The characteristics and pathophysiological mechanisms of stroke in COVID-19 patients
Saltanat Mert1*, Dila Zafer1, İbrahim Acur2, Çağrı Erdim3, Murat Çabalar1

INTRODUCTION
In 2019, several unexplained pneumonia cases were diagnosed in China. Later, similar cases were reported worldwide, creating a pandemic. SARS-CoV-2 causes COVID-19. Fever, dry cough, dyspnea, and hypoxia are the characteristic symptoms. Interstitial pneumonia features are present on thoracal X-ray or computed tomography (CT) scan (1,2) Nevertheless, COVID-19 affects organs beyond the respiratory system, including the central nervous system (CNS). Patients who have had COVID-19 may present with symptoms such as headache, seizure, mental status changes, and anosmia (38, 39, 40, 41). Neuromuscular disorders and stroke are among the most common manifestations of COVID-19 (41).

Cerebrovascular disease (CVD) is one of the complications of COVID-19 and may represent both ischemic and haemorrhagic stroke (3,4). The relation of COVID-19 and stroke has been studied well (42,43,44). Although there have been many studies reported regarding the pathophysiological mechanism of stroke in COVID-19 patients (10,45,46), it was not completely understood.

ABSTRACT

Objective: Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome (SARS)-like coronaviruses (SARS-CoV-2). Although the respiratory system is mainly affected, multiple organ systems like the central nervous system (CNS) might be complicated by COVID-19. Stroke is one of the most common complications of COVID-19. In the literature, the symptoms and effects of COVID-19 on stroke have been reported but potential reasons and results remain unclear. In this study, we aimed to determine whether COVID-19 plays a role in stroke and affects the prevalence of stroke and mortality by investigating blood parameters, day of stroke after COVID-19, death status, and infarct volume.

Methods: In this cross-sectional clinical research, 74 individuals participated. Twenty-two patients were COVID-19 cases without stroke; thirty participants were patients with COVID-19 and stroke, while twenty-two were cases of non-COVID-19 and stroke. Data were collected from a single center, Basaksehir Cam and Sakura City Hospital and were presented as mean ± standard deviation (SD).

Results: There was a statistically significant relationship among the age, D-dimer, INR, and lymphocyte values of the living group compared to those of the exitus group. The association between death and COVID-19 status was found to be statistically significant, indicating that the number of deaths in the COVID-19 and stroke group was higher than in the only stroke group (i.e., non-COVID-19 cases). No statistically significant relationship was observed between the alive and exitus groups in terms of the volume of infarction.

Conclusions: This study comprehensively evaluated the relationship between COVID-19, stroke, and mortality. Given the relatively limited number of cases in this study, further investigation is needed to elucidate the connection among COVID-19, neurological complications of the disease, and mortality. In the meantime, the results of this study contribute to the understanding of the relationship between COVID-19, neurological complications, and mortality, providing additional valuable data to the existing literature.

Keywords: Ischemia; retrospective; acute phase reactant; anticoagulant; antiaggregant; infarct
Since there are several stroke cases following COVID-19 in the literature, we aimed to determine stroke in COVID-19 and its possible relationship with age, sex, acute phase reactant (APR), platelet (PLT), white blood cell (WBC), procalcitonin (PROC), D-dimer, international normalized ratio (INR) levels, the time between COVID-19 symptom beginning and the infarct volume. We aimed to enlighten pathophysiological mechanisms and characteristics of stroke development in COVID-19 patients.

MATERIAL and METHODS

Experimental procedure

The present research was a retrospective, cross-sectional clinical study. All participants were patients hospitalized in Basaksehir Cam and Sakura City Hospital, Istanbul, in the neurology in-patient clinics between January 2021 and December 2021. Participants with negative COVID-19 PCR tests and no pneumonia findings in the thoracic CT scan but with stroke were included in the COVID-19 – negative only-stroke patient group. In contrast, the ones with negative COVID-19 PCR tests, no pneumonia in the thoracic CT scan, and no stroke were included in the only- COVID-19–positive patient group. Ischemic stroke patients between April 2021 and September 2021 with positive COVID-19 PCR tests were included in COVID-19–positive ischemic stroke groups.

Statistical Analysis

The 2021 NCSS (Number Cruncher Statistical System) program was used for statistical analysis (2007, Kaysville, Utah, USA). While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) and the data distribution were evaluated with the Shapiro-Wilk Test. The Mann-Whitney U Test was used to compare two groups of quantitative data. Chi-square analysis was used to determine the relationship between qualitative data. Logistic regression analysis was performed to determine the factors affecting the dependent variable. Significance was evaluated at p<0.01 and p<0.05 levels.

