Correlation of C-Reactive Protein (CRP) Levels with D-Dimer Levels in COVID-19 Patients

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ABSTRACT
Coronavirus disease 2019 is caused by SARS-CoV-2 infection. COVID-19 causes increased levels of proinflammatory cytokines, so CRP and d-dimer levels in COVID-19 patients tend to increase. This study aimed to analyze the correlation between C-Reactive Protein (CRP) levels and D-dimer levels in COVID-19 patients. This research method is analytic observational by using cross-sectional secondary data. The population of this study were all COVID-19 inpatients at Budhi Asih Hospital, East Jakarta, with a sample of 338 patients and were taken by random sampling. The results of this study found that female and male COVID-19 patients had the same risk of being infected with female patients as much as 52,7% and male patients amounting to 47,3%. Most COVID-19 patients occurred at the age of ≥60 years, namely 32,2%. All patients, which is 100% patients had high CRP levels, with a mean of 76,06 mg/L. As for D-dimer levels, 47,9% of patients had normal D-dimer levels and 52,1% had high D-dimer levels with an average of 721,48 ng/mL. The results of the Spearman’s correlation test obtained a p value = 0,000, so it can be seen that there is a correlation between C-Reactive Protein (CRP) levels and D-dimer levels in COVID-19 patients with a correlation strength of 0,300 (medium). An increase in CRP levels followed by an increase in D-dimer levels but evaluation of other laboratory examination parameters also needs to be considered.

Keywords: COVID-19; C-Reactive Protein (CRP); D-dimer
Hasil dari penelitian ini didapatkan bahwa pasien COVID-19 berjenis kelamin perempuan dan laki-laki, memiliki risiko yang sama untuk terinfeksi dengan pasien perempuan sebanyak 52,7% dan pasien laki-laki berjumlah 47,3%. Pasien COVID-19 paling banyak terjadi pada usia ≥60 tahun yaitu 32,2%. Seluruh pasien yaitu 100% memiliki kadar CRP yang tinggi, dengan rata-rata 76,06 mg/L. Sedangkan untuk kadar D-dimer, 47,9% pasien memiliki kadar D-dimer normal dan 52,1% memiliki kadar D-dimer yang tinggi dengan rata-rata 721,48 ng/mL. Hasil Uji korelasi Spearman’s didapatkan nilai p = 0,000, sehingga dapat diketahui bahwa terdapat korelasi antara kadar C-Reactive Protein (CRP) dengan kadar D-dimer pada Pasien COVID-19 dengan kekuatan korelasi sedang (r = 0,300). Peningkatan kadar CRP yang diikuti dengan peningkatan kadar D-dimer namun evaluasi terhadap parameter pemeriksaan laboratorium lainnya juga perlu diperhatikan.

Kata Kunci: COVID-19; C-Reactive Protein (CRP); D-dimer

INTRODUCTION

Coronavirus disease 2019 or better known as COVID-19 is a disease caused by infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is a new type of virus discovered from β-coronavirus. The first case of COVID-19 was reported in December 2019 in the city of Wuhan, Hubei Province, China, which then spread to various countries and became a pandemic ([Wilson et al., 2020]). COVID-19 has spread to 223 countries with a total of 1,745,880 cases as of 31 December 2021 (World Health Organization, 2021) and on the same day the Indonesian government reported 4,262,720 confirmed cases of COVID-19 with 144,094 of them declared dead (COVID-19 Handling Task Force, 2021).

DKI Jakarta Province as the capital city of Indonesia had 865,297 positive COVID-19 cases as of December 31 2021, making DKI Jakarta one of the provinces with the highest number of COVID-19 cases in Indonesia and particularly East Jakarta the region as the most COVID-19 cases with cases reaching 213,389 ([Dinas Kesehatan DKI Jakarta, 2022a]). Referral hospitals for COVID-19 patients in the East Jakarta area, one of which is RSUD Budhi Asih (Dinas Kesehatan DKI Jakarta, 2022b).

The SARS-CoV-2 virus spreads through respiratory droplets with an incubation period of 1-14 days (Wilson et al., 2020). Each patient can show different symptoms, with the most common symptoms that can be experienced are fever, cough, fatigue, and loss of the ability to taste and smell. Apart from that, patients can also experience less common symptoms such as sore throat, headache, pain, diarrhea, skin rashes and eye irritation (WHO, 2022). Patients with higher degrees of disease can show severe clinical manifestations such as severe pneumonia,
sepsis, septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS) (Wilson et al., 2020).

