Journal of Medical and Health Studies
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
AL-KINDI CENTER FOR RESEARCH AND DEVELOPMENT

| RESEARCH ARTICLE

Correlation of Interleukin 6 Levels with C-Reactive Protein in Various Severity of Covid-19 Patients in Rsup Dr. Mohammad Hoesin Palembang

Zen Ahmad[1], Rizha Zhetira[2] ✉ Phey Liana[3] and Erial Bahar[4]

[1234]Internal Medicine Department, Faculty of Medicine Sriwijaya University, Mohammad Hoesin Central General Hospital Palembang, Indonesia

Corresponding Author: Rizha Zhetira, **E-mail**: rizhazhetira89@gmail.com

| ABSTRACT

COVID-19 is an acute infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. Changes in inflammatory mediators in the laboratory can be related to the phase of the disease course and the patient's clinical course. The results help determine the degree and predict the severity of COVID-19. This study aims to determine the correlation between Interleukin 6 levels and quantitative CRP levels to the severity of COVID-19 disease. This study is an analytic observational study with a cross-sectional design. This research was conducted in the COVID-19 isolation ward of RSMH Palembang from September 2021 to February 2022, with the subjects confirmed COVID-19 with various severity. Those confirmed with COVID-19 were interviewed, checked vital signs, laboratory tests for Interleukin 6, and quantitative CRP. Statistical analysis of the correlation test used Spearman and Gamma. Sample of 39 patients, consisting of 16 patients (41%) moderate, 15 patients (38.5%) severe, 8 patients (20.5%) critical. There was a significant correlation between interleukin six levels and the degree of COVID- a disease with r = 0.719. A positive correlation with moderate strength was found between interleukin six levels and quantitative CRP levels so that these two parameters can be used as predictors of the severity of COVID-19 and have a positive correlation.

| KEYWORDS

COVID-19, Interleukin 6 levels, CRP

| ARTICLE INFORMATION

ACCEPTED: 20 October 2022 **PUBLISHED:** 28 October 2022 **DOI:** 10.32996/jmhs.2022.3.4.14

1. Introduction

In 2020, the world was shocked by the incidence of severe infections with unknown causes, which began with a report from China to the World Health Organization (WHO) of 44 severe pneumonia patients in an area, namely Wuhan City, Hubei Province, China, on the last day of the year 2019. At the end of January 2020, WHO declared a global emergency for this virus case. On February 11, 2020, the WHO named it COVID-19 (Coronavirus Disease 2019) (WHO, 2021).

Pro-inflammatory cytokines such as TNF-, IL-6, and IL-1 have an essential role associated with various inflammatory diseases, especially IL-6, which is highly correlated with the severity of the subject. After activating IL-6, it stimulates the output of acute phase proteins secreted by hepatocytes in the early stages of inflammation, namely C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, and a1-antichymotrypsin.

The severity of the disease can be classified into three stages, namely "early infection", "pulmonary phase", and "hyperinflammation phase" each phase has specific characteristics of biochemical changes. The "hyperinflammation phase", characterized by systemic inflammation, or cytokine storm, leads to ARDS (acute respiratory distress syndrome) and MOF (multiple organ failure) characterized by increased inflammatory mediators such as CRP, LDH, IL-6, D-Dimer, and Ferritin (Siddiqi, 2020; Liu, 2021).

Based on the inflammatory mechanism, increased levels of IL-6 and CRP have the same pathophysiological pathway that can cause these two things to influence each other. This study aims to find the correlation of IL 6 levels with CRP at various degrees of disease severity of COVID-19 patients at RSMH Palembang.

2. Method

This study used a cross-sectional design. Subjects were taken in the COVID-19 Isolation Room at Dr. Moh Hoesin Hospital Palembang. Data was taken from September 2021 – February 2022. This study was approved by the Medical Research Ethics Committee, Sriwijaya University Medical School, Dr. Moh. Hoesin Hospital Palembang. Each subject received informed consent before data collection.

Inclusion criteria were patients aged >18 years with confirmed COVID-19. Exclusion criteria were patients with chronic liver disease and quantitative CRP levels <5 mg/dL. All patients received treatment for COVID-19 according to the guidelines. Each subject was interviewed, and physical examination, complete blood chemistry, and IL 6 sampling were carried out using the pg/mL ELISA method.