RESULTS

The ages of participants ranged from 39 to 90, averaging 68.31±13.9 years. COVID-19 symptom onset days ranged from 1 to 28, with an average of 5.63±6.55 days. Of the participants, 75.7% (n=56) were alive, while 24.3% (n=18) died. There were 27 (36.5%) female and 47 (63.5%) male participants. Among the participants, 75.7% of them (n=56) had an additional disease, while 24.3% of them (n=18) did not. While 52.7% (n=39) of the participants were under AA or AC treatment, 47.3% (n=35) were not. Although 7.7% (n=4) of the participants had large vessel occlusion, 92.3% (n=48) did not. The living group’s age was lower than the exitus group’s (p=0.001; p<0.05).

The C-reactive protein (CRP) value ranged from 0.8 to 217.3 mg/L, with an average of 66.03±65.73 mg/L. WBC values ranged from 1060 to 27340 per microliter, with a mean of 8606.89±3992.94 per microliter. The PROC value ranged from 0.2 to 50.5 mg/mL, averaging 1.57±7.46 mg/mL. The D-dimer value ranged from 0.2 to 35.2 g/L, with an average of 3.45±6.57 0.2 g/L. The fibrinogen value was between 60 and 871 mg/dL, with a mean of 457.79±187.24 mg/dL. The INR value varied between 0.9 and 3.18, with a mean of 1.13±0.28. The PLT value was between 56000 and 604000 per microliter, with an average of 239000±104318.66 per microliter. The lymphocyte value ranged from 170 to 4080 per microliter, with an average of 1459.46±947.48 per microliter (table 1). The infarct volume value was between 25.398 and 115995 cm3, with an average of 16373.58±28441.76 cm3.

The COVID-19 symptom onset day, CRP, WBC, and PROC values did not show a statistically significant difference according to death status (p>0.05). The D-dimer value of the living group was lower than that of the exitus group (p=0.001; p<0.05) (figure 1). The fibrinogen values showed a statistically insignificant difference according to death status (p>0.05) (figure 1). The INR value of the living group was lower than that of the exitus group and was statistically significant (p=0.001; p<0.05). The PLT value did not show a statistically significant difference according to death status (p>0.05). The lymphocyte value of the living group was higher than that of the exitus group (p=0.001; p<0.05) while the volume values did not show a statistically significant difference according to the death status (p>0.05).

A statistically significant relationship was found between death and disease status (p=0.001; p<0.01). It was found statistically significant that the number of deaths in the covid and stroke group was higher than the only stroke and covid group (p=0.001; p<0.01). The relationship between death status and gender was statistically insignificant (p>0.05) while there was statistically insignificant relationship between mortality and comorbidity (p>0.05). There was no statistically significant relationship between mortality and AA/AC use (p>0.05), and the relationship between death status and large vessel occlusion was statistically insignificant (p>0.05).

Multiple logistic regression analysis revealed (table 2) that the effect of independent variables on mortality was statistically significant (X2=27.663, p<0.001). The independent variables in the model explained 31.2% of the total variance in abuse (p<0.01). When the regression coefficients were examined, it was found that age (β=0.898, p<0.01) and COVID-19 and stroke (β=0.105, p<0.01) variables had a positive and significant effect on mortality. As a result, the age of the exitus group was higher than that of the living group, and it was found statistically significant that the morbidity of the group with COVID-19 and stroke was higher than that of the living group (p=0.001; p<0.01).
Table 1. Blood parameters mean and median values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±Sd</th>
<th>Min-Max (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (CRP)</td>
<td>66,03±65,73</td>
<td>0.8-217.3 (42)</td>
</tr>
<tr>
<td>White blood cells (WBC)</td>
<td>8606,89±3992.94</td>
<td>1060-27340 (8115)</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>1.57±7.46</td>
<td>0.02-50.5 (0.15)</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>3.45±6.57</td>
<td>0.2-35.2 (0.95)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>457,79±187,24</td>
<td>60-871 (420)</td>
</tr>
<tr>
<td>International normalized ratio (INR)</td>
<td>1,13±0.28</td>
<td>0.9-3.18 (1.04)</td>
</tr>
<tr>
<td>Platelets (PLT)</td>
<td>239000±104318.66</td>
<td>56000-604000 (225500)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>145946±947,48</td>
<td>170-4080 (1270)</td>
</tr>
<tr>
<td>Infarct Volume</td>
<td>16373,58±28441.76</td>
<td>25,398-115995 (2953,55)</td>
</tr>
</tbody>
</table>