With symptoms that have been recognized, examination parameters are needed that can have good diagnostic accuracy in confirming COVID-19. The gold standard for COVID-19 diagnostics is Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) which is a type of Nucleic Acid Amplification Test (NAAT) method (Indonesian Ministry of Health, 2021). In addition, supporting examinations are required such as physical examination, routine hematology and chemistry tests, computed tomography (CT), and serology for COVID-19 immunoglobulin (Carpenter et al., 2020). Laboratory supporting examinations are needed because the virus can damage the vital organs of the heart, liver and kidneys and the main examinations used are complete blood count, coagulation and fibrinolysis tests, and parameters for inflammation examination (Pourbagheri-sigaroodi, 2020).

The SARS-CoV-2 virus attacks the human respiratory tract, especially the cells lining the alveoli. The virus has a glycoprotein in the enveloped spike (Protein S) which then binds to the ACE 2 receptor on the plasma membrane of human cells to infect. The virus will replicate the required genetic material and proteins and form new virions on the cell surface (Levani, Prastya and Mawaddatunnadila, 2021).

When the virus enters the cell, the viral antigen will be presented to the Antigen Presentation Cell (APC) which then T cells and B cells will mediate the immune and cellular system response. The humoral immune system will produce IgM and IgG, but viruses can evade the immune system by inducing double membrane vesicles that do not have pattern recognition receptors (PRRs) and replicating in these vesicles (Levani, Prastya and Mawaddatunnadila, 2021). Proinflammatory mediators such as interleukin 6 (IL-6) and IL-1β also increase and produce CRP in response (McFadyen et al., 2018). Evaluation of C-reactive protein (CRP) levels is routinely used to assess inflammatory markers, the levels of which will then increase in most COVID-19 patients, and can indicate the severity of the disease (Luo et al., 2020). CRP was chosen to evaluate inflammation because it is cheap and easy to perform with very specific results (Zadeh et al., 2018) and has superior diagnostic value compared to procalcitonin (Pourbagheri-sigaroodi, 2020), and can
differentiate well between severe and non-severe pneumonia in COVID-19 (Vita and Syambani, 2020). As a result of the increase in pro-inflammatory mediators that occur, it will cause lung organ damage with the formation of fibrotic tissue (Levani, Prastya and Mawaddatunnadila, 2021). The tissue is broken down into soluble fragments (D-dimers) formed from enhanced fibrin synthesis activating plasminogen and plasmin (Grobler et al., 2020). D-dimer examination, which is a fibrin degradation product, was used because it has proven useful in clinical decision rules for pulmonary embolism (Yu et al., 2020). Potential mechanisms of increased D-dimer levels in patients with COVID-19 are pulmonary endothelial injury with inflammation-related intra-alveolar fibrin deposits as well as systemic endothelial injury with diffuse thrombosis of smaller vessels (Valerio et al., 2021). Elevated D-dimer may effectively contribute to reflect disease progression towards an unfavorable clinical picture (Pourbagheri-sigaroodi, 2020).

In research by Yu et al (2020), it was found that increasing D-dimer levels was related to inflammatory markers, namely CRP. Research by Valerio et al (2021) shows that increased levels of D-dimer and CRP occur in COVID patients with a high level of severity so that these parameters can help monitor disease activity (Valerio et al., 2021). In research conducted in Indonesia by Wardika and Sikersa (2021), it was also found that CRP and D-dimer levels showed a significant relationship with the severity of infection and mortality. However, there has been no research on the correlation between CRP levels and D-dimer levels in COVID-19 patients conducted at Budhi Asih Regional Hospital with data from the first examination after the patient was confirmed positive for SARS-CoV-2 and was treated at the hospital.

Based on the description above, the author wants to analyze the correlation between C-Reactive Protein (CRP) levels and D-dimer levels in COVID-19 patients.

**METHOD**

This research has received permission from the research ethics commission of the Budhi Asih Jakarta Regional General Hospital with ethics letter number No. 50/KEP-ETIK/III/2022 dated March 18 2022. This research is observational analytic with a cross sectional design.

This research, which was conducted at the Budhi Asih Regional General Hospital in January - June 2022, used all data on 1319 COVID-19 inpatients in 2021 at the Budhi
Asih Regional General Hospital as the population and 338 patients were selected as samples by random sampling. The samples used were patients who had odd medical record numbers.

The research procedure begins with submitting a letter of application for an ethical review and research permit to the Poltekkes institution, Ministry of Health, Jakarta III, then the application letter along with the other requirements were handed over to the Budhi Asih Regional Hospital. After the ethics letter and permission letter for data collection have been processed, the medical record data containing CRP and D-dimer data is sorted, with the examination result data is recorded, recapitulated, and is presented in the form of tables and narratives.

