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Correlation of Interleukin-6 Levels with Clinical Features and Chest X-Ray Imaging in Coronavirus Disease-19 (COVID-19) Patients at Dr. Mohammad Hoesin General Hospital Palembang

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ABSTRACT

Background. COVID-19 infection, both moderate and severe symptoms can cause pneumonia that can be detected on a chest X-ray. Along with the increasing severity of the clinical picture of COVID 19, it can also trigger a cytokine storm, one of which is an increase in Interleukin-6 levels. This study was conducted to see the correlation between IL-6 levels with clinical features and chest radiographs in patients with COVID-19
Methods: This research is a cross-sectional study using an observational analytic. The samples in this study were confirmed COVID-19 patients who were being treated at Dr. Mohammad Hoesin General Hospital, Palembang. A history and physical examination were performed to determine the clinical picture as well as a chest X-ray and IL-6 levels. **Results:** There were 31 samples of COVID 19 patients. High levels of IL-6 were found in 26 (83.9%) samples. The clinical picture of the patient was dominated by dyspnea as much as 19 (61.3%), fever 16 (5.6%), low O2 saturation 12 (38.4%) and a chest X-ray of pneumonia 26 (83.9%). There was a significant relationship (P<0.05) between IL-6 levels with clinical features and chest X-rays. The R-value on the thorax with pneumonia (0.692), lesion area (0.711) and clinical features with temperature (0.906), respiratory rate (0.706) indicated a strong correlation, while O2 (-0.732) indicated a strong negative correlation. **Conclusion:** There is a significantly strong correlation between Interleukin 6 levels with clinical features and chest X-rays in patients with COVID-19.

1. Introduction

In December 2019 there were reports of the Corona virus from the city of Wuhan, Hubei province, China.[1] This virus has become a pandemic that has spread throughout the world until now.[2] The name COVID 19 stands for Corona Virus Diseases 2019 or also known as SARS-Cov-2.[3] While this research was being conducted, COVID-19 cases were increasing, reaching 96.2 million in the world, 977 thousand positive cases in Indonesia and 13,599 thousand positive cases in South Sumatra.[4] COVID-19 infection with moderate or severe symptoms can cause pneumonia with an opaque appearance that can be detected on a chest CT scan, pulmonary edema, and accumulation of pleural fluid in the lungs.[5] The genetic sequence of SARS-CoV-2, showed that COVID 19 belongs to the β-coronavirus genus, with 79% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV.[6] Inoculation with SARS-CoV-2 of human respiratory tract epithelial cells in vitro

caused a cytopathic effect and cessation of ciliary movement of respiratory epithelial cells, similar to the cytopathic effect observed in SARS-CoV infection.[6]

COVID-19 infection was initially directed at the chemical structure of the SARS-CoV-2 receptor binding to the receptor *angiotensin-converting enzyme* 2 (*ACE2).*[7] The presence of *ACE2* on the cell membrane is critical for the activity of the virus, which lacks *ACE2* that is resistant to SARS-CoV-2 infection.[8] Structural analysis identified residues on the SARS-CoV-2 receptor binding critical for *ACE2*, mostly conserved or have chemical chain properties similar to those in SARS-CoV. The similarity of viral entry between SARS-CoV-2 and SARS-CoV was correlated with the neutralizing activity that could be detected in the serum of patients who recovered from SARS-CoV.[9] As the severity of COVID 19 increases, it can trigger a cytokine storm. COVID-19 mortality correlates with respiratory distress syndrome (RDS) which requires urgent invasive ventilation.[10] Several studies concluded several clinical predictors to see the severity and mortality of COVID 19 such as secondary infection with lymphopenia10, comorbidities such as cardiovascular disease, chronic respiratory infections, diabetes mellitus (DM), hypertension, obesity, and cancer.[11] Several other studies have reported the production of a storm of cytokines and serum ferritin suggesting elevated serum creatinine, D-dimer, lactate dehydrogenase, C-reactive protein (CRP), an elevated white blood cells may be indicative of respiratory failure and require treatment. invasive oxygen supply.[12-14]

