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Characteristics of COVID-19 Related Stroke: A Single-center Prospective Study

COVID-19 İlişkili İnmenin Özellikleri: Tek Merkezli Bir Prospektif Çalışma

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) seems more related to stroke than other respiratory viruses. Acute stroke has become increasingly conspicuous during a typical COVID-19 infection. In the present study, we aim to evaluate stroke characteristics in the context of COVID-19 infection.

Method: We conducted a single-center prospective study and evaluated characteristics of stroke patients who had concomitant definite COVID-19 (dCOV) (n=24), suspected COVID-19 (sCOV) (n=31), and no COVID-19 (CG) (n=19). Then we classified all participants into two groups according to the modified Rankin scale (mRS) scores (0-2 indicating good outcome, 3-6 indicating poor outcome). A logistic regression analysis and a receiver operating characteristic area under the curve were performed to evaluate the variables, which predict a poor prognosis.

Results: Just over half of the patients in the dCOV were admitted with stroke symptoms and diagnosed with COVID-19 at admission, and nearly half of the patients initially had a COVID-19 diagnosis. They had developed stroke after a gap of 4-21 days. Ischemic stroke was the most common stroke subtype in dCOV. The dCOV had higher mRS indicating poor outcomes. Patients with poor outcomes had higher levels of D-dimer, neutrophil-to-lymphocyte ratio (NLR), procalcitonin, and aspartate aminotransferase. NLR reliably predicts poor outcome, overall with an accuracy of 86%.

Conclusion: COVID-19 related stroke is associated with high inflammatory biomarkers, poor outcome, and high mortality. NLR is a potential, cost-effective, and easy-to-use marker for poor prognosis in COVID-19 related stroke.

Keywords: Cerebrovascular disease, COVID-19, neutrophil-to-lymphocyte ratio, prognosis, stroke

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) diğer solunum yolu virüslerine kıyasla inme ile daha çok ilişkili gibi görünmektedir. Tipik bir COVID-19 enfeksiyonu sırasında akut inme giderek daha göze çarpar hale gelmiştir. Bu çalışmada COVID-19 enfeksiyonu bağlamında inme özelliklerini değerlendirmeyi amaçladık.

Yöntem: Bu tek merkezli prospektif çalışmada kesin COVID-19 tanısı olan (dCOV) (n=24), şüpheli COVID-19 tanısı olan (sCOV) (n=31) ve COVID-19 tanısı olmayan (CG) (n=19) inme hastasının özellikleri değerlendirildi. Ardından tüm katılımcılar modifiye Rankin skalası (mRS) skorlarına göre iki gruba ayrıldı (0-2 iyi sonlanım, 3-6 kötü sonlanım göstergesi). Lojistik regresyon analizi ve receiver operating characteristic eğri altında kalan alan analizi yapılarak kötü prognozu öngören değişkenler değerlendirildi.

Bulgular: dCOV grubundaki hastaların yarısından biraz fazlası inme semptomlarıyla başvurdu ve beraberinde COVID-19 tanısı aldı. Yaklaşık yarısı ise başvuru sırasında halihazırda COVID-19 tanısına sahipti. Bu hastalarda COVID-19 tanısından 4-21 gün sonra inme semptomları ortaya çıkmıştı. dCOV grubunda en fazla görülen inme türü iskemik inmeydi. dCOV grubu diğerlerine kıyasla daha yüksek mRS'ye sahipti. Kötü sonlanımı olan hastalar daha yüksek D-dimer, nötrofil-lenfosit oranı (NLR), prokalsitonin ve aspartat aminotransferaz düzeyine sahipti. NLR kötü sonlanımı genel olarak %86 doğrulukla öngörmekteydi.

Sonuç: COVID-19 ile ilişkili inme, yüksek enflamatuvar biyoişaretleyiciler, kötü sonlanım ve yüksek mortaliteyle ilişkilidir. NLR, COVID-19 ile ilişkili inmede potansiyel, uygun maliyetli ve kullanımı kolay bir kötü prognoz belirtecidir.

