
| RESEARCH ARTICLE

Correlation of Quantitative CRP Values with Fibrinogen Levels in Covid-19 Patients at Dr. Mohammad Hoesin Hospital Palembang

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| ABSTRACT

COVID-19 is a contagious acute respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In COVID-19 infection, there may be a high inflammatory response, causing thromboinflammatory processes through cytokine storm mechanisms, complement activation, and endothelial damage. Thus, the sequence of events can be seen from increased levels of CRP, fibrinogen, and other acute-phase proteins synthesized by the liver. The CRP value is useful for assessing the severity of inflammation which is widely used in predicting disease severity, prognosis, and mortality in COVID-19 patients, while fibrinogen levels are useful for assessing the severity of disease and hypercoagulation in COVID-19 patients. This study aims to determine the correlation between quantitative CRP and fibrinogen levels, as well as the correlation of fibrinogen levels with the severity of COVID-19 disease. This study was an observational correlative analytic study with a retrospective approach. The research was conducted at the Department of Internal Medicine of RSMH Palembang in May 2022 by taking medical record data of COVID-19 patients from May 2021 to September 2021. The research subjects are adult COVID-19 confirmed case patients who have not received standard therapy and anticoagulant drugs. The data taken are general characteristics, routine blood tests, blood chemistry, blood gas analysis, and hemostasis function. Data processing and analysis were done using SPSS version 25.0 for windows. There were 263 subjects, consisting of 26 subjects (26.2%) with mild symptoms, 95 subjects (36.1%) with moderate symptoms, 49 subjects (18.6%) with severe symptoms, and 50 subjects (19%) with critical symptoms. The correlation between CRP values and fibrinogen levels was obtained with a correlation coefficient of $r = 0.574$, while the correlation between fibrinogen levels and the severity of disease was obtained at $r = 0.490$. In this study, there was a strong correlation between quantitative CRP value and fibrinogen levels and a moderate correlation between fibrinogen levels and the severity of illness in COVID-19 patients at RSMH Palembang. These two parameters can be used as predictors of the severity of COVID-19 disease.

| KEYWORDS

COVID-19, fibrinogen, quantitative CRP

| ARTICLE INFORMATION

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1. Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This virus first appeared in Wuhan, China, and spread rapidly throughout the world and was declared a pandemic by the World Health Organization (WHO) on March 12, 2020, causing high morbidity and mortality rates (Handayani, 2020). Globally, the incidence of COVID-19 is 625 million cases, while in Asia, it is 190 million cases, and in Indonesia, it is 6.4 million cases and continues to increase (World Health Organization, 2022; Indonesian Ministry of Health, 2022).

The clinical course of COVID-19 is classified into "early infection", which is the initial stage of the virus infiltrating the lung parenchyma and characterized by lymphopenia, followed by the "pulmonary phas", where there is local inflammation in the lungs, characterized by an increase in C-reactive protein (CRP), fibrinogen and *interleukin-6* (IL-6). In the third stage, namely the

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"hyperinflammation phase", systemic inflammation, cytokine storm, *acute respiratory distress syndrome* (ARDS), and *multiple organ failure* (MOF) occur, characterized by the same biomarkers as the "pulmonary phase" which are significantly elevated (Ciaccio, 2020; Mueller, 2020).

Hypercoagulation occurs as one of the complications of COVID-19 disease and has a poor prognosis. Patients with a high inflammatory response result in a thromboinflammatory process through cytokine storm mechanisms, complement activation, and endothelial damage. Increased levels of IL-6, IL-1, and tumor necrosis factor- α (TNF- α) in COVID-19 patients are reflected in increased levels of CRP, fibrinogen, and other acute-phase proteins synthesized by the liver. On the other hand, the increase in proinflammatory cytokines also activates the coagulation cascade, mainly due to vascular endothelial damage (Guo, 2020).

