D-dimer correlation as a marker of coagulopathy with neuroimaging abnormalities on head CT scans of COVID-19 patients

Anak Agung Dewi Adnyani¹,², Farhan Anwary²

ABSTRACT

Background: COVID-19 is a coronavirus disease with the main symptoms in the respiratory tract which can cause hypoxia. The duration and severity of the hypoxia can lead to oxidative stress that can affect the brain. The phenomenon of thromboembolism was also found in the form of an increase in coagulopathy markers which can cause abnormalities in small blood vessels in various organs, including the brain.

Methods: We conducted a prospective cross-sectional study of 23 samples that met the inclusion criteria. Duration of hypoxia, degree of hypoxia based on oxygen saturation, and D-Dimer level as independent variables underwent Spearman correlation test with neuroimaging abnormalities on head CT scan.

Results: The sample population consisted of 14 men (60.90%) and 9 women (39.10%), with the highest age group being 61–80 years old (56.50%) who underwent a head CT scan without contrast administration. Eighteen samples were found to have brain infarction, while 5 samples were without abnormalities. The Spearman correlation test found a correlation (p=0.003) with moderate correlation (r=0.558) between the D-Dimer level as a coagulopathy marker and abnormal findings on the head CT scan of samples. Where 15 samples with high D-Dimer levels (D-Dimer values above the normal level) and 3 samples with normal D-Dimer levels were found to have brain infarction. Meanwhile, the duration and degree of hypoxia based on the oxygen saturation value did not show a significant correlation with neuroimaging abnormalities (p>0.05).

Conclusion: There was a moderate correlation between the D-Dimer value. No significant correlation was found between the duration of hypoxia and the degree of oxygen saturation toward neuroimaging abnormalities in COVID-19 patients.

Keywords: COVID-19, D-Dimer, head computed tomography.

INTRODUCTION

COVID-19 is the fifth coronavirus pandemic since 1918. The first case was reported as viral pneumonia on December 1, 2019, in Wuhan, China. Symptoms of coronavirus are usually mild upper respiratory tract disorders. Still, two types of viruses, namely SARS-CoV and MERS-CoV, can cause severe pneumonia symptoms and even cause death in humans. This virus is highly contagious, continuously evolving and widespread in human populations worldwide.¹

Abnormalities in the lungs associated with infection (such as occurs in COVID-19 infection) accompanied by widespread inflammation of the respiratory tract, airway obstruction, respiratory tract remodeling and emphysema can cause decreased oxygenation in the blood and tissues (hypoxia).² The virus can take many pathways until it finally enters the brain. It is suspected that the SARS-CoV-2 virus binds to angiotensin-converting enzyme type II at the entrance of the virus through the mouth, nose, and eyes and is widely distributed to the lungs, heart, liver, kidneys and intestines. So that the virus can simultaneously infect the brain through the blood vessel system, peripheral nervous system, lymphatics and cerebrospinal fluid.³ After physical contact of the virus with the mucosa of the laryngopharynx, trachea, lower respiratory tract, alveolar epithelium, and gastrointestinal tract SARS-CoV-2 can trigger an immune response in the host body that causes increased cytokine release, increased tissue damage, and increased nervous susceptibility to COVID-19, especially in hypoxic conditions caused by lung damage.³

Coagulopathy abnormalities may cause thromboembolism in severe COVID-19 patients. It is uncertain whether hypercoagulation is a primary effect of viral interaction with the endothelium wall, even without nerve invasion or is due to an abnormal inflammatory response initiated by the virus. The phenomenon of thromboembolism in COVID-19 is mainly found in acute cases and several subacute and chronic cases. We suspected a correlation between hypoxia conditions (length and degree of hypoxia) and coagulopathy in COVID-19 patients in the presence of neuroimaging abnormalities.
METHOD

We conducted a prospective cross-sectional study of 23 samples that met the inclusion criteria; COVID-19 patients between June and October 2021 at Bangli Hospital who experienced mild to severe neurological symptoms without a history of stroke or degenerative brain disorders underwent a head CT scan without contrast using consecutive sampling technique. Duration of hypoxia, degree of hypoxia based on oxygen saturation, and D-Dimer level as independent variables underwent Spearman correlation test with neuroimaging abnormalities on head CT scan. All independent variables are numerical data collected from medical record documentation. While the neuroimaging picture of COVID-19 patients was evaluated from the results of a head CT Scan without contrast at the radiology department of Bangli Hospital using a 16-slice GE CT Scan by a radiologist with >5 years of experience. The independent variable is declared to correlate with the dependent variable if the 2-tailed significant value is less than 0.01. the strength of the relationship is determined by the value of the correlation coefficient. Data were analyzed using SPSS version 20 for Windows

RESULTS

Twenty-three samples that met the inclusion and exclusion criteria were obtained in this study. The research sample consisted of 14 men (60.90%) and 9 women (39.10%), with the highest age group of 61-80 years of 13 people (56.50%) (Table 1).

From all samples, it was found that the longest hypoxic condition was 14 days in 1 subject, and the lowest oxygen saturation was 72.00% in 1 subject. There were 10 subjects without a decrease in oxygen saturation. The value of D-Dimer as a marker of coagulopathy increased in 17 subjects, with the highest D-Dimer value of >10,000 ng/ml found in 2 subjects. All samples underwent head CT scans, and abnormalities were found in 18 samples (72.80%), consisting of 17 samples with lacunar infarction and one with watershed infarction, while five samples were without abnormalities (Figure 1).