Anahtar kelimeler: COVID-19, inme, nötrofil-lenfosit oranı, prognoz, serebrovasküler hastalık

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Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2, has been declared as a global pandemic by the World Health Organization in March 2020. Although this new syndrome is characterized by respiratory symptoms, accumulated evidence shows that it may also involve many other systems and organs including the nervous system, resulting in manifestations such as anosmia, headache, stroke, acute confusional state, and encephalitis (1).

Although it is known that many viral infections and sepsis may trigger stroke, COVID-19 seems more related to stroke than other respiratory viruses, seven-fold greater compared to influenza (2).

In a retrospective study, 36% of the patients with COVID-19 had neurological complications, 5.7% of them had an acute stroke, mainly in patients with severe respiratory symptoms (3).

The incidence of acute stroke in COVID-19 patients has been reported as 0.4-8.1% in the subsequent studies (4), more commonly in older patients with stroke risk factors (RF) (3,5,6), and ischemic stroke has been reported to be more frequent than hemorrhagic stroke (4). COVID-19 related stroke patients have a poor prognosis (7,8).

It is still not known whether there is a causal relationship between COVID-19 and stroke, and the pathophysiological mechanism is still unclear. Still, inflammation, hypercoagulability, and hypoxia appear to be major contributors (9).

Perhaps the most critical point for clinicians during the COVID-19 pandemic was to separate patients with and without COVID-19 infection with precision and to ensure the isolation of patients in inpatient wards. Reverse transcriptase-polymerase chain reaction (RT-PCR) assay is the primary diagnostic tool for COVID-19. Still, the sensitivity of RT-PCR has been reported between 42% and 83% (10), and false-negative results have also been reported (11,12). Since the RT-PCR test takes hours to days, chest computed tomography (CCT) has been used for faster evaluation in clinical practice as a first-line screening tool. To standardize the various reported CCT findings of COVID-19, the COVID-19 reporting and data system (CO-RADS) was proposed (10).

In the present study, we aim to evaluate stroke characteristics in COVID-19 by comparing demographic, clinical, radiological, and laboratory findings of stroke patients who had concomitant definite COVID-19 (dCOV), suspected but unproven COVID-19 (sCOV), and no COVID-19 (nCOV).

Materials and Methods

Participants

The study was performed between January 2021 and May 2021, and a total of 171 patients who were diagnosed with acute cerebrovascular disease (aCVD) were prospectively included.

The CCT was used to evaluate all patients, which is a part of the hospital inpatient admission policy. CO-RADS scores were determined by experienced radiologists. Among them, those having a travel history to another country within the last two weeks, a contact history with a known COVID-19 patient, respiratory symptoms, or suggestive CCT findings underwent a nasopharyngeal swab RT-PCR. Those with a positive RT-PCR were included in the dCOV group. If the two consecutive RT-PCRs were negative, they were included in the sCOV group. If all the four criteria for an RT-PCR test were absent, the patient was included in the nCOV group, which also served as the candidate control group (CG).

After the initial workup for COVID-19, all the nCOV patients were followed up for infectious diseases (other system infections, sepsis) during the hospital stay and for respiratory symptoms for two weeks. Those who did not develop respiratory symptoms and whose relatives were not diagnosed with COVID-19 within that period and those who did not develop other infectious diseases during the stay were included in the final CG.

According to a protocol approved by the Local Ethics Committee of the University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (date: 15/01/2021, number: 2021.01.1.12.213.r1.012) and the relevant committee of the Turkish Ministry of Health, written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

After excluding patients who did not consent to the study, 24 patients were included in the dCOV group, 31 patients in the sCOV group, and 19 patients in the CG.

Data on RF, medication, electrocardiography (ECG) (sinus rhythm or atrial fibrillation), CO-RADS score, outcome (home discharge, transfer to another center, being still hospitalized, in-hospital death), admission platelet, hemoglobin, white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer,

procalcitonin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and fibrinogen were collected and recorded.

Stroke types were classified as ischemic stroke, transient ischemic attack, and hematoma. Ischemic stroke was further classified into four main groups, including total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), posterior circulation infarction (POCI), and lacunar infarction (LACI) according to the Bamford clinical classification (13).

Hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, heart failure, previous stroke, smoking, obesity, and dyslipidemia were the RFs for stroke.