CRP has been widely used to predict disease severity, prognosis, and mortality in COVID-19 patients (Imran, 2020). However, there are still few who use fibrinogen levels to assess the severity of disease, hypercoagulation, and thrombosis, especially pulmonary capillaries in COVID-19 patients. This study aims to assess the correlation between quantitative CRP values and fibrinogen levels in COVID-19 patients at RSMH Palembang.

2. Method

2.1 Research Subject

This study used a correlative analytic observational design with a retrospective approach. The study was conducted at the Department of Internal Medicine, Dr. Mohammad Hoesin Hospital, Palembang. The data taken is the medical records of COVID-19 patients in May - September 2021. This study was approved by the Medical Research Ethics Committee, Faculty of Medicine, Sriwijaya University, Dr. Mohammad Hoesin Hospital Palembang. The inclusion criteria were patients with confirmed cases of COVID-19 from the SARS-CoV-2 RT-PCR test examination, aged 18 years (Micco, 2021). Exclusion criteria were patients who had been given standard therapy and anticoagulant drugs and patients with incomplete medical record data (Warmbier, 2020; Klein, 2016).

Every COVID-19 patient who met the inclusion and exclusion criteria was collected and collected identification data (name, age, gender, education, and occupation), patient history and comorbid data, vital signs and physical examination data, and disease classification data based on the 5th edition of the Indonesian COVID-19 Management Guideline, routine blood laboratory data, clinical chemistry, blood gas analysis, and hemostasis function, then a correlation analysis of quantitative CRP values and fibrinogen levels in COVID-19 patients was carried out.

2.2 Statistic analysis

Data analysis was performed with SPSS 25.0 (SPSS Inc., Chicago, USA). Clinical and laboratory data are presented in the form of mean and standard deviation for normal distribution variables or median and range for abnormal distribution variables. A normality test is carried out; if the distribution is normal, then the Pearson correlation test is used; if the distribution data is not normal, the Spearman correlation test is used. To assess the relationship between independent variables and the severity of COVID-19 disease, an unpaired t-test was used for normally distributed numerical variables (or Mann-Whitney if not normally distributed). The Chi-Square test (or Fisher test) was used for the categorical variables of gender, education level, employment status, and patient comorbidities. The relationship between the independent and dependent variables was considered significant if $p < 0.05$.

3. Results

A total of 263 subjects who received treatment in May - September 2021 were included in this study (Table 1). In this study, most of the subjects (58.9%) were female, with an average age of 52 years. The largest age group was 46-59 years old, with 83 subjects (31.6%), and 60 years old group, with 77 subjects (29.3%). Body mass index (BMI) obtained a median value of 22.8 kg/m², with most patients having a normal BMI (59.3%). Most occupations are housewives, with 87 subjects (33.1%). The most comorbid was hypertension with a total of 65 subjects (24.7%). While the severity of COVID-19 disease was obtained mild symptoms in 69 subjects (26.2%), moderate symptoms in 95 subjects (36.1%), severe symptoms in 49 subjects (18.6%), and critical symptoms in 50 subjects (19%).

Table 1. General characteristics and degrees of COVID-19 disease in research subjects

General characteristics	N	(%)
Age (years)		
• 18 – 30	46	(17.5%)
• 31 – 45	57	(21.7%)
• 46 – 59	83	(31.6%)
• 60	77	(29.3%)
Gender		
• Man	108	(41.1%)

