

Prevalence of symptomatic acute cerebral infarction among patients with COVID-19 and D-dimer as a predictor of cerebral infarction

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Abstract

Objectives: This study sought to investigate the frequency of symptomatic acute cerebral infarction (sACI) among patients with novel coronavirus (COVID-19) disease and the predictive value of laboratory parameters such as D-dimer and neutrophil-to-lymphocyte ratio (NLR) in sACI. **Methods:** This retrospective case-control study analyzed the data of 2,378 patients with COVID-19 registered in our database between April 1, 2020 and November 30, 2020. Of these patients, a total of 119 subjects were included in the study, including 31 COVID-19 patients with sACI (patient group) and 88 randomly selected COVID-19 patients without sACI (control group). Categorical variables were compared using Chi-square test and predictive value of the variables was analyzed using receiver operating characteristics (ROC) curve analysis. **Results:** Thirty one (1.30%) of 2,378 COVID-19 patients had sACI. Mann-Whitney U test showed that median D-dimer, neutrophil and NLR values were significantly higher in the sACI group compared to the control group ($p = 0.004$, $p < 0.048$ and $p = 0.007$, respectively). ROC analysis yielded the following areas under the ROC curve: D-dimer = 0.674 (95% CI, 0.569-0.779), NLR = 0.663 (95% CI, 0.559-0.767) and neutrophils = 0.620 (95% CI, 0.509-0.73).

Conclusion: The results of the present study showed that elevated D-dimer levels can be used as a predictor of sACI in COVID-19 patients.

Keywords: COVID-19 disease, symptomatic, D-dimer, acute cerebral infarction, frequency, neutrophil/lymphocyte ratio

INTRODUCTION

The novel coronavirus (COVID-19) disease emerged in Wuhan, China in 2019 and resulted in a pandemic, causing millions of deaths worldwide.¹ In addition to being a fatal disease, it has been shown to affect many organ systems, thereby causing a variety of diseases in humans. Associated neurological diseases include Guillain-Barré syndrome, Miller-Fisher syndrome, ischemic and hemorrhagic stroke, cerebral venous thrombosis, epileptic seizures, posterior reversible encephalopathy syndrome, meningoencephalitis and acute myelitis.² Previous studies have investigated inflammatory parameters such as neutrophil-to-lymphocyte ratio (NLR)³ and C-reactive protein (CRP) that may be associated with ischemic stroke in COVID-19 disease.⁴ However, the association between D-dimer and symptomatic acute cerebral infarction (sACI) concomitant with COVID-19 has not been well

characterized.

This retrospective study was designed based on the hypothesis that elevated D-dimer and NLR levels may serve as predictors of sACI concomitant with COVID-19. This study also investigated the frequency of sACI among COVID-19 patients.

METHODS

Data of 2,378 patients with COVID-19 who were hospitalized and treated for COVID-19 at Aksaray University Training and Research Hospital between April 1, 2020 and November 30, 2020 were screened using our database. Of these patients, 119 subjects were included in the study, including 31 patients with sACI (patient group) and 88 non-sACI patients (control group). Subjects were included if they had a definite diagnosis of COVID-19 confirmed by PCR test, were above 18 years of age, had complete data, had

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sACI concomitant with COVID-19 or developed sACI within one week while receiving treatment for COVID-19.

Laboratory parameters of the patients were analyzed using an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan) in the hematology laboratory of our hospital. C-reactive protein-to-albumin ratio (CAR) was calculated using the C-reactive protein level divided by the albumin level and NLR was calculated using neutrophil count divided by lymphocyte count.

This study received ethical approval from Aksaray University Human Research Ethics Committee (dated 18.12.2020 and protocol number 2020/13-24) and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Results were presented as mean \pm standard deviation for normally- distributed data, median (min- max) for abnormally- distributed data. To investigate the distribution pattern of the data, Kolmogorov- Smirnov normality test was used. The age, albumin and hemoglobin data distributed normally, thus Student's independent samples *T* test was used for comparison; and the other blood test parameters did not distribute normally, thus Mann Whitney U test was used for comparison. To compare the categorical variables, we used Chi- square test. To assess the predictive value of variables, receiver operating characteristics (ROC) curve analysis test was used. If the area under the ROC curve is 0.5, the model does not discriminate; 0.5-0.7, the model has poor to fair discrimination; 0.7-0.8, the model has acceptable discrimination; 0.8-0.9, the model has excellent; 0.9-1.0, is a very rare outcome.⁵ For statistical analysis of all data, we used SPSS 23.0 software for MacOS (SPSS Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered statistically significant.

RESULTS

sACI was detected in 31 (1.30%) of 2378 COVID-19 patients registered in our hospital database. This study was conducted with a total of 119 COVID-19 patients, 88 (control group) without sACI and 31 patients with sACI, randomly selected from 2378 COVID-19 patients. The sACI group consisted of 31 patients (15 males and 16 females, mean age: 74.35 \pm 10.9 years) and the control group consisted of 88 patients (47 males and 41 females, mean age: 74.95 \pm 9.7 years). The groups were age and gender -matched ($p=0.775$ and $p=0.63$, respectively).