The temporal relationship of COVID-19 diagnosis with stroke diagnosis and delay of stroke after the onset of COVID-19 were recorded if applicable.

Echocardiography and computed tomography angiography (CTA) results were evaluated by two neurologists (Z.Y., S.O.), and echocardiography results were classified as normal, mild findings, low ejection fraction (EF), and/or akinetic wall, aortic stenosis, cardiac mass/intracardiac thrombus, prosthetic valve. CTA results were classified as normal, atherosclerotic changes, symptomatic stenosis, asymptomatic stenosis, and vasculitic findings.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean, standard deviation, median, minimum, maximum, frequency, and percentage. Then all participants were classified into two groups according to the modified Rankin scale (mRS) scores. Group 1 included participants with mRS scores of 0-2, indicating good outcome, and group 2 included participants with mRS scores of 3-6, indicating poor outcome. In the comparison of demographic and clinical data, the Kruskal-Wallis and Mann-Whitney U tests were used. In the presence of a significant difference in the Kruskal-Wallis test, the Tamhane's T2 test was used for the paired comparison of subgroups. The Pearson chi-square and Fisher's Exact tests were employed to compare the frequencies and percentages.

A logistic regression analysis (LRA) was performed with outcome groups as the dependent variable and the significantly different variables between these two outcome groups as the predictors.

A "receiver operating characteristic" (ROC) area under the curve (AUC) was used in the statistical evaluation of the sensitivity and specificity of the NLR.

Results

The comparison of the demographic and clinical variables of CG, sCOV, and dCOV groups are shown in Table 1. There were no significant differences among the groups in terms of age (p=0.437), gender (p=0.226), the RF (p=0.672), medication (p=0.796), type of stroke (p=0.879), ECG findings (p=0.387), echocardiography findings (p=0.386), CTA findings (p=0.419), outcome (p=0.65), WBC (p=0.634), hemoglobin (p=0.158), ESR (p=0.107), D-dimer (p=0.265), procalcitonin (p=0.271), BUN (p=0.136), and creatinine (p=0.773).

All sCOV patients and 13 patients from the dCOV had synchronous COVID-19 (suspected or definite) and CVD diagnoses. They were admitted for stroke and evaluated for COVID-19 for safety reasons. On the other hand, 11 patients from the dCOV had CVD symptoms 4-21 days after the onset of COVID-19. While there was no significant difference among the groups regarding outcome (p=0.650), mRS scores were significant between the groups (p=0.006). Post-hoc analysis revealed that the mRS score of the dCOV was significantly higher than that of the CG (p=0.002). Also, mortality rate was 16.7% (n=4) in dCOV and 9.7% (n=3) in sCOV, while there was no mortality in the CG.

Platelet count (p=0.041), NLR (p=0.007), CRP (p=0.027), AST (p=0.004), ALT (p=0.001), and fibrinogen (p=0.002) were significantly different among the three groups. While post-hoc analysis revealed no significant difference between the groups with regard to platelet count, NLR of the dCOV was significantly higher than that of CG (p=0.004). CRP level of the dCOV was significantly higher than that of CG (p=0.009). AST level was higher in dCOV than in CG (p=0.005) and sCOV (p=0.011). ALT level of dCOV was higher than that of CG (p=0.001). Fibrinogen level of CG was lower compared to both the sCOV (p=0.036) and the dCOV (p=0.004).

The proportion of patients aged under 65 years and over in the groups was compared. 50% (n=12) of the dCOV, 22.6% (n=7) in sCOV and 42.1% (n=8) in CG were under 65 years. Although the proportion of younger patients was higher in dCOV, there was no significant difference between the groups (p=0.094).

There was a single hemorrhagic case in dCOV, and the etiology was arteriovenous malformation.

Six patients in dCOV who had no prior RF for stroke are listed in Table 2.