• Woman	155	(58.9%)
BMI (kg/m ²)		
• 18.5	19	(7.2%)
• 18.6 – 25.0	156	(59.3%)
• 25.1 – 27.0	50	(19.0%)
• > 27	39	(14.8%)
Education		
• Elementary School	39	(14.8%)
• Junior high school	25	(9.5%)
• Senior high school	118	(44.9%)
• Bachelor	81	(30.8%)
Work		
• Housewife	87	(33.1%)
• Private sector worker	62	(23.6%)
• Civil servant	48	(18.3%)
• Pension	20	(7.6%)
• Unemployed	18	(6.8%)
• Farmer	17	(6.5%)
• Student	11	(4.2%)
Fever		
• Yes	197	(74.9%)
• Not	66	(25.1%)
Other Symptoms		
• Out of breath	127	(48.3%)
• Cough	92	(35.0%)
• Anosmia/ageusia	33	(12.5%)
• Diarrhea	3	(1.1%)
• No symptoms	8	(3.0%)
Comorbid		
• Hipertension	65	(24.7%)
• Diabetes mellitus	39	(14.8%)
• Cancer /malignansi	31	(11.8%)
• Heart disease	21	(8.0%)
• Pregnancy	18	(6.8%)
• Chronic kidney disease	11	(4.2%)
• Asthma	5	(1.9%)
• Sistemic Lupus Eritematous	3	(1.1%)
• Nephrotic syndrome	2	(0.8%)
• Hepatic cirrhosis	1	(0.4%)
• No comorbid	67	(25.5%)
Degree of disease COVID 19		
• Mild	69	(26.2%)
• Moderate	95	(36.1%)
• Severe	49	(18.6%)
• Critical	50	(19.0%)

Table 2. shows that subjects with severe and critical illness were older than patients with mild and moderate disease (median age at mild symptoms was 39 years, at moderate symptoms was 52 years, at severe symptoms was 55 years, and at critical symptoms was 62.5 years).). The group of subjects with severe and critical illness had a higher quantitative CRP than subjects with mild and moderate symptoms (mean CRP for mild symptoms 8 g/L, moderate symptoms 35.5 g/L, severe symptoms 114 g/L, and critical symptoms 134 g/L). The group of subjects with higher disease severity had higher fibrinogen levels than subjects with lower disease

severity (mean fibrinogen at mild symptoms 290 g/L, moderate symptoms 410 g/L, severe symptoms 763 g/L, and critical symptoms 1149 g/L).

Table 2. Characteristics of distribution of study subjects based on the severity of COVID 19

Variable	COVID-19 Symptom Level				P value
	Light (N=69)	Medium (N=95)	Heavy (N=49)	Critical (N=50)	
Age (years), median (range)	39 (18-74)	52 (19-84)	55 (20-85)	62.5 (22-85)	0.000*
SpO2 (%), median (range)	98 (95-99)	95 (94-99)	90 (86-93)	86 (54-92)	0.000*
BMI (kg/m ²), mean ±SD	22.439±3.0412	23.571±4.0	23.204±3.89	24.006±4.04	0.099**
Leukocytes (/μl), median (range)	7760 (2800-31040)	8575 (3210-32000)	11085 (3370-23900)	10905 (2320-38380)	0.000*
Platelets (x 10 ³ /μl) , median (range)	241 (78-665)	235.5 (67-795)	257 (37-828)	243.5 (8-425)	0.642*
N/L Ratio, median (range)	3 (0.3-30)	4.6 (0.8-31)	8.75 (1.5-31.3)	12.75 (2.5-97)	0.000*
CRP (g/L) , median (range)	8 (3.68-144.8)	35.5 (4-302)	114 (11-315)	134 (48-475)	0.000*
Fibrinogen (mg/dL) , median (range)	418 (232-771)	482 (230-963)	597 (216-1054)	621 (180-1192)	0.000*
Ferritin (g/dL), median (range)	290 (3.7 – 2259)	410 (26.1-4187)	763 (24.10-6480)	1149 (161.3-7406)	0.000*
D-Dimer (g/mL), median (range)	0.69 (0.27-6.25)	1.22 (0.27-20)	2.28 (0.58-20)	3.38 (0.8-20)	0.000*
PaO ₂ /FiO ₂ ratio, median (range)	320 (34-729)	200 (39-753.9)	111.7 (38-373.3)	69.9 (36-178)	0.000*
Pneumonia X-ray, n (%)	0 (0%)	95 (100%)	49 (100%)	50 (100%)	0.000***

*Kruskal-Wallis test. **One-way ANOVA test. ***Chi-Square test. The value of p<0.05 was considered statistically significant.

