)-6 and ferritin as mediators for respiratory failure, shock, and multiorgan dysfunction. Thus serial measurements of IL-6 and ferritin may be important in identifying disease progression among patients infected with COVID-19. Elevated levels of IL-6 and ferritin have been shown to be good biological markers for the severity of the COVID-19 virus infection leading to respiratory failure or ARDS. [4, 5, 6.7]

2. Purpose

This study aims to determine the levels of IL-6 and ferritin as predictors of the severity of COVID-19 patients treated at the HAM Hospital, so that they can be considered in the management of COVID-19 patients.

3. Research Methods

This research is an observational study with *cross sectional* data collection method. The study was conducted at the Department of Clinical Pathology, USU Medical Faculty / H. Adam Malik Hospital, Medan in collaboration with the Pulmonology Department of USU Medical Faculty / H. Adam Malik Hospital, Medan, from February to Mei 2021. The research subjects were patients with COVID-19 who were treated at H. Adam Malik Hospital Medan, and has the inclusion criteria

The sample size in this study was determined as many as 34 research subjects. The inclusion criteria in this study were all COVID-19 patients with positive RT – PCR results who were hospitalized and willing to participate in the study. Exclusion criteria included patients taking IL-6 inhibitor drugs, liver cancer patients and patients with hematological malignancies

Examination of IL-6 and ferritin was carried out at the Department of Clinical Pathology, USU Medical Faculty / H. Adam Malik Hospital, Medan using the Cobas 401 automatic analyzer using the ECLIA method and using the Architect i 2000 tool with the Chemiluminescent Microparticle Immunoassay (CMIA) method.

4. Statistical Analysis

Data analysis was performed using SPSS software (*Statistical Package for Social Sciences*, Chicago, IL, USA) for Windows. The description of the characteristics of the research subjects is presented in tabulated form and described. The correlation between IL-6 levels in COVID-19 using the *Pearson* correlation *test* if the data is normally distributed. If the data is not normally distributed, *Spearman's* test is used. All statistical tests with p value < 0.05 were considered significant.

5. Results

Subjects with male sex were 22 people (64.7%) with an average age of 55 years, with the youngest age being 31 years old and the oldest being 73 years old. The subjects who showed comorbid diseases were 26 people (76.5%) with the most comorbidities being DM and hypertension as many as 8 people (23.5%).

Table 1: Characteristics of Research Subjects

Subject Characteristics	n = 34
Gender, n (%)	
Man	22 (64.7)
Woman	12 (35.3)
Age, years	
Average (SD)	55 (11.54)
Median (Min – Mak)	57 (31 – 73)
> 40 years	29 (85.3)
≤ 40 years	5 (14.7)
Comorbid	
DM	3 (8.8)
Hypertension	5 (14.6)
Hepatitis	1 (2.9)
DM and Hypertension	8 (23.5)
Hypertension and CHF	3 (8.8)
DM and PJK	1 (2.9)
Hypertension and CAD	1 (2.9)
DM, Hypertension and CAD	1 (2.9)
DM, Hypertension and CHF	1 (2.9)
DM, Hypertension and Asthma	1 (2.9)
Hypertension, AKI and HIV	1 (2.9)
There is not any	8 (23.5)
Breathing Device, n (%)	
Ventilator	19 (55.9)
Non-ventilator	15 (44.1)
Severity, n (%)	
Heavy	23 (67.6)
Currently	11 (32.4)
Mortality, n (%)	
Yes	17 (50)
Not	17 (50)
Ferritin, ng/mL	
Average (SD)	1222.63 (689.32)
Median (Min – Mak)	1245.65 (154.69-2000)
Interleukin 6, pg/mL	
Average (SD)	129.90 (199.94)
Median (Min – Mak)	31.35 (1.5-614.20)

Table 2: Relationship between Research Subject Characteristics and COVID-19 Severity