Two patients in CG had no prior RF. One of them had intracardiac thrombus, and one was cryptogenic. Six

Table 1. Demographic, clinical, radiological, and laboratory findings according to the diagnostic groups and according to the outcome groups

	CG (n=19)	sCOV (n=31)	dCOV (n=24)		Good outcome mRS 0-2 (n=37)	Poor outcome mRS 3-6 (n=37)	
	n mean ± SD	n mean ± SD	n mean ± SD	p	n mean ± SD	n mean ± SD	p
Group							
dCOV	NA	NA	NA		7	17	0.043‡*
sCOV	NA	NA	NA		18	13	
CG	NA	NA	NA		12	7	
Age (range)	65.7±16.6 (40-94)	69.2±13.4 (33-89)	64.3±15.5 (28-93)	0.437†	66.2±15.3 (28-93)	67.2±14.7 (33-94)	0.922‖
≤65 y	8	7	12	0.094‡	13	14	0.809‡
Gender (Female: Male)	7:12	16:15	7:17	0.226‡	17:20	13:24	0.344‡
Temporal relationship COVID-19 diagnosis with stroke diagnosis					NA	NA	NA
Synchronous	NA	31	13	<0.001§*			
Asynchronous		-	11				
Delay of stroke after the onset of COVID-19 (range)	NA	NA	11.5±5.4 (4-21)	NA	NA	NA	NA
Risk factors and comorbidities							
1 RF	4	10	5	0.672§	13	6	0.222§
2 RF	9	9	6		11	13	
≥3 RF	4	4	6		4	10	
No RF	2	6	6		7	7	
Malignancy	0	2	1		2	1	
Medication							
None	4	11	8	0.796§	14	9	0.287§
Antiaggregants	5	11	8		12	12	
Anticoagulants	1	1	2		1	3	
Other	8	7	6		8	13	
Irregular use of antiaggregants	1	1	0		2	0	
Stroke type							
TACI	2	3	5	0.879‡	3	7	0.780‡
PACI	8	11	11		16	14	
POCI	3	6	4		6	7	
LACI	4	6	2		7	5	
TIA	0	2	1		2	1	
Hematoma	2	3	1		3	3	
ECG							
Sinus rhythm	18	25	21	0.387§	32	32	1.000‡
Atrial fibrillation	1	6	3		5	5	
CO-RADS							
1	19	0	0		12	7	0.038§*
2	0	0	0		0	0	
3	0	5	0	<0.001§*	4	1	
4	0	11	0		8	3	
5	0	15	0		6	9	
6	0	0	24		7	17	

Echocardiography							
Normal	2	3	4	0.386§	6	3	0.082§
Mild findings	7	14	8		14	15	
Low EF and/or akinetic wall	3	2	4		6	3	
Aortic stenosis	0	1	0		0	1	
Cardiac mass/intracardiac thrombus	3	1	0		4	0	
Prosthetic valve	1	0	0		0	1	
CTA							
Normal	6	9	7	0.419§	14	8	0.580§
Atherosclerotic changes	4	6	3		6	7	
Symptomatic stenosis	5	9	11		10	15	
Asymptomatic stenosis	2	3	2		4	3	
Vasculitic findings	1	0	0		1	0	
Outcome							
Home discharge	15	24	17	0.650§	33	23	0.019§*
Transfer to another center	1	2	1		1	3	
Still hospitalized	3	2	2		3	4	
In-hospital death	0	3	4		0	7	
mRS	1.8±1.5	2.5±1.9	3.9±1.6	0.006†*	NA	NA	
Blood biochemistry							
WBC	9.4±2.6	9.8±3.6	9.4±4.3	0.634†	9.1±3.5	10.2±3.7	0.112‖
Hemoglobin	13.4±2.8	12.7±2.1	12.6±1.7	0.158†	13.0±1.8	12.7±2.5	0.799‖
Platelet	242.2±81.7	304.4±103.1	262.7±119.8	0.041†*	269.6±93.9	280.2±117.9	0.841‖
NLR	3.3±1.7	4.2±3.9	6.1±3.4	0.007†*	3.0±1.6	6.7±4.1	<0.001‖*
CRP	16.8±14.4	32.1±58.3	73.2±82.8	0.027†*	29.4±50.7	53.5±74.3	0.077‖
ESR	26.6±29.7	36.1±24.4	44.3±29.6	0.107†	30.5±29.0	40.0±27.2	0.115‖
D-dimer	0.9±0.6	0.6±0.8	1.1±1.1	0.265†	0.6±0.8	1.1±0.9	0.033‖*
Procalcitonin	0.9±2.4	0.4±1.5	0.9±2.2	0.271†	0.3±1.5	0.9±2.3	0.002‖*
AST	21.9±6.9	29.3±10.1	33.6±15.0	0.004†*	24.7±8.3	32.9±13.8	0.009‖*
ALT	15.5±6.8	19.8±13.4	29.8±16.4	0.001†*	20.7±14.6	23.1±13.9	0.284‖
BUN	38.1±14.6	44.4±15.5	50.6±23.6	0.136†	40.1±14.3	49.4±21.4	0.074‖
Creatinine	0.9±0.2	0.9±0.3	0.9±0.3	0.773†	0.9±0.3	0.9±0.2	0.280‖
Fibrinogen	433.1±87.4	451.3±149.9	559.5±99.0	0.002†*	461.9±135.8	505.8±180.5	0.394‖