Table 2. Logistic regression analysis results

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>S. error</td>
</tr>
<tr>
<td>1</td>
<td>Age</td>
<td>-0.089</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Covid and stroke</td>
<td>-2.169</td>
<td>0.639</td>
</tr>
<tr>
<td></td>
<td>Only covid</td>
<td>2.322</td>
<td>1.065</td>
</tr>
</tbody>
</table>

**p<0.01  *p<0.05

Figure 1A: This figure shows the mean value of d-dimer and fibrinogen.* means p=0.006. Mean of fibrinogen level does not differ between the groups.

Figure 1B:

Figure 1A and 1B: This figure shows the mean value of d-dimer and fibrinogen.* means p=0.006. Mean of fibrinogen level does not differ between the groups.
DISCUSSION

Cerebrovascular disease (CVD) is one of the complications of COVID-19. The mechanisms of cerebrovascular manifestations in patients with COVID-19 are multifactorial. They might be related to conventional stroke mechanisms triggered by COVID-19. On the other hand, they could be caused by COVID-19 (5,6,7).

As presented in our results, coagulation cascade activation resulting in increased d-dimer value in the exitus group might be an important finding to understand mortality risk in COVID-19 and stroke patients. Our study showed that the time point of stroke development after COVID-19 incidence was very similar to the findings shown in the other studies. In addition to that, our findings presented the high mortality rate in patients with stroke and COVID-19. Moreover, we showed the affect of age and INR value on mortality among the groups.

The activation of the coagulation pathway with high D-dimer and fibrinogen levels is a common feature of severe COVID-19 infections. This coagulopathy, named sepsis-induced coagulopathy (SIC), is related to the infection-induced systemic inflammatory response and may increase thrombosis and stroke risk (8, 9). The D-dimer value of the living group in our study was lower than that of the exitus group (p=0.001; p<0.05), which is entirely compatible with this information and these studies (8, 9). In addition, anti-phospholipid (aPL) antibodies, including IgA anti-cardiolipin, Immunoglobulin (Ig) A, and IgG beta 2 glycoprotein I antibodies, have been reported in critically infected patients with cerebral infarcts (10, 11). Hypercoagulability may lead to ischemic stroke resulting in venous thromboembolism and paradoxical embolism that can explain stroke from large vessel occlusion in young people without any vascular risk factors, where plaque rupture or in situ thrombosis is less possible (12). SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor to enter the cells (13). This receptor is expressed in the lungs, heart, kidneys, and vascular endothelium, and viral invasion of endothelial cells causes inflammation or endothelitis, as one of the substrates for the thrombotic complications of COVID-19 (14). Besides, the binding of SARS-CoV-2 to the ACE-2 receptor causes a decrease in its availability via endocytosis and, in the end, a down-regulation of the renin-angiotensin system (RAS) (15). The unrestricted generation of Angiotensin II, no more amended by Angiotensin 1-7, aggravates lung injury and is responsible for endothelial dysfunction. This state may lead to increased sympathetic activity, blood pressure dysregulation, and vasoconstriction, resulting in ischemia (16).

The nonstop and unbalanced immune system activation by the viral infection results in excessive cytokine release (i.e. cytokine storm), which may cause brain damage. Cytokines/chemokines accelerate atherosclerosis, plaque rupture, and thrombosis (17). Together with endothelial damage, they promote tissue factor (TF) expression and a prothrombotic state (18).

Various myocardial injury types, including viral myocarditis, have been reported previously. The myocardial dysfunction caused by the cytokine storm, oxygen supply and demand mismatch, and stress cardiomyopathy because of the sympathetic nervous system stimulation may lead to cardiac arrhythmias and intracardiac thrombus formation. All these may increase the risk of cardioembolic stroke (19, 20).

Some patients with COVID-19 may be sensitive to cerebrovascular damage from hypoxemia (21). For those with pre-existing intracranial stenosis, hypoxemia can cause infarction because of a mismatch between oxygen supply and demand (22). Cerebral hypoperfusion due to the RAS down-regulation may increase the large vessel and SVD infarction risk (23, 24).

COVID-19-related haemorrhagic strokes are less common than ischemic strokes (7). The affinity of the SARS-CoV-2 for ACE-2 receptors lets the virus damage intracranial arteries, resulting in vessel wall rupture. The RAS down-regulation raises blood pressure and puts patients at a higher risk for haemorrhagic stroke (25). Therefore, older individuals with age-related ACE-2 deficiency are especially exposed to the intracranial hemorrhage (ICH) risk.