The correlation of fibrinogen levels with quantitative CRP values was analyzed using the *Spearman correlation test*. Table 3 shows that fibrinogen levels and quantitative CRP values have a positive correlation, with a strong correlation strength, with an R-value of 0.547 and a degree of significance of p = 0.000.

Table 3. Correlation of fibrinogen levels with C -Reactive Protein in COVID 19

Variable	C-Reactive Protein
Fibrinogen Level	r = 0.547** p = 0.000*

* Spearman correlation test (p-value is significant if < 0.05)

** If the value of r = 0.00-0.25 (very weak correlation), r = 0.26-0.50 (medium correlation), r = 0.51-0.75

(strong correlation), r = 0.76-0.99 (very strong correlation), r = 1 (perfect); with a “-” sign indicating the direction of the negative correlation.

4. Discussion

The mean age of the COVID-19 patients in this study was 52 years, with a proportion of female patients (58.9%) than male patients (41.1%). This study is slightly different from data from WHO, the prevalence of confirmed cases of COVID-19 spread throughout the world is the highest in men (51%) and women (49%). However, this research is almost the same as the data from the Indonesian Ministry of Health that confirmed cases of COVID-19 were more in women (50.3%) and men (47.6%). Sex differences are seen in males who are more susceptible and have a more severe symptoms of COVID-19 disease than women, partly because of a direct link to the involvement of androgen receptor activity required for transcription of the TMPRSS2 gene. In addition, in the adaptive immune system, women have higher CD4+ T cell counts, stronger CD8+ T cell cytotoxic activity, and higher B cell immunoglobulin production than men. Women produce more type 1 interferon (IFN-1) to fight the virus. This increase in IFN production is associated with the concentration of sex hormones and the number of X chromosomes present (Klein, 2016).

In this study, the median BMI was 22.8 kg/m², with a maximum range of 33.6 kg/m² and a minimum range of 16.3 kg/m². Normal BMI was 156 subject (59.3%), overweight was 50 subject (19%), and obese was 39 subject (14.8%). Meanwhile, based on the severity of the disease, the average BMI in the critical disease was 24,006 kg/m², the BMI average in the severe disease was 23,204 kg/m², the BMI average in the moderate disease was 23,571 kg/m², and the BMI in the mild disease was 22,439 kg/m². These results show that individuals with excess BMI have more severe symptoms. This study is similar to the study reported by Sharma et al. (2021); obesity predisposes individuals to develop many other comorbid conditions, including diabetes mellitus, hypertension, dyslipidemia, and some types of cancer. Levels of several major cytokines and chemokines, such as IL-6, IL-1 β , IL-8, and TNF- α are increased in obese people compared to normal BMI people. Consistently increased levels of these inflammatory molecules disrupt the mucosal lining of the airways (Sharma, 2021).

From the results of the correlation analysis of fibrinogen levels with quantitative CRP values, a positive correlation was obtained, with a strong correlation strength, with a value of $r = 0.547$ and a degree of significance of $p = 0.000$. Based on this analytical test, the correlation between fibrinogen levels and quantitative CRP values was clinically and statistically significant. In this study, it can be concluded that the higher the fibrinogen level, the higher the quantitative CRP value, and vice versa. The results of this study are in line with the results of Chen et al. (2020), where the increase in fibrinogen levels is directly proportional to the increase in quantitative CRP values in COVID-19 patients (Chen, 2019). Likewise, the study of Tang et al. (2020), who reported an increase in quantitative CRP values, was also followed by an increase in fibrinogen levels measured when the patient was admitted to the hospital (Tang, 2020). The study of Ranucci et al. (2020), which measured the levels of IL-6, fibrinogen, and CRP in COVID-19 patients at the start of treatment, showed an increase in IL-6 correlated with an increase in quantitative fibrinogen and CRP levels, these results confirm the association between inflammation and procoagulant conditions (Ranucci, 2020).