CG: Control group, sCOV: Suspected COVID-19, dCOV: Definite COVID-19, RF: Vascular risk factors, TIA: Transient ischemic attack, ECG: Electrocardiography, EF: Ejection fraction, CTA: Computed tomography angiography, mRS: Modified Rankin scale, WBC: White blood cell count, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, COVID-19: Coronavirus disease-2019, SD: Standard deviation, *p<0.05, †Kruskal-Wallis test, ‡Pearson chi-square test, §Fisher's Exact test, ‖Mann-Whitney U test

patients in sCOV had no prior RF. Three of them had hyperlipidemia, and three of them had large vessel occlusion.

The comparison of the demographic and clinical variables of outcome groups is shown in Table 1. When all participants were divided into two groups according to mRS scores, three diagnostic groups showed significant differences indicating that the poor outcome in the dCOV group was higher than the sCOV and CG (p=0.043). There was a significant difference in terms of CO-RADS scores (p=0.038), NLR (p<0.001), D-dimer (p=0.033), procalcitonin (p=0.002) and AST (p=0.009) between the two groups.

RFs, medication, echocardiography and CTA were then classified into two groups as normal vs. abnormal, and outcome was classified into three groups as home discharge, still hospitalized and death in order to improve the quality of statistical analysis. There were no significant differences among the CG, sCOV, and dCOV groups in terms

Table 2. Six patients in COVID-19 definite group who had no prior risk factors for stroke

	Age	Infarct location	Echocardiography	CTA	Detected risk factors
Patient 1	48	Unilateral multifocal posterior circulation	Normal	Normal	ANA +
Patient 2	53	Right large MCA territory	NA	Right ICA stenosis	Hyperlipidemia and large vessel occlusion
Patient 3	55	Bilateral anterior circulation multifocal	Normal	Normal	Lupus anticoagulant +
Patient 4	28	Bilateral anterior circulation multifocal	Normal	Normal	Cryptogenic
Patient 5	63	Bilateral anterior and posterior circulation	Normal	Normal	Hyperlipidemia
Patient 6	46	Bilateral anterior and posterior circulation	Normal	Normal	Hyperlipidemia

CTA: Computed tomography angiography, ANA: Antinuclear antibody, MCA: Middle cerebral artery, ICA: Internal carotid artery, COVID-19: Coronavirus disease-2019

Table 3. Predictor variables of outcome groups

	B	p	Exp (B)	95% CI for EXP (B)
D-dimer	0.376	0.452	1.456	0.546-3.881
NLR	1.246	0.004*	3.478	1.480-8.172
Procalcitonin	0.302	0.157	1.353	0.890-2.055
AST	0.002	0.970	1.002	0.907-1.107

NLR: Neutrophil-to-lymphocyte ratio, AST: Sspartate aminotransferase, CI: Confidence interval, *Whole model test p<0.001

of RFs (p=0.483), medication (p=0.541), echocardiography (p=0.587), CTA (p=0.971), and outcome (p=0.421). There were also no significant differences among the good outcome and poor outcome groups in terms of RFs (p=0.234), medication (p=1.0), echocardiography (p=0.293), and CTA (p=0.799).