Data analysis was performed with SPSS 25.0 (SPSS Inc., Chicago, USA). Clinical and laboratory data are presented as means and standard deviations for normal distribution variables or medians and ranges for abnormal distribution variables. If the data distribution is normal, then the Pearson correlation test is used, if the distribution data is not standard, the Spearman correlation test is used, and the result is significant if $p < 0.05$.

3. Result

A total of 42 subjects were taken, and 39 people were included in the study inclusion criteria from September 2021 – February 2022. Characteristics of the subjects, including age, gender, education, occupation, body mass index, clinical, comorbid, and disease severity, are shown in table 1.

Table 1 Baseline Characteristics

Characteristics	n	%
Gender		
Male	23	59.0
Female	16	41.0
Education		
Undergraduate	20	51.3
Senior high school	18	46.2
Junior high school	1	2.6
Comorbid		
Diabetes melitus	13	33.3
Hypertension	33	84.6
Cardiovaskular	9	23.1
Renal	3	7.7

Note: (n: amount)

In this study, the mean age of the research subjects was 60 years, the youngest was 27 years, and the oldest was 71 years. Gender is dominated by 23 male subjects (59%). Based on education, undergraduate 20 subjects (51.3%), high school 18 subjects (46.2%), and junior high school one subject (2.6%). The distribution of comorbidities was divided into four comorbid groups diabetes 13 (33.3%), hypertension 33 (84.6%), heart disease 9 (23.1%), and kidney disease 3 (7.7%).

3.1 The correlation of interleukin six levels with quantitative CRP levels

The correlation of interleukin six levels with quantitative CRP levels in this study was analyzed using the Spearman correlation test because the interleukin six and quantitative CRP data were not normally distributed. From the analysis results, it was found that interleukin six levels with quantitative CRP levels had a positive correlation with $p<0.0001$ and $r=0.583$, which means that the increase in CRP levels was in line with the increase in IL-6 levels with moderate correlation strength. The correlation of interleukin 6 to quantitative CRP can be seen in table 2.

Table 2 The correlation of interleukin 6 to quantitative CRP

Variable	CRP kuantitatif	
	p	r
Interleukin 6	0.000	0.583

*Note: Gamma correlation (significant p < 0,05) **r value = 0,00-0,25 (very weak), r = 0,26-0,50 (moderate), r = 0,51- 0,75 (strong), r = 0,76-0,99 (very strong), r = 1 (excellent)*

3.3 Distribution of IL-6 and CRP based on the severity of COVID-19

IL-6 in subjects with a critical degree was 87.00 pg/mL; in subjects with a severe degree, 59.20 pg/mL, and the moderate degree of IL-6 was 21.45 pg/mL. CRP levels in subjects with a critical degree of 105 mg/L, subjects with a severe degree of 100 mg/L, and a moderate degree of 40 mg/L.

Table 3 Distribution of IL-6 and CRP based on the severity

Variable	Degree		
	Critical	Severe	Moderate
Interleukin 6 (IL-6)	87.00 (4.20 – 240.00)	59.20 (12.70 – 490.00)	21.45 (8.00 – 244.00)
CRP	105.00 (20.00 – 158.00)	100.00 (36.00 – 175.00)	40.00 (15.00 – 190.00)

4. Discussion

In this study, sex was dominated by 23 men (59%) and 16 women (41%). Based on data published by WHO that the prevalence of confirmed cases of COVID-19 spread throughout the world, the highest number of reported cases were in men, with a percentage of 51%, and in women, at 49%. Men are more prone to have a more severe degree of COVID-19 disease than women, the reason being that there is a direct relationship to the involvement of androgen receptor activity required for transcription of the TMPRSS2 gene (Warmbier, 2020; Jurado, 2020).

Based on education, it was dominated by 20 undergraduate subjects (51.3%), followed by high school with 18 subjects (46.2%) and 1 (2.6%) junior high school. In the study of Petra et al., the role of education and skills in understanding the impact of COVID-19 on the spread and survival rate (Rattay, 2021).