The cytokine storm can impair the integrity of the blood–brain barrier (BBB) during the SARS-CoV-2 infection (25, 26). In addition to ICH, the BBB breakdown may enlighten the haemorrhagic posterior reversible encephalopathy syndrome (PRES) cases and haemorrhagic transformation of ischemic strokes in COVID-19 (27).

COVID-19 can cause coagulopathy related to fibrinogen consumption that may increase ICH risk (5). Perivascular microhemorrhages visible on susceptibility-weighted (SW) MRI have been reported in COVID-19 as neurologic complications (28). Their location in the corpus callosum, the subcortical and deep white matter, resembled the anatomical distribution found in patients with hypoxic-ischemic encephalopathy, suggesting a potential role of cerebral hypoxia in brain damage during COVID-19 (28).

In a recent review on COVID-19 and stroke, the median age was 65.3 (61.4–67.6) years, and the majority was male (62.4%) (7). In the present study, the ages ranged from 39 to 90, averaging 68.3 (61.4–67.6) years, and the majority was male (62.4%) (7). In the present study, the ages ranged from 39 to 90, averaging 68.3±13.9 years, and 63.5% (n=47) were male, which was compatible with the literature.

A meta-analysis of 95 Chinese and American studies, including approximately 30 million tested individuals, demonstrated that 40.5% of SARS-CoV-2-infected individuals were asymptomatic (29). The incubation period for COVID-19 is usually within 14 days following exposure; in most cases, symptoms occur about four to five days after exposure. According to our study, the COVID-19 symptom onset day value ranged from 1 to 28, with an average of 5.63±6.55 days, similar to some of the previous studies (30, 31, 32). The living group’s age value was lower than the exitus group’s (p=0.001; p<0.05), which meant that older patients were more prone to death. This finding supported the recent reviews (7).

Sepsis is a term used to describe the often life-threatening systemic host response to infection.
The exaggerated inflammatory response in sepsis may lead to multisystem organ dysfunction (MODS). Inflammation and disturbances in coagulation are firmly related and act as positive feedback for the activation of the other (33). Coagulation abnormalities are common in sepsis and play a significant role in MODS, leading to coagulopathy of acute sepsis (CAS). The CAS may vary from thromboembolism to microvascular fibrin deposition. In the worst cases, fulminant disseminated intravascular coagulation (DIC) is characterized by disseminated thrombosis and haemorrhage (34). Therefore, the measurement of coagulation disturbances in acute sepsis is fundamental. Classical coagulation laboratory tests (CCTs) like prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen have limitations. CCTs do not show in-vivo coagulation and do not provide us with qualitative or functional information (35). So, more coagulation tests like INR are essential. The more INR gets, the higher the fatal sepsis is. We found that the INR value of the living group was lower than that of the exitus group and was statistically significant (p=0.001; p<0.05), which supported previous data.

Lymphopenia or lymphocytopenia is a condition with low blood counts of lymphocytes. In recent studies, about 85% of the highly ill patients of COVID-19 were lymphopenic (36). T cells may increase at the beginning of COVID-19, but patients tend to have a low lymphocyte count, which is associated with increased COVID-19 fatality. Hence, patients who died of COVID-19 had lower lymphocyte levels than survivors (37). In our study, the lymphocyte value of the living group was statistically higher than that of the exitus group (p=0.001; p<0.05), which was an expected result.

It was found that the COVID-19 and stroke group had the number of deaths higher than the only stroke and COVID-19 group (p=0.01; p=0.01). Similar to our study, it was found that despite receiving the same acute stroke treatments in equal proportions, patients with stroke and COVID-19 infection showed higher mortality than non-COVID-19 patients with stroke (7). An additional stroke status was expected to be much more mortal than a non-stroke COVID-19 state.

There were only 74 participants in this retrospective cross-sectional study. A prospective and longitudinal study with a larger group could supply more data.

CONCLUSION

In conclusion, this study was one of the studies that evaluated COVID-19, stroke, and mortality in detail. The relationship between COVID-19, neurological complications of the disease, and mortality may need further clarification. Therefore, the results of this study could be used to explain the relationship between COVID-19, neurological complications of the disease, and mortality and supply valuable data in the literature.

Acknowledgements: None

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions: SM, DZ, İA, ÇE, MC; Designed and directed the study, Literature search, Data collection, SM: Article writing, Final revisions. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee.

REFERENCES