Data were analyzed univariately to describe the results of examination of CRP and D-dimer levels in COVID-19 patients at Budhi Asih Regional Hospital in the form of mean, median, standard deviation, minimum value, and maximum value. Bivariate analysis using statistical software for Windows were also carried out using Kolmogorov-Smirnov for data normality distribution and continued with Spearman test because the data is not normally distributed.

RESULTS AND DISCUSSION

Table 1 Frequency distribution of COVID-19 patients based on gender and age at Budhi Asih Regional Hospital in 2021

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>160</td>
<td>47.3</td>
</tr>
<tr>
<td>Woman</td>
<td>178</td>
<td>52.7</td>
</tr>
<tr>
<td>Total</td>
<td>338</td>
<td>100</td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>6-19</td>
<td>7</td>
<td>2.1</td>
</tr>
<tr>
<td>20-29</td>
<td>25</td>
<td>7.4</td>
</tr>
<tr>
<td>30-39</td>
<td>42</td>
<td>12.4</td>
</tr>
<tr>
<td>40-49</td>
<td>66</td>
<td>19.5</td>
</tr>
<tr>
<td>50-59</td>
<td>88</td>
<td>26</td>
</tr>
<tr>
<td>≥60</td>
<td>109</td>
<td>32.2</td>
</tr>
<tr>
<td>Total</td>
<td>338</td>
<td>100</td>
</tr>
</tbody>
</table>

Age categorized based on DKI Jakarta Health Service (https://corona.jakarta.go.id/id/terminologi-lama)

The characteristics of COVID-19 patients can be seen in Table 1 and it is known that the characteristics based on gender consist of 178 people (52.7%) female and 160 male

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patients (47.3%). This is in line with data from the DKI Jakarta Health Service (2022) which shows that almost equal proportions of confirmed cases of COVID-19 are 51.04% female and 48.96% male. In Satria, Kuncioho and Chalidyanto’s (2020) research, results were also obtained with balanced proportions, namely from 253 data, 50.2% of whom were women. A fairly balanced proportion can also be seen in the research of Maryati et al. (2022), namely 55.9% of COVID-19 experienced by men with a total of 501 data. This research also shows that COVID-19 most often occurs in people aged ≥60 years, namely 109 patients (32.2%), followed by with ages 50-59 years, namely 88 patients (26%). This is in line with research conducted by Nanda Nur Illah (2021) which states that the risk of being infected with a virus will increase when a person reaches the age of 40 because a person's immunity tends to decrease so that their susceptibility to pathogens becomes higher. Apart from that, those aged 45-60 years have a high level of productivity and mobility (Nanda Nur Illah, 2021). These results are also reinforced by research conducted by Biswas et al. (2021) which explains that someone over 50 years of age has a higher risk of exposure to the virus and death than those under age, which is related to higher ACE2 gene expression in older patients (Biswas et al., 2021).

**Table 2.** Descriptive analysis of CRP and D-dimer examination results in patients COVID-19 at Budhi Asih Regional Hospital in 2021

<table>
<thead>
<tr>
<th>Variable</th>
<th>SD</th>
<th>Mean</th>
<th>Median</th>
<th>Max.</th>
<th>Min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>65,615</td>
<td>76,06</td>
<td>60,50</td>
<td>200</td>
<td>5</td>
</tr>
<tr>
<td>D-dimer</td>
<td>573,397</td>
<td>721,48</td>
<td>538,50</td>
<td>2000</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2** Frequency distribution of COVID-19 patients based on CRP levels and D-dimer levels at Budhi Asih Regional Hospital in 2021

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRP levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥5 mg/L)</td>
<td>338</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>338</td>
<td>100</td>
</tr>
<tr>
<td><strong>D-dimer levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&lt;500 ng/mL)</td>
<td>162</td>
<td>47.9</td>
</tr>
<tr>
<td>Increased (≥500 ng/mL)</td>
<td>176</td>
<td>52.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>338</td>
<td>100</td>
</tr>
</tbody>
</table>