This study has several limitations, including the study was only conducted at one hospital center, and this retrospective study requires further validation with prospective studies. To confirm the results of this study, it is necessary to conduct a prospective cohort study to assess the dynamic changes in fibrinogen values along with the clinical course of COVID-19 patients. Future research is expected to be able to make a comparison between fibrinogen levels and D-dimer values on the severity of COVID-19 disease.

5. Conclusion

COVID-19 is a contagious acute respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In COVID-19 infection, there may be a high inflammatory response, causing thromboinflammatory processes through cytokine storm mechanisms, complement activation, and endothelial damage. Thus, the sequence of events can be seen from increased levels of CRP, fibrinogen, and other acute-phase proteins synthesized by the liver. The CRP value is useful for assessing the degree of inflammation which is widely used in predicting disease severity, prognosis, and mortality in COVID-19 patients, while fibrinogen levels are useful for assessing the severity of disease and hypercoagulation in COVID-19 patients. This study aims to determine the correlation between quantitative CRP and fibrinogen levels, as well as the correlation of fibrinogen levels with the severity of COVID-19 disease. The results of the study revealed that the Fibrinogen levels and quantitative CRP values have a strong positive correlation, so they are clinically and statistically significant. These results show that the higher the fibrinogen level, the higher the quantitative CRP value, and vice versa.

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References

- [1] Ciaccio M, and Agnello L. (2020). Biochemical biomarkers alterations in coronavirus disease 2019 (COVID-19). *Diagnosis*;7(4):365-372
- [2] Chen G, Wu D, and Guo W. (2019). Clinical and immunologic features in severe and moderate Coronavirus Disease. *J Clin Invest.* 2020; 130: 2620-2629
- [3] Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, and Jin HJ. (2020). The origin, transmission, and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. *Mile Med Res*; 7(1):11
- [4] Huang Y, Lyu X, Dan L, Wang L, Wang Y, and Zou W. (2020). A cohort study of 676 patients indicates D-Dimer is a critical risk factor for the mortality of COVID-19. *PLoS One*; 15(11):1-2
- [5] Handayani D, Hadi DR, Isbaniah F, Burhan E and Agustin H. (2020). Corona Virus Disease 2019. *J Respir Indo*; 40(2):119-129
- [6] Indonesian Ministry of Health. (2022). Current situation of the development of coronavirus disease (COVID-19) [Internet]. Jakarta: Indonesian Ministry of Health; 2022[updated 2022 October 29th; cited 2022 October 29th]. Available from: Emerging Infections Ministry of Health RI (kemkes.go.id)
- [7] Imran S, Fatima SA, Yunus N, and Taj S. (2020). Association of plasma CRP level with the severity of COVID-19. *Int J Sci*; 9(11): 20-23
- [8] Klein SL, and Flanagan K. (2016). Six differences in the immune response. *Nature reviews*; 16: 626-638
- [9] Micco P, Russo V, Carannante N, Imparato M, Cardillo G, and Lodigiani C. (2021). Prognostic Value of Fibrinogen among COVID-19 Patients Admitted to an Emergency Department: An Italian Cohort Study. *Journal of Clinical Medicine*; 9:4134
- [10] Mueller AA, Tamura T, Crowley CP, DeGrado JR, Haider H, and Jezmir JL. (2020). Inflammatory Biomarker Trends Predict Respiratory Decline in COVID-19 Patients. *CellReport Medicine*: 3-6
- [11] Ranucci M, Ballotta A, and Di Dedda U. (2020). The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*; 18:1747-1751
- [12] Sharma J, and Yadav U. (2021). COVID-19 severity in obese patients potential mechanism and molecule targets for clinical intervention. *Obesity research and clinical practice*; 163-171
- [13] Tang N, Li D, Wang X and Sun Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020; 18:844-847
- [14] World Health Organization. (2022). WHO coronavirus disease (COVID-19) dashboard [Internet]. Geneva: World Health Organization; 2022[updated 2022 October 29th; cited 2022 October 29th]. Available from: WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard
- [15] Warmbier C.G and Goren A. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen-mediated. *J Am Academy Dermatol*; 83(1): 308-309.