Characteristics Subject	Severity		p	RP (95%IK)
	Heavy	Currently		
Gender, n (%)				
Man	18 (81.8)	4 (18.2)	0.026 [a]	1, 964
Woman	5 (41.7)	7 (58.3)		0.977-3.946
Age, years				
> 40 years	21 (72.4)	8 (27.6)	0.300 [a]	1, 810
≤ 40 years	2 (40)	3 (60)		0.605-5.421
Comorbid				
There is	19 (73.1)	7 (26.9)	0.388 [a]	1, 462
There is not any	4 (50)	4 (50)		0.704-3.036

[a] Fischer's Exact

Table 3: Relationship between Ferritin and IL-6 levels with the severity of COVID-19

	Severity		P
	Heavy	Currently	
Ferritin, ng/mL			
Median (Min – Mak)	1923 (154.69-2000)	817.53 (167.73-1240)	0.002 [a]
Interleukin 6, pg/mL			
Median (Min – Mak)	55.80 (3-614.20)	27.80 (1.5-607.2)	0.204 [a]

[a] Mann Whitney

Using the Mann Whitney test showed that there was no significant relationship between IL-6 and the severity of COVID-19 (p = 0.204).

The results of the analysis using the ROC curve (figure 1) obtained that the AUC (Area Under Curve) area of ferritin levels in predicting the severity of COVID-19 was 83% with p = 0.002 and 95% IK 69.2%-96.8%. This shows that ferritin levels can be used to predict the severity of COVID-19 with a good level of ability (AUC > 80%). Based on the line graph in Figure 1, the cut off value for ferritin levels to predict the severity of COVID-19 is 1245.65 ng/mL.

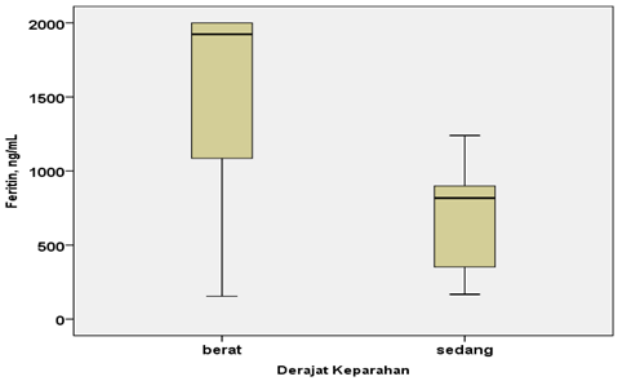

Figure 1: ROC Curve of Ferritin Levels against Severity of COVID-19

The results of the analysis using the ROC curve (figure 2) showed that the AUC area of interleukin-6 levels in predicting the severity was 63.6% with p = 0.204 and 95% CI 44.1%-83.1%. This shows that interleukin-6 levels cannot be used to predict the severity of COVID-19.

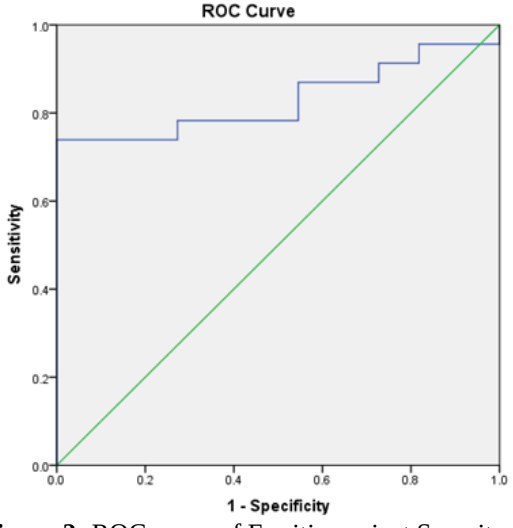

Figure 2: ROC curve of Ferritin against Severity of COVID-19

Table 4: Ferritin Accuracy in Predicting the Severity of COVID-19

	Severity		sensitive vitality	Specific sitas	NDP	NDN	Accuracy
	Yes	Not					
Ferritin, ng/mL							
≥ 1245.65	17	0	73.9%	100%	100%	64.7%	82.4%
< 1245.65	6	11					

6. Discussion

In this study, 22 male subjects (64.7%) with an average age of 55 years, with the youngest age 31 years and the oldest 73 years. The subjects who showed comorbid diseases were 26 people (76.5%) with the most comorbid types being DM and hypertension, which amounted to 8 people (23.5%).