An LRA was performed with outcome groups as the dependent variable and D-dimer, NLR, procalcitonin, and AST as the predictor variables. A total of 43 cases were analyzed, and the full model was significantly reliable (chi-square =30.6, df =4, p<0.001). This model accounted for between 50.9% and 67.9% of the variance in the outcome groups, with 90.5% of the good outcome participants successfully predicted, and 81.8% of the poor outcome participants successfully predicted. Overall, 86.0% of predictions were accurate. Predictor variables are shown in Table 3. Only NLR reliably predicted good and poor outcome (odds ratio =3.478, confidence interval =1.480-8.172, p=0.004).

ROC analysis was applied to determine the cut-off values where NLR had high sensitivity and specificity in distinguishing patients with poor outcomes from the patients with a good outcome. It was found that NLR indicated patients with poor outcome with an 0.831 AUC. The optimum cut-off was 3.7 as the sensitivity and specificity were both 75.7% (Figure 1).

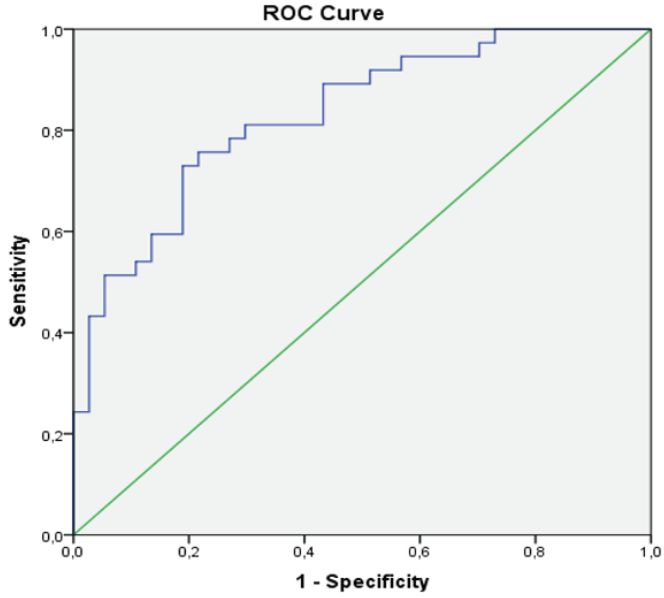

Figure 1. Neutrophil-to-lymphocyte ratio prediction of poor outcome

Area under curve: 0.831

Discussion

In this prospective study, three groups of stroke patients were evaluated. There were no differences among the groups in terms of demographical, clinical, and neuroradiological features. In the dCOV, just over half of the patients were admitted with stroke symptoms and diagnosed with COVID-19 at admission, and nearly half of the patients initially had a COVID-19 diagnosis. They were treated at home or hospital, and after a gap of 4-21 days, they had developed a stroke. Ischemic stroke was the most common stroke subtype in dCOV. The dCOV group had higher mRS scores indicating poor outcomes. Higher mortality was evident in dCOV and sCOV groups than CG. There was a trend in abnormal NLR, CRP, AST, ALT, and fibrinogen findings for the dCOV. Patients with poor outcomes had higher levels of D-dimer, NLR, procalcitonin,

and AST. NLR predicts reliably poor outcomes, overall with an accuracy of 86.0%.

Consistent with the literature (5,14), 75% (n=18) of the dCOV had at least one RF. Younger patients with COVID-19 and stroke have been reported in early reports of the pandemic (15). Still, subsequent studies and meta-analyses have shown that older age, male gender, and vascular RF are associated with COVID-19 related stroke (16). COVID-19 may trigger the pathogenesis in older patients with COVID-19, especially those with traditional RF (2).

In our study, as in previous literature, ischemic stroke was predominant in dCOV (17).

Delay of stroke after the onset of COVID-19 has been reported in several studies as 8.8 (6.3-11.6) days (4), 12 days (6), 8-24 days (18). This delay stands for the late thromboembolism complications of immune-mediated coagulopathy (16,19).

In the meta-analyses and the large studies, a male predominance has been reported (4,16,17). The majority of COVID-19 patients in our study were also male, but there was no difference among the groups in terms of gender.