Comorbidities affect the outcome of this COVID-19, including the length of stay of the patient. In this study, the most comorbidities were hypertension, namely in 21 subjects (53.8%), followed by diabetes mellitus (DM) in 13 subjects (33.3%), heart disease in 9 subjects (23.1%), and kidney disease in 3 subjects (7.7%). In Indonesia, the most comorbidities were hypertension 50.7%, DM 35.8%, heart disease 17.6% and cancer 1.7%. According to a book from the Indonesian Ministry of Health entitled Guidelines for Prevention and Control of COVID-19, the fifth revision, patients with congenital heart disease have a mortality rate of 10.5%, patients with diabetes 7.3%, and patients with chronic respiratory diseases 6.3%. , patients with hypertension 6%, and patients with cancer 5.6%. The mortality rate for patients with comorbidities is higher than for patients without comorbidities.[7]

Sutaryono et al. (2020), in the diagnosis and epidemiology of COVID-19 in Indonesia, the most comorbid results were hypertension at 34.85%, followed by DM at 25.76% and heart disease at 17.05%. This is because the renin-angiotensin-aldosterone (RAA) system of SARS-CoV2 binds to the ACE2 receptor to enter host cells and downregulate this receptor. Loss of ACE2 receptor activity will lead to the inactivation of angiotensin two and at least the formation of angiotensin 1-7. The imbalance between the overactivity of angiotensin two and the lack of formation of angiotensin 1-7 will lead to inflammatory activity and thrombosis (Sutaryono, 2020).

The correlation of quantitative CRP levels with IL 6 levels in this study was analyzed using the Spearman correlation test. The results show that interleukin six levels with quantitative CRP levels have a positive correlation with p <0.0001 and r = 0.583, which means that the increase in CRP levels was in line with the increase in IL-6 levels with moderate correlation strength. Cruz et al. (2021) concluded that increased levels of CRP and IL 6 were associated with the severity of COVID-19 (r = 0.550, p < 0.0001). Jean Remi Lavillegrand et al. levels of CRP and IL 6 also correlated with disease severity with a significant value of p < 0.01.

5. Conclusion

COVID-19 is an acute infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. Changes in inflammatory mediators in the laboratory can be related to the phase of the disease course and the patient's

clinical course. The results help determine the degree and predict the severity of COVID-19. This study aims to determine the correlation between Interleukin 6 levels and quantitative CRP levels to the severity of COVID-19 disease. This study is an analytic observational study with a cross-sectional design. The results of the study revealed that there is a positive correlation with moderate strength between interleukin six levels and quantitative CRP levels. With the correlation between these two parameters, CRP levels can describe an increase in IL 6.

Funding: This research received no external funding.
Conflicts of Interest: The authors declare no conflict of interest.
Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers.

References

[1] Jurado A, Martin M, and Molina CA. (2020). COVID-19: age, Interleukin-6, C-reactive protein, and lymphocytes as key clues from a multicentre retrospective study. *Immunity and Ageing. 17*(22): 1-15.
[2] Kementerian Kesehatan RI. (2020). Pedoman Pencegahan dan Pengendalian COVID 19: Revisi kelima. Jakarta. 2020.
[3] Lavillegrand JR, Garnier M, and Spaeth A. (2021). Elevated plasma IL-6 and CRP levels are associated with adverse clinical outcomes and death in critically ill SARS-CoV-2 patients: inflammatory response of SARS-CoV-2 patients. Annals of Intensive Care;11(9):1-10.
[4] Liu X, Wang H, and Shi S (2021). Association between IL-6 and severe disease and mortality in COVID-19 disease: a systematic review and meta-analysis. *Postgraduate Medical Journal*;0:1–9.
[5] Rattay P, Michalski N, and Domanska OM. (2021). Differences in risk perception, knowledge, and protective behaviour regarding COVID-19 by education level among women and men in Germany. Results from the COVID-19 Snapshot Monitoring (COSMO) study. PLoS One. 16(5):1-26.
[6] Sutaryono, Andasari SD, and Kasjono HS. (2020). Diagnosis and epidemiology of coronavirus disease (COVID-19) outbreak in Indonesia. *J Tek Lab*; 9(1): 49-57
[7] Santa-Cruz A, Mendes-Frias A, and Oliveira AI. (2021). Interleukin-6 Is a Biomarker for the Development of Fatal Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia. Frontiers in Immunology. February; 12(613422):1-10.
[8] Siddiqi HK, and Mehra MR. (2020). COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. *The Journal of Heart and Lung Transplantation. 39*(5): 405-407.
[9] World Health Organization. (2021). WHO *Corona Virus Disease* (COVID-19) dashboard. Geneva: World Health Organization; 2021[updated 2021 Mei 11th; cited 2021 Mei 11th]. Available from: WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard
[10] Warmbier CG, and Goren A. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen-mediated. *J Am Acad Dermatol 83*(1): 308-309