This is in line with the research conducted by Farghaly et al, 2021. They conducted a retrospective study of 574 Covid patients, the study population was dominated by male patients as much as 54%, while the female sex was 45%, their study population, the youngest age > 30 years and the oldest age > 70 years. [8]

Comorbidities such as diabetes mellitus, hypertension and heart disease are common in COVID-19 patients and are associated with a higher risk of morbidity and mortality than patients without comorbidities. This can happen because people with comorbid diseases have weaker immune systems. [9]

In line with the study conducted by King et al, 2020. They conducted a study of 164 COVID-19 patients, they found that 67.5% of COVID-19 patients who were on a ventilator and needed ICU care were older patients with an average age of 67. years, 47% were male and 57% had comorbidities. [9]

Using the Mann Whitney test, this study showed that there was a significant relationship between ferritin and the severity of COVID-19 (p = 0.002). Using the Mann Whitney test showed that there was no significant relationship between IL-6 and the severity of COVID-19 (p = 0.204)

In contrast to the study by Gorham et al, 2020. There was a significant difference in IL-6 levels between survivors and non survivors over time (p = 0.001); In addition, non survivors had significantly higher maximal IL-6 values when compared to survivors (720 [349–2116] vs. 336 [195–646] pg/mL, p = 0.01). [10]

Zhou et al 2020 reported that COVID-19 patients with high serum ferritin levels had a greater risk of developing severe cases and were more likely to die (P = 0.0016). [11]

Using the Mann Whitney test, this study showed that there was a significant relationship between ferritin and the severity of COVID-19 (p = 0.002). Using the Mann Whitney test showed that there was no significant relationship between IL-6 and the severity of COVID-19 (p = 0.204).

The results of this study are not in line with the study conducted by Galvan Roman et al., 2020. They conducted an observational study of COVID-19 patients, they did an IL-6 examination days 3 and 9 since the patient was admitted to the hospital, an evaluation of the use of a ventilator was also carried out. during treatment. Their results showed that IL-6 levels greater than 30 pg/mL could be used as the best predictor to assess the severity of COVID-19 patients and the need for ventilatory support (odds ratio, 7.1; P <.001). [12]

A study conducted by Saji et al, 2021, performing ROC analysis for these significant variables showed that the amount of SpO2/FiO2, IL-6, SARSCoV-2 RNA, CRP, and lymphocytes could predict fatal outcome in COVID-19 patients. Specifically SpO2/FiO2, IL-6 had high accuracy with AUCs > 0.80 for risk prediction (AUC SpO2/FiO2: 0.90, AUC IL-6: 0.87. Finally, combining SpO2/FiO2, IL- 6 shows the highest accuracy (AUC: 0.93, 95%CI: 0.83-0.98) with a sensitivity of 92% and a specificity of 80%. [13]

Hyperferritinemia is caused by excessive inflammation due to COVID-19 infection and is associated with an indication for admission to the intensive care unit and with high mortality. Decreased serum ferritin is closely associated with recovery in severe COVID-19 patients, and those with more severe lung lesion impairment have elevated serum ferritin levels. [14]

Qin L et al reported that COVID-19 patients with high serum ferritin levels had a greater proportion of severe cases and were more likely to die (P = 0.0016). [15]

7. Conclusion

Using the Mann Whitney test, this study showed that there was a significant relationship between ferritin and the severity of COVID-19 (p = 0.002). Using the Mann Whitney test showed that there was no significant relationship between IL-6 and the severity of COVID-19 (p = 0.204).

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