Several pathogenic mechanisms such as coagulopathy, inflammation, and platelet activation for COVID-19-related stroke have been proposed (2). Elevated D-dimer and fibrinogen levels, both of which are the biomarkers of inflammation and hypercoagulable state (20), are the most reported findings in COVID-19 patients with stroke (3,6) and proposed to be the source of venous and arterial thromboembolism (21-24). Although D-dimer levels were elevated in all groups in our patients, there was no significant difference between the diagnostic groups. The poor outcome group had higher levels of D-dimer than the good outcome group. D-dimer greater than 1 mg/mL was associated with severe COVID-19 and mortality (25). A D-dimer level greater than 1 mg/mL was found in the dCOV group in our study. Elevated inflammatory markers such as interleukin, ESR, and CRP have also been reported (6). COVID-19 related stroke patients also have higher lactate dehydrogenase, ALT, and AST levels than COVID-19 negative stroke patients (7). Similar to the previous studies, the dCOV group in our study also had higher levels of inflammatory markers, ALT, and AST. Interleukin-6 levels were not available in this study.

The dCOV group in our study had a higher NLR than the CG. The poor outcome group had higher NLR, D-dimer, procalcitonin, and AST. The NLR levels predicted poor outcome. NLR is another inflammatory marker that is associated with poor outcome, higher intensive care requirement, and higher complications of COVID-19 and has also been reported as a predictor of poor outcome in ischemic stroke (20,26,27). Increased level of NLR is thought to be evidence of dysregulated neutrophil extracellular traps (NETs). NETs are networks of extracellular fibers including chromatin, proteins, antimicrobial peptides, and enzymes (26,27), which may promote platelet adhesion and thrombus formation (28). The relationship between NETs and ischemic stroke and NETs and COVID-19 have been described (26), but the role of NETs in COVID-19 related stroke still needs to be clarified. Our study showed that higher NLR levels are also a predictor of the poor outcome in COVID-19 related stroke with an optimum cut-off value of 3.7. The cut-off value of NLR has previously been reported as 4.795, with 83.9% sensitivity and 75.0% specificity for the severity of COVID-19 (29).

The positivity of anti-phospholipid antibodies has also been reported in COVID-19 related stroke patients (30). One patient had ANA positivity, and one patient had lupus anticoagulant positivity in our study.

Most importantly, the dCOV group in our study had worse outcomes and higher mortality. A more extended stay in the hospital, increased mortality, and higher need for intensive care unit have been reported in COVID-19 related stroke patients (2,7,31).

Although this study cannot provide a causality between COVID-19 and stroke, it clarifies the clinical characteristics of COVID-19 related stroke. In addition to highlighting higher mortality in COVID-19 related stroke, it also shows that NLR levels higher than 3.7 are a predictor of poor outcome in COVID-19 related stroke.

Study Limitations

This study has several limitations. First, this is a single-center study with a limited number of patients. Second, our study did not include patients who had acute stroke treatment because our center does not have an acute stroke unit, and we cannot perform acute treatment of patients with thrombolysis and thrombectomy. Such patients are referred to appropriate centers by the emergency call center. Third, our group definitions are not sufficiently precise due to diagnostic challenges. The sCOV group is theoretically a heterogeneous group that we are not sure whether they have COVID-19 pneumonia or another viral pneumonia. And we could not totally rule out COVID-19 diagnosis in the CG; there may be asymptomatic carriers.

Conclusion

COVID-19 related stroke is associated with high inflammatory biomarkers, poor outcome, and high mortality rates. Therefore COVID-19 related stroke should be a priority for public health. NLR is a potential, cost-effective, and easy-to-use marker of poor prognosis in COVID-19 related stroke. Further studies, especially multi-center large studies, are needed to better understand the relationship between these two clinical entities.

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Ethics

Ethics Committee Approval: According to a protocol approved by the Local Ethics Committee of the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date:15/01/2021, number: 2021.01.1.12.213.rl. 012) and the Relevant Committee of the Turkish Ministry of Health, all participants provided written informed consent, per the Declaration of Helsinki.