<table>
<thead>
<tr>
<th>Age group (year)</th>
<th>Male, n (%)</th>
<th>Female, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18 - 20</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>21 – 40</td>
<td>2 (8.70)</td>
<td>1 (4.40)</td>
<td>3 (13.00)</td>
</tr>
<tr>
<td>41 - 60</td>
<td>3 (13.00)</td>
<td>3 (13.00)</td>
<td>6 (26.10)</td>
</tr>
<tr>
<td>61 - 80</td>
<td>8 (34.80)</td>
<td>5 (21.70)</td>
<td>13 (56.50)</td>
</tr>
<tr>
<td>≥ 81</td>
<td>1 (4.40)</td>
<td>0 (0.00)</td>
<td>1 (4.40)</td>
</tr>
<tr>
<td>Total</td>
<td>14 (60.90)</td>
<td>9 (39.10)</td>
<td>23 (100.00)</td>
</tr>
</tbody>
</table>

Figure 1. Lacunar infarction in the left internal capsule in a normal D-Dimer(a) sample. Lacunar infarction in the left corona radiata in an elevated D-Dimer(b) sample. Watershed infarction in samples with D-Dimer value > 10,000 ng/ml(c).

Table 1. Samples characteristics

<table>
<thead>
<tr>
<th>D-Dimer value (ng/ml)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500</td>
<td>6 (26.00)</td>
</tr>
<tr>
<td>501 – 1000</td>
<td>5 (21.70)</td>
</tr>
<tr>
<td>1001 – 2000</td>
<td>2 (8.70)</td>
</tr>
<tr>
<td>2001 – 3000</td>
<td>4 (17.50)</td>
</tr>
<tr>
<td>3001 – 4000</td>
<td>2 (8.70)</td>
</tr>
<tr>
<td>4001 – 5000</td>
<td>2 (8.70)</td>
</tr>
<tr>
<td>9001 - 10000</td>
<td>2 (8.70)</td>
</tr>
<tr>
<td>Total</td>
<td>23 (100.00)</td>
</tr>
</tbody>
</table>

Table 2. Samples distribution based on D-Dimer

There were 15 samples (65.00%) with D-Dimer above the normal value who had neuroimaging abnormalities in the form of lacunar infarcts in 14 samples and watershed infarcts in one sample, which had very high D-Dimer values (>10,000 ng/ml). Three samples (13.00%) with normal D-Dimer values had neuroimaging abnormalities in the form of lacunar infarction (Table 2).

Based on the classical assumption test and the one-sample Kolmogorov-Smirnov test, the data distribution was abnormal, so the parametric test cannot be applied. Spearman nonparametric test was conducted to assess the correlation between variables. The results found were a correlation between the D-Dimer value and neuroimaging abnormalities in COVID-19 patients (significant 2-tailed value 0.003), which was smaller than the value α 0.01 and has a moderate correlation (correlation coefficient value 0.588).

While the duration of hypoxia and the degree of oxygen saturation in statistical tests were found to be unrelated to neuroimaging abnormalities of COVID-19 patients, where the significant 2-tailed value for the duration of hypoxia was 0.206 and for oxygen saturation was 0.610, both of these values were greater than the value α 0.01.

DISCUSSION

Approximately 72.80% of the samples had neuroimaging abnormalities in lacunar and watershed infarcts, and 65% had elevated D-Dimer values. This is in line with the findings in New York, where the incidence of thromboembolic infarcts such as lacunar infarcts, extensive infarcts, and watershed infarcts are common in COVID-19 patients.44 Similarly, in a...
cohort study by Helms J it was found that 95% of COVID-19 patients with thrombotic complications had elevated D-Dimers and fibrinogen.7

In the Journal The Spectrum of Neuroimaging Findings on CT and MRI in adult coronavirus disease, it was said that there was a suspicion of a mechanism of endotheliopathy in which the virus interacts directly with the vascular endothelium so that abnormalities were found in the patient even though the inflammatory parameters, coagulation was within normal limits.8 And in this study, we found 3 samples with those criteria. Another thing that must be considered is the presence of comorbid disorders that accompany the patient, especially in the elderly group, such as in this study where the age group is 61-80 years old and diabetes mellitus, and hypertension are found. These comorbid disorders can trigger atherosclerosis in small vessels, which can cause neuroimaging disorders.8

The duration of hypoxia and the degree of oxygen saturation in this study were unrelated to neuroimaging abnormalities of COVID-19 patients. This is different from the findings in the journal by Maurya VK et al., which mentioned neuroimaging abnormalities that can be found in hypoxic conditions such as infarction.9 In an article in Neurology Harvard Medical School it was explained that the effect of hypoxia on brain cells was more significant when it occurs together with ischemic conditions. In contrast, pure hypoxia activates brain autoregulation to increase cerebral blood flow (CBF). From this study, it can be assumed that hypoxia without ischemic factors is less associated with abnormalities in the brain, but there can be a joint contribution between coagulopathic conditions that can cause ischemia and hypoxic conditions in causing brain abnormalities in COVID patients.10-12

CONCLUSION
There was a moderate correlation between the D-Dimer value. No significant correlation was found between the duration of hypoxia and the degree of oxygen saturation toward neuroimaging abnormalities in COVID-19 patients. For further research, we recommend that it be carried out with a larger sample size to meet the normality of the data distribution so that multivariate parametric tests can be applied and also consider the comorbid status of COVID-19 patients, which may be a confounding variable.

CONFLICT OF INTEREST
There was no conflict of interest from the writers in this research.

ETHICAL CONSIDERATIONS
This study has been approved by the Ethic Commission for Public Health, Bangli General Hospital.

FUNDING
The author is responsible for funding this research without involving other parties.

AUTHOR’S CONTRIBUTION
The authors contributed equally to the writing of this research report, from the stage of proposal preparation, data collection and analysis to the preparation of reports in the form of publications.

REFERENCES

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