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

Nandi Hermawan¹ ☞ Zen Ahmad², Yenny Dian Andayani³ and Erial Bahar⁴
¹²³⁴Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/RSUP Dr. Moh. Hoesin Palembang, Indonesia

Corresponding Author: Nandi Hermawan, E-mail: nandyhermawan@gmail.com

| 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 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. 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 degrees, 95 subjects (36.1%) with moderate degrees, 49 subjects (18.6%) with severe degrees, and 50 subjects (19%) with critical degrees. 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 |
ACCEPTED: 20 October 2022  PUBLISHED: 28 October 2022  DOI: 10.32996/jmhs.2022.3.4.15

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, 2021; Indonesian Ministry of Health, 2021).

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 phase," 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 "

Copyright: © 2022 The Author(s). This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) 4.0 license (https://creativecommons.org/licenses/by/4.0/). Published by Al-Kindi Centre for Research and Development, London, United Kingdom.
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. Moh 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. Moh. 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 COVID-19 Management Manual, 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 norm weight BMI (59.3%). Most occupations are housewives, with 87 subjects (33.1%). The most comorbid was hypertension in as many as 65 subjects (24.7%). While the severity of COVID-19 disease was obtained by 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

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 18 – 30</td>
<td>46</td>
<td>(17.5%)</td>
</tr>
<tr>
<td>• 31 – 45</td>
<td>57</td>
<td>(21.7%)</td>
</tr>
<tr>
<td>• 46 – 59</td>
<td>83</td>
<td>(31.6%)</td>
</tr>
<tr>
<td>• 60</td>
<td>77</td>
<td>(29.3%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Man</td>
<td>108</td>
<td>(41.1%)</td>
</tr>
<tr>
<td>• Woman</td>
<td>155</td>
<td>(58.9%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- 18.5 19 (7.2%)
- 18.6 – 25.0 156 (59.3%)
- 25.1 – 27.0 50 (19.0%)
- > 27 39 (14.8%)

Education
- SD 39 (14.8%)
- JUNIOR HIGH SCHOOL 25 (9.5%)
- SENIOR HIGH SCHOOL 118 (44.9%)
- BACHELOR 81 (30.8%)

Work
- IRT 87 (33.1%)
- Private 62 (23.6%)
- civil servant 48 (18.3%)
- Pension 20 (7.6%)
- Doesn’t work 18 (6.8%)
- Farm workers 17 (6.5%)
- Student 11 (4.2%)

Fever
- Yes 197 (74.9%)
- Not 66 (25.1%)

Other Symptoms
- Congested 127 (48.3%)
- Cough 92 (35.0%)
- Anosmia/ageusia 33 (12.5%)
- Diarrhea 3 (1.1%)
- No symptoms 8 (3.0%)

Comorbid
- Hypertension 65 (24.7%)
- Diabetes mellitus 39 (14.8%)
- Cancer/malignancy 31 (11.8%)
- Heart disease 21 (8.0%)
- Pregnancy 18 (6.8%)
- CKD 11 (4.2%)
- bronchial asthma 5 (1.9%)
- SLE 3 (1.1%)
- nephrotic syndrome 2 (0.8%)
- Liver cirrhosis 1 (0.4%)
- No comorbid 67 (25.5%)

Degree of disease COVID 19
- Light 69 (26.2%)
- Currently 95 (36.1%)
- Heavy 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 disease (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 degrees had higher fibrinogen levels than subjects with lower disease degrees (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

<table>
<thead>
<tr>
<th>Variable</th>
<th>COVID-19 Symptom Level</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Light (N=69)</td>
<td>Medium (N=95)</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>39 (18-74)</td>
<td>52 (19-84)</td>
</tr>
<tr>
<td>SpO2 (%), median (range)</td>
<td>98 (95-99)</td>
<td>95 (94-99)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>22.439±3.0412</td>
<td>23.571±4.0</td>
</tr>
<tr>
<td>Leukocytes (/μl), median (range)</td>
<td>7760 (2800-31040)</td>
<td>8575 (3210-32000)</td>
</tr>
<tr>
<td>Platelets ( x 10³ /μl), median (range)</td>
<td>241 (78-665)</td>
<td>235.5 (67-795)</td>
</tr>
<tr>
<td>N/L Ratio, median (range)</td>
<td>3 (0.3-30)</td>
<td>4.6 (0.8-31)</td>
</tr>
<tr>
<td>CRP ( g/L ), median (range)</td>
<td>8 (3.68-144.8)</td>
<td>35.5 (4-302)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL), median (range)</td>
<td>418 (232-771)</td>
<td>482 (230-963)</td>
</tr>
<tr>
<td>Ferritin ( g/dL ), median (range)</td>
<td>290 (3.7 – 2259)</td>
<td>410 (26.1-4187)</td>
</tr>
<tr>
<td>D-Dimer ( g/mL ), median (range)</td>
<td>0.69 (0.27-6.25)</td>
<td>1.22 (0.27-20)</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio, median (range)</td>
<td>320 (34-729)</td>
<td>200 (39-753.9)</td>
</tr>
<tr>
<td>Pneumonia X-ray, n (%)</td>
<td>0 (0%)</td>
<td>95 (100%)</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Variable</th>
<th>C-Reactive Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen Level</td>
<td>r = 0.547**</td>
</tr>
</tbody>
</table>

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

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 degree 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 necessary to conduct a prospective transcription of the TMPRSS2 gene. In addition, in the adaptive increase in fibroblast growth factor 23 (FGF23), as interleukin (IL)-6, fibrinogen, and CRP 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.

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