Informed Consent: Informed consent was obtained.

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Authorship Contributions

Concept: Z.Y., S.Ö., E.Ç., N.K., Design: Z.Y., S.Ö., E.Ç., N.K., Data Collection or Processing: Z.Y., S.Ö., E.Ç., N.K., Analysis or Interpretation: Z.Y., S.Ö., Literature Search: Z.Y., S.Ö., Writing: Z.Y., S.Ö., E.Ç., N.K.

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References

1. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020;87:18-22.
2. Stein LK, Mayman NA, Dhamoon MS, Fifi JT. The emerging association between COVID-19 and acute stroke. Trends Neurosci 2021;44(7):527-537.
3. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683-690.
4. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke 2021;16(2):137-149.
5. Guan WJ, Ni ZY, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382(18):1708-1720.
6. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020;5(3):279-284.
7. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology 2020;95(7):e910-e920.
8. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. Stroke 2020;51(7):2002-2011.
9. Altable M, de la Serna JM. Cerebrovascular disease in COVID-19: Is there a higher risk of stroke? Brain Behav Immun Health 2020;6:100092.
10. Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, et al. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. Radiology 2020;296(2):E97-E104.
11. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020;296(2):E32-E40.
12. Yusuf S, Ahmad H, Zeb R, Zeb U, Zeb AA. High-Resolution CT Chest Findings in Suspected COVID-19 Pneumonia Patients With Negative Real-Time Polymerase Chain Reaction Assay. Cureus 2021;13(3):e14023.
13. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337(8756):1521-1526.
14. Fatima N, Saqqur M, Qamar F, Shaukat S, Shuaib A. Impact of COVID-19 on neurological manifestations: an overview of stroke presentation in pandemic. Neurol Sci 2020;41(10):2675-2679.
15. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 2020;382(20):e60.
16. Yamakawa M, Kuno T, Mikami T, Takagi H, Gronseth G. Clinical Characteristics of Stroke with COVID-19: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis 2020;29(12):105288.
17. Shahjouei S, Tsivgoulis G, Farahmand G, Koza E, Mowla A, Vafaei Sadr A, et al. SARS-CoV-2 and Stroke Characteristics: A Report From the Multinational COVID-19 Stroke Study Group. Stroke 2021;52(5):e117-e130.
18. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020;91(8):889-891.
19. McFadyen JD, Stevens H, Peter K. The Emerging Threat of (Micro) Thrombosis in COVID-19 and Its Therapeutic Implications. Circ Res 2020;127(4):571-587.
20. Wijeratne T, Sales C, Karimi L, Crewther SG. Acute Ischemic Stroke in COVID-19: A Case-Based Systematic Review Front Neurol 2020;11:1031.
21. Hess DC, Eldahshan W, Rutkowski E. COVID-19-Related Stroke. Transl Stroke Res. 2020;11(3):322-325.
22. Iba T, Levy JH, Warkentin TE, hachil J, van der Poll T, Levi M, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost 2019;17(11):1989-1994.

23. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 2004;10(2):342-324.

24. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4):844-847.

25. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-1062.

26. Wijeratne T, Gillard Crewther S, Sales C, Karimi L. COVID-19 Pathophysiology Predicts That Ischemic Stroke Occurrence Is an Expectation, Not an Exception-A Systematic Review. Front Neurol 2020;11:607221.

27. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. J Med Virol 2020;92(11):2573-2581.

28. Kaplan MJ, Radic M. Neutrophil extracellular traps: double-edged swords of innate immunity. J Immunol 2012;189(6):2689-2695.

29. Imran MM, Ahmad U, Usman U, Ali M, Shaukat A, Gul N. Neutrophil/lymphocyte ratio-A marker of COVID-19 pneumonia severity. Int J Clin Pract 2021;75(4):e13698.

30. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med 2020;382(17):e38.

31. Topcuoglu MA, Pektezel MY, Oge DD, Bulut Yüksel ND, Ayvacioglu C, Demirel E, et al. Stroke Mechanism in COVID-19 Infection: A Prospective Case-Control Study. J Stroke Cerebrovasc Dis 2021;30(8):105919.