A study states that pneumonia is the most frequent and serious complication in cases of COVID 19, which is an infection with SARS-COV-2. SARS-CoV-2 infection induces an exaggerated and aberrant immune response associated with acute respiratory distress syndrome*(* ARDS) with findings on chest radiographs, in many critically ill patients, often referred to as cytokine storm. The characteristics of plasma increase many cytokines that will create long-term damage and fibrosis in lung tissue. Another study applied anti-IL-6 administration to patients with COVID 19 and found a significantly strong correlation between decreased IL-6 levels and the severity of COVID 19.[13-15]

IL-6 levels of 100 pg/ml were sufficient to identify infected patients. COVID-19 with a high risk of respiratory failure. Coupled with the presence of serum SARS-CoV-2 nucleic acid (RNAaemia), which can be associated with a cytokine storm, it correlates closely with very high serum IL-6 levels.[16] A study concluded that serial measurement of serum IL-6 in COVID-19 patients can identify disease progression, predict respiratory failure, and can serve as an alternative test in asymptomatic COVID-19 patients. High levels of IL-6 can clarify the severity of COVID-19 sufferers by confirming clinical symptoms such as shortness of breath, fever, diarrhea, severe hypoxia, high blood pressure, and chest X-ray.[17-21] Many studies have focused on IL-6 levels and the severity of COVID-19. However, not many have seen the correlation with chest X-ray images, especially in Palembang, South Sumatra.

2. Methods

The research design is an analytic observational study with a cross-sectional approach. A total of 31 research subjects who were confirmed COVID-19 patients were treated in the inpatient room of confirmed COVID-19 patients at Dr. Mohammad Hoesin General Hospital Palembang from March 2021 to February 2022. This study was approved by the research ethics committee of Dr. Mohammad Hoesin General Hospital Palembang, Indonesia (No. 14/kepkrsmh/2022). The subject of the next study was given informed consent and identification was carried out including name, age, gender, address, telephone number that could be contacted. Next, a history (autoanamnesis/alloanamnesis) is performed which includes: the chief complaint, additional complaints, medical history, and medications that have been used, history of chronic disease (comorbidities). Anamnesis was carried out by researchers via telephone and telecommunications equipment in the inpatient room. Then a physical examination was carried out to see the clinical picture which included general condition, consciousness, blood pressure, respiratory rate, axillary temperature, weight, height, O2 saturation. levels examination was carried out by the nurse on duty in the inpatient room and viewed from the

patient's monitor screen. Furthermore, the reading of the results of the chest X-ray and the interpretation of the results of the chest X-ray was carried out by RSMH radiologists to determine the extent of the morphology of the lesion and measure the infiltrate. Applications in radiological measurements and assessments use a computer application, namely RadiAnt Dicom viewer by radiologists at RSMH, where radiologists do not know the patient's diagnosis to be interpreted. Then, the serum IL-6 level was examined by taking 10 cc of blood and measured by immunochemical quantification using the ELISA (Enzyme-Linked Immunosorbent Assay) method which was carried out in a private laboratory in Palembang.

All data from history taking, physical examination, and laboratory were processed using SPSS for Windows program. The data is presented in the form of tables and graphs. The data were tested whether the distribution was normal or not, as well as a correlation test with the significance level used was $p < 0.05$.

3. Results

Table 1 shows that there are more male subjects than female subjects, namely 19 (61.3%) patients while the female sample is 12 (38.7%) patients with the youngest age being 21 years and the oldest age 95 years with a mean age 58 years ± 16.2. The majority of the nutritional status of the sample in this study had a BMI of more than 23 (74.2%) samples with a low BMI of 20.4 and the highest BMI of 31.2. Most of the samples in this study had comorbid hypertension in as many as 19 (61.3%) patients, 3 (9.7%) of them had diabetes mellitus, 2 (6.5%) samples had comorbid hypertension and DM. Of the 31 samples of COVID 19 patients, 26 (83.9%) samples had high IL-6 levels (≥100 pq/mL) and 5 (16.1%) of them had normal IL-6 levels with the lowest IL-6 levels being 2.7 pg/mL and the highest IL-6 level was 244 pg/mL, from the clinical symptoms of the patients were dominated by shortness of breath as many as 19 (61.3%) samples with a minimum respiratory rate of 20 breaths/minute and a maximum of 30x/minute with a mean 25.2x/minute ±3.4.