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Based on Table 3, all subjects from this study, namely 338 patients (100%) experienced an increase in CRP levels with a mean of 76.06 mg/L with a range of 5-200 mg/L which can be seen in Table 2. These results are in line with the theory that the SARS-CoV-2 virus can induce CRP production which is mediated by increased Angiotensin II activity, this plays a role in the severity of COVID-19 (Mosquera-Sulbaran et al., 2021). This theory is also strengthened by research from Chen et al. (2020) which shows that there is a positive relationship between CRP levels and the severity of COVID-19 and the duration of hospitalization, and research by Zhang et al. (2020) explains that the most common laboratory findings for COVID-19 patients is an increase in CRP levels (Zhang et al., 2020). Meanwhile, in the D-dimer level variable, 162 patients (47.9%) had normal levels and the other 176 patients (52.1%) experienced an increase with a mean of 721.48 ng/mL with a level range of 100-2000 ng/mL. This is in line with research conducted by Shi et al. (2020) which shows that coagulopathy that occurs in patients shows increased levels of D-dimer as well as research by Zhou et al. (2020) which states that there are COVID-19 patients with increased levels of D-dimer and some have not increased. After attachment of the SARS-CoV-2 virus then ACE2 dysregulation will occur and then angiotensin II regulation will increase and induce plasminogen activator inhibitor-1 (PAI-1) which is a suppressor of fibrinolysis and may also explain the fibrin deposits seen in the lung alveoli (Manzoor et al., 2021). Due to the high fibrinolytic capacity of the lungs, vigorous fibrinolysis occurs which causes the production of D-dimer in the bloodstream (Samprathi and Jayashree, 2021).

Table 3: Cross tabulation of CRP and D-dimer examination results in patients COVID-19 at Budhi Asih Regional Hospital in 2021

<table>
<thead>
<tr>
<th>Variable</th>
<th>D-dimer levels</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Increased CRP levels</td>
<td>162</td>
<td>176</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>176</td>
</tr>
</tbody>
</table>

Table 4 shows that there were 162 COVID-19 patients who experienced increased CRP levels but had normal D-dimer levels, while 176 patients experienced increased CRP levels followed by increased D-dimer levels. This is in line with the results of research by Ullah et al. (2020) which explains that increasing D-dimer levels is a more sensitive
marker of severity, so that increasing CRP levels followed by increasing D-dimer levels will result in high disease severity as well as in research Zhu et al. (2020) stated that the majority of patients with high and critical severity experienced increased CRP levels and D-dimer levels.

Patients who have high CRP levels but normal D-dimer levels can occur because the data used is data from the first examination (screening) after the patient was confirmed positive for SARS-CoV-2, besides that CRP, which is an acute phase protein, can increase first before coagulation occurs. inside the body. Meanwhile, patients who have both high CRP and D-dimer levels can experience hyperinflammation triggered by chronic inflammatory comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease (smokers), coronary heart disease, kidney failure, as well as autoimmunity and age continued (Sumantri, 2022). In research data, it is known that COVID-19 often occurs at ages ≥ 60 and patients are at very high risk of having comorbid diseases that cause hyperinflammation, so in this study the results showed high CRP levels followed by high D-dimer levels.

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP levels</td>
<td>0.000</td>
</tr>
<tr>
<td>D-dimer levels</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The results of the data normality test using the Kolmogorov-Smirnov test showed that CRP levels and D-dimer levels had a p-value = 0.000 (p<0.05). It can be concluded that both data have a non-normal distribution, so the Spearman test is used for correlation test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>CRP levels</td>
<td>338</td>
</tr>
<tr>
<td>D-dimer levels</td>
<td></td>
</tr>
</tbody>
</table>

The Spearman correlation test in Table 6 revealed p = 0.000 so there is a correlation between C-Reactive Protein (CRP) levels with D-dimer levels in COVID-19 patients with moderate correlation strength (r = 0.300). In this study, moderate correlation
results were obtained with a positive test direction, meaning if there is an increase in CRP levels it can be followed by an increase in D-dimer, but not in every case of COVID-19 patients. The results of this study are in line with the results of research conducted by Yu et al. (2020), namely that there is a moderate correlation between CRP levels and D-dimer levels ($r = 0.426$, $P < 0.05$) and in research conducted by Wati et al. (2021) also showed moderate correlation results in a positive direction towards CRP and D-dimer levels in COVID-19 patients ($r = 0.517$; $p = 0.000$).

**CONCLUSION**

Research conducted at the Budhi Asih Regional General Hospital with data on 338 COVID-19 patients for the period January – December 2021 concluded that COVID-19 dominantly occurred in women (52.7%) at vulnerable ages of $\geq 60$ years (32.2%). Meanwhile, all patients revealed an increase in CRP levels in comparison with D-dimer levels which were varied (176 patients of high-level group and 162 patients of normal group). Analysis of both CRP and D-dimer indicated that there is a correlation between CRP levels and D-dimer levels ($P = 0.000$) with a positive direction and moderate strength ($r = 0.300$), meaning high CRP levels can be followed by high D-dimer levels, age and comorbid diseases can be factors in the high levels of both that. Nevertheless, evaluation of other laboratory examination parameters also needs to be considered.

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