The comparison of blood parameters between the groups was presented in Table 1. According to the Student's *T* test, the mean hemoglobin and albumin value did not significantly differ between the groups ($p=0.342$ and $p= 0.655$). Mann Whitney U test revealed that the median CRP, C-reactive protein/albumin ratio (CAR), WBC, lymphocyte, platelet, PLR, RDW-CD, RDW-SD and ferritin values did not significantly differ between the groups. ($p= 0.541$, $p= 0.603$, $p= 0.157$, $p= 0.209$, $p= 0.398$, $p= 0.098$, $p= 0.373$, $p= 0.232$ and $p= 0.894$, respectively). However, the median D-dimer, neutrophil and NLR values were significantly higher in the sACI group, compared with the control group ($p=0.004$, $p<0.048$ and $p=0.007$, respectively).

Figure 1 shows the ROC curve representing the predictive value of D-dimer, neutrophil and NLR for sACI in patients with COVID-19. The areas under curve were: D-dimer= 0.674 (95% CI, 0.569-0.779), NLR= 0.663 (95% CI, 0.559-0.767) and neutrophil= 0.620 (95%CI, 0.509-0.73).

Table 2 presents the comparison of categorical variables (presence) between the groups. According to Chi- square test, the rates of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation and hyperlipidemia were not different between the groups ($p=0.957$, $p=0.196$, $p=0.539$, 0.819 and $p=0.066$, respectively).

DISCUSSION

Of the 2,378 COVID-19 patients screened in this retrospective case-control study, 31 (1.30%) were found to develop sACI. In addition, D-dimer, neutrophil and NLR levels were higher in the sACI group compared to the control group. ROC analysis showed D-dimer level to have a predictive value for sACI in COVID-19 disease.

Previous studies have shown that COVID-19 infection can lead to acute stroke.⁶ A neuroimaging screening study of 3,556 patients hospitalized with COVID-19 found that 32 of these patients (0.9%) developed ischemic stroke with D-dimer peak and increased troponin.⁷ However, that study also included patients with asymptomatic disease. Conversely, our study found the prevalence of sACI to be 1.3% among COVID-19 patients.

D-dimer is a molecule that can be measured in complete blood or plasma. This molecule is a biomarker of fibrin formation and degradation which play a role in coagulation.⁸ While D-dimer remains low in healthy individuals, it increases in conditions associated with thrombosis.⁹ It has been shown that D-Dimer is usually elevated in COVID-19 patients and the higher its level,

Table 1: The comparison of blood parameters between the groups

	sACI	Control	P value
Albumin, g/L	33.84 ±4.75	34.29 ±4.85	0.655
Hemoglobin, g/dL	13.73 ± 2.04	13.29 ± 2.28	0.342
D-dimer, ng/ml	1876 (730-16700)	1145 (197-10900)	0.004
C- reactive protein, mg/dL	98 (8.62-254.52)	80 (1.28-334.9)	0.541
CAR	2.74 (0.21- 9.26)	2.47 (0.03- 10.12)	0.603
White blood cell, 10 ⁹ /L	8.08 (3.26-16.5)	6.68 (2.16-30.02)	0.157
Neutrophil, 10 ⁹ /L	6.52 (2.43-14.69)	5.02 (1.6-22.09)	0.048
Lymphocyte, 10 ⁹ /L	0.91 (0.36-3.4)	1.07 (0.27-22.89)	0.209
NLR	6.5 (2.13-35.28)	4.49 (0.27-25.87)	0.007
Platelet, 10 ⁹ /L	208 (84-612)	198 (37-565)	0.398
PLR	207.32 (76.22-708.33)	166.92 (5.59-758.49)	0.098
RDW-CV, %	13.8 (12.2-19.7)	14 (12.1-21.5)	0.373
RDW-SD, fL	44.1 (35.9-59.9)	44.1 (35.7-66.8)	0.232
Ferritin, ml/ng	292.8 (21.7-1500)	328.95 (16.8-1500)	0.894

CAR, C-reactive protein/albumin ratio; sACI, symptomatic acute cerebral infarction, NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; RDW, red cell distribution width