Samples with normal body temperature were slightly higher than samples with fever, as many as 16 (5.6%) and 15 (48.6%) samples had normal body temperatures. The lowest body temperature of the research sample was 36.4°C and the highest temperature was 39.5°C with a mean of 37.5°C ± 0.9. Of the 31 (38.4%) of them had low O2, low O_2 saturation12 was 88% and the highest was 99% with an average of 94.7% ±3.7. Chest X-ray results showed 26 (83.9%) samples had pneumonia and 14 (45.2%) samples had extensive lesions, 7 (22.6%) had moderate lesions and 5 (16.5%) had minimal lesions.

Table 1. Characteristics of research subjects

General Characteristics	Frequency	%	Mean±SD
Age			58±16.2
40 years	5	16.1	
>40 years	26	83.9	
Gender			
Male	19	61.3	
Female	12	38.7	
BMI (20,4-31.2)			24.9±2.7
Normal	8	25.8	
More	23	74.2	
Comorbid			
Hypertension	19	61.3	
Diabetes Mellitus (DM)	3	9.7	
Hypertension and DM	2	6.5	
None	7	22,6	
IL-6			68.09±69.7
Normal	5	16.1	
Height	26	83.9	
Respiratory rate			25.2±3.4
Normal	12	38.4	
Shortness	19	61.3	
Body temperature			37.5±0.9
Normal (36-37.4)	16	51.6	
Fever (>37.5)	15	48.6	
O_2 saturation			94.7±3.7
Normal	19	61.3	
Low	12	38.4	
X-ray of Thorax			
Pneumonia	26	83.9	
No Pneumonia	5	16.1	
Lesion Area			
Minimum lesion	5	16.5	
Moderate lesion	7	22.6	
Extensive lesion	14	45.2	
None	5	16.5	

Table 2 presents data regarding the correlation of serum IL-6 levels in COVID 19 patients with clinical features and a chest X-ray. The results of the analytical test using Spearman rho showed that chest X-ray and clinical symptoms had a significant relationship with IL-6 levels. On a chest X-ray, samples diagnosed with pneumonia and having lesion areas were strongly correlated with high levels of IL-6 (r> 0.6). In clinical symptoms, O2 saturation. was strongly negatively correlated with IL-6 levels, while respiratory rate and temperature were strongly correlated with IL-6 levels (r>0.6).

Table 2. Correlation of serum IL-6 levels in patients with COVID 19 with clinical features and chest X-ray

Clinical features and chest X-ray	**r**	**p**
Chest X-ray		
Area of lesions	0.711	0.000
Pneumonia	0.692	0.029
Clinical Symptoms		
Temperature	0.906	0.000
Respiratory rate	0.706	0.000
O_2 saturation	-0.732	0.000

*Spearman correlation test rho, p value is significant if p < 0.05, correlation strength (r) is very weak if r < 0.2, weak if r=0,21-0,4, moderate if r=0,41-0,6, strong if r=0,61-0,8 and very strong if r>0,8

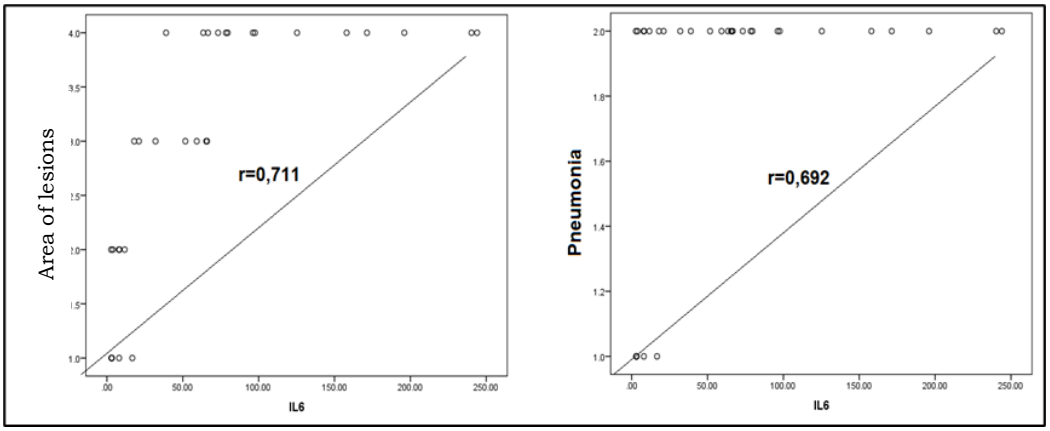

Figure 1. Correlation between levels of IL- 6 Confirmed COVID-19 patients with chest X-ray