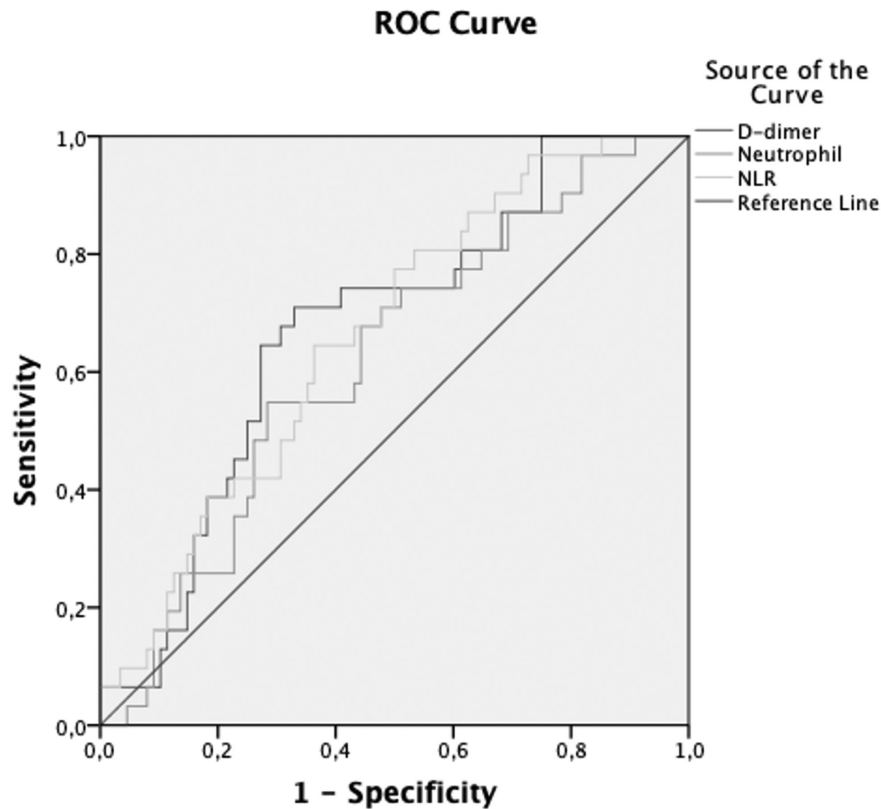


Figure 1. ROC curve representing the predictive value of D-dimer, neutrophils and NLR for symptomatic acute cerebral infarction in patients with COVID-19

Table 2: The comparison of categorical variables (presence) between the groups

	sACI (n=31)	Control (n=88)	P value	X ² value
Hypertension	22 (% 70.9)	62 (70.4%)	0.957	0.003
Diabetes Mellitus	15 (48.4%)	31 (35.2%)	0.196	1.674
Coronary artery disease	11 (35.5%)	26 (29.5%)	0.539	0.377
Atrial fibrillation	4 (12.9%)	10 (11.36%)	0.819	0.52
Hyperlipidemia	14 (45.1.3%)	24 (27.3%)	0.066	3.375

sACI, symptomatic acute cerebral infarction

the more severe the course of COVID-19 disease.^{10,11} Acute systemic inflammation caused by COVID-19 creates a predisposition to hypercoagulability due to increased concentrations of proinflammatory cytokines (e.g., interleukin) and serum inflammatory factors (e.g., CRP).¹² One study found that 10 of 219 COVID-19 patients developed acute cerebral infarction and these patients had extremely high D-dimer levels.⁶ Similarly, our study found higher D-dimer levels in sACI patients compared to the control group. In addition, the results of ROC analysis performed in this study suggest that D-dimer may serve as a predictor of sACI in COVID-19 patients.

NLR reflects systemic inflammation and is one of the indicators of elevated neutrophil count in serum.¹³ The present study found higher NLR levels and neutrophil counts in the sACI group compared to the control group. One study showed that COVID-19 patients with a good clinical course had lower NLR levels compared to COVID-19 patients who were admitted to intensive care or died.¹⁴ Another study showed that NLR has a good predictive value in identifying patients likely to have severe COVID-19 infection.^{15,16} Of note, it has been argued that patients with NLR values above 3 were more likely to require intensive care.¹⁷ Yet another study suggested that patients with elevated NLR at admission were more likely to develop complications related to COVID-19 infection.¹⁸ Moreover, elevated NLR has been said to be a predictor of poor prognosis for patients who develop complications after ischemic stroke.¹⁹⁻²¹ The results of the ROC analysis performed in the present study suggest that elevated serum NLR levels may be a predictor of sACI concomitant with systemic inflammatory diseases such as COVID-19.

To the best of our knowledge, our study is the first to investigate this issue, which can be considered as one of its strengths, but it also has some limitations: the subtypes of COVID-19 were not analyzed, which precluded

determination of whether sACI was associated with the subtypes of COVID-19. This study was conducted with a small number of sACI patients and its retrospective nature meant that it excluded patients with asymptomatic cerebral infarction. Finally, this study is a single-center study and has a retrospective design.

In conclusion, patients with systemic inflammation such as COVID-19 are likely to develop sACI, probably as a consequence of increased systemic inflammation. Moreover, elevated D-dimer and NLR levels may predict cerebral infarction in conditions involving systemic infection such as COVID-19.

DISCLOSURE

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