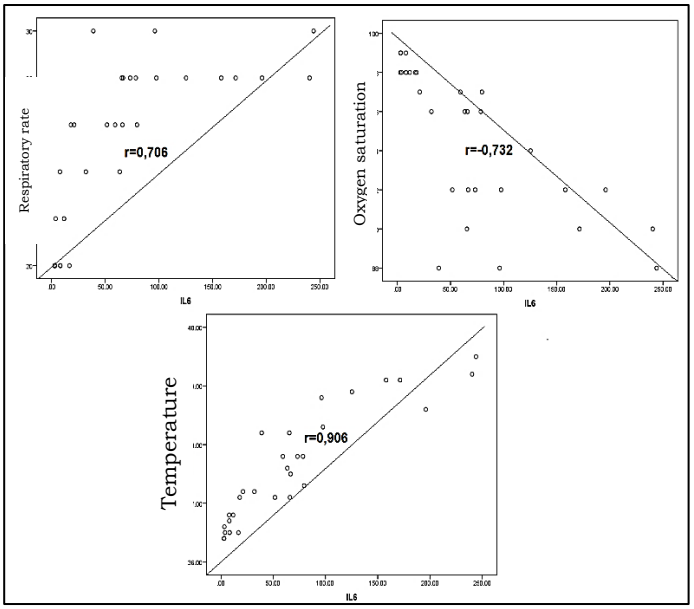

Figure 2. Correlation between IL-6 levels of confirmed COVID-19 patients and clinical symptoms

4. Discussion

Interleukin 6 (IL-6) is a multifunctional proinflammatory cytokine that produces a variety of cell types. IL-6 involves several types of physiological processes such as T cell activation, induction of acute-phase proteins, stimulating growth and differentiation in hematopoietic cell precursors, liver, skin, and nerve cell proliferation, bone metabolism, fat, and tissue fibrosis. Elevated tissue and high serum IL-6 are implicated in much inflammatory and autoimmune pathogenesis including rheumatic diseases and also implicated with cytokine release syndrome (CRS).[22] IL-6 modulates host defense through several immune-stimulating mechanisms: control of monocytes and differentiation into macrophages[23], modulation of antigen-dependent B-cell differentiation, increased production of IgG by B cells, and promotion of Th2 responses by inhibiting Th1 polarization. The findings of clinical trial data conducted in China and Italy proved that the administration of neutralizing IL-6 to COVID 19 patients who were on ventilation had recovered.[15,16] Several studies have found a strong correlation between serum IL-6 levels and the likelihood of impending respiratory failure.[16-20]

In line with this study, a study found a moderate correlation between pneumonia and IL-6 levels.[16] Another study also found a strong correlation between IL-6 levels in COVID-19 with pneumonia compared to the COVID-19 population without pneumonia.[24] Other studies have also found a high correlation between COVID 19 and pneumonia and pulmonary tuberculosis detected on CT scans with IL-6, CRP, and Erythrocyte Sedimentation Rate (ESR).[25] Another study revealed a strong correlation between serum IL-6 levels with respiratory failure and pneumonia in COVID 19 patients.[26] This suggests that even moderately high IL-6 levels above 100 pg/ml are sufficient to identify infected patients. COVID-19 with a high risk of respiratory failure.[27] In addition, serum SARS-CoV-2 nucleic acid (RNAaemia), which is strongly associated with cytokine storm, is closely correlated with very high serum levels of IL-6.[22-24] It is also suggested that serial measurements of IL-6 are important in identifying disease progression or, when evaluated immediately after confirmation of a COVID-19 diagnosis, can predict impending respiratory failure or asymptomatic disease among SARS-CoV-2 infected people.[28]

5. Conclusion

There is a significantly strong correlation between Interleukin 6 levels and clinical features and chest X-rays in patients with COVID-19.

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