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RESEARCH ARTICLE **ÖZGÜN ARAŞTIRMA**

ISCHEMIC STROKE IN COVID-19 PATIENTS: SINGLE CENTER, ONE YEAR EXPERIENCE

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ABSTRACT

INTRODUCTION: The clinical presentation of COVID-19 varies greatly. Even though, disease cause predominantly respiratory manifestations, because of the inflammatory nature of the disease, it also triggers thromboembolic conditions. We aim to describe the features of COVID-19 positive ischemic stroke patients of 1-year experiences of a single center.
METHODS: A total of 258 patients, diagnosed with ischemic cerebrovascular disease (25 patients of with strokes had respiratory symptoms at initial presentation and COVID-19 diagnosis), were evaluated retrospectively during the study period.
RESULTS: A majority of these patients strokes were in anterior circulation territory and most of them were large vessel occlusion. Eighteen of the patients had positive COVID-19 RT-PCR results, while 7 of the patients had negative results but their thorax CTs made the diagnosis of COVID-19. Hypertension (56%), diabetes (44%), and atrial fibrillation (44%) were the most comorbidities. Thirteen patients stroke etiology was cardioembolism, 9 had atherosclerosis. Fourteen of the patients NIHSS were >10, and 13 of them died. Patients with high levels of CRP (13/25), D-Dimer (15/25) and Ferritin (14/25) had mRS>3 at admission. Most of the patients (19/25) had CO-RADS 5 scores at admission. Two patients had mRS 4-5, 9 patients had mRS 0-3 at the discharge period. Fourteen patients died at the hospital period.
DISCUSSION AND CONCLUSION: The admission NIHSS scores determined significantly the prognosis. Moreover, higher age, women gender, LVO in neuroimagining, high CRP, Ferritin, D-dimer levels, COVID-19 RT-PCR positivity, presence of hypertension and atrial fibrillation comorbidities showed poor outcome.
Keywords: COVID-19, ischemic stroke, COVID-19 reporting and data system (CO-RADS), National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS).

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COVİD-19 HASTALARINDA İSKEMİK İNME: TEK MERKEZİN BİR YILLIK TECRÜBESİ

ÖZ

GİRİŞ ve AMAÇ: COVİD-19'un klinik özellikleri değişkenlik göstermektedir. Hastalık sıklıkla solunum sistemi semptomları ile prezente olmakla birlikte hastalığın inflamatuar doğası sonucu tromboembolik olaylar da tetiklenebilmektedir. Çalışmamızda bir yıl içerisinde merkezimizde tanı alan ve COVİD-19 ile birliktelik gösteren iskemik inme hastalarının klinik özelliklerini tanımlamayı amaçladık.

YÖNTEM ve GEREÇLER: Kliniğimizde bir yıl boyunca iskemik serebrovasküler hastalık tanısı konulan toplam 258 hasta geriye dönük olarak tarandı. Bu hastaların klinik, laboratuar ve görüntüleme bulguları retrospektif olarak değerlendirildi. Toplam 25 hasta COVİD-19 tanısı almış olup, çalışmaya dahil edilmiştir.

BULGULAR: Hastalardan 18'inin COVID-19 RT-PCR sonucu pozitif olarak, 7'sinin ise negatif olmasına rağmen toraks BT'lerinde tipik COVID-19 pnömoni bulguları olması nedeniyle klinik ve radyolojik olarak tanı konulmuştur. Hastaların çoğunluğunda anterior dolaşımda, geniş damar oklüzyonu sonucu enfarkt oluşumu gözlenmiştir. En sık eşlik eden hastalıklar hipertansiyon (%56), diyabet (%44) ve atriyal fibrilasyon (%44) olarak belirlenmiştir. On üç hastada kardiyoembolizm, 9 hastadaysa ateroskleroz inme etyolojisi olarak tespit edilmiştir. NIHSS skoru 10'un üzerinde olan 14 hastadan 13'ü mortal seyretmiştir. CRP (13/25), D-Dimer (15/25) ve Ferritin (14/25) düzeyleri yüksek olan hastalarda mRS>3 bulunmuştur. Hastaların çoğunda (19/25) Toraks BT görüntüleme bulgusu CORADS 5 olarak değerlendirilmiştir. Taburculuk döneminde iki hastada mRS 4-5, 9 hastada mRS 0-3 şeklindedir. Toplamda 14 hasta ise mortal seyretmiştir.

TARTIŞMA ve SONUÇ: Prognozu belirlemede önemli parametrelerden biri ilk değerlendirmedeki NIHSS skorları olduğu düşünülmektedir. Ayrıca, ileri yaş, kadın cinsiyet, beyin görüntülemede geniş damar oklüzyonu varlığı, yüksek CRP, Ferritin, D-dimer seviyeleri, COVID-19 RT-PCR pozitifliği, hipertansiyon ve atriyal fibrilasyon komorbiditeleri olan hastaların prognozu kötü seyretmiştir.

Anahtar Sözcükler: COVID-19, iskemik inme, COVID-19 reporting and data system (CO-RADS), National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS).

INTRODUCTION

Starting with Wuhan, December 2019, Coronavirus 2019 (COVID-19) has been creating a pandemic. Up to February 2022, there have been 396.558.014 confirmed diagnosis, including 5.745.032 deaths (1,2). The clinical presentation varies greatly from asymptomatic infection to severe respiratory dysfunction that may cause death. Even though, disease cause predominantly respiratory manifestations (flu-like symptoms to pneumonia), because of the inflammatory nature of the disease, it also triggers thromboembolic conditions (3,4).

From a neurological perspective, COVID-19 can cause smell and taste dysfunction, neuropathy, myopathy, encephalopathy, demyelinating conditions, and cerebrovascular diseases (CVD) (5). In CVD, especially ischemic stroke prevalence increased in this period and generally with a poor outcome (5–7). Several studies have been presented on the underlying mechanisms of the COVID-19 related stroke. Angiotensin-converting enzyme-2 (ACE-2), regarded as the binding site of the virus, associated vasoconstriction, hypertension, and thrombosis, also immune-mediated vascular endothelial damage, hypercoagulation, and thromboembolism have been regarded as the potential etiologies of stroke (8,9).

We aim to describe key features of COVID-19 positive ischemic stroke patients hospitalized in a single center in a 1-year duration. We also want to determine the factors that seem to affect the prognosis in this patient population.

METHODS

Patient Selection: This study included ischemic stroke patients who had also COVID-19 diagnosis between April 2020 and May 2021 at Çankiri State Hospital Neurology Department. Data were collected retrospectively from the electronic registry system. Patients with ICD diagnostic code I67.9 (Cerebrovascular Diseases, unspecified), G46.8 (Other vascular syndromes of brain in cerebrovascular diseases) were analyzed and 25 cases with COVID-19 were included. Patients whose COVID-19 reverse transcriptase polymerase chain reaction (RT- PCR) test positive and/ or who had pneumonia compatible with COVID-19 in thorax computed tomography (CT) examination even though the tests were not positive. The study was performed in accordance with Helsinki Declaration and ethical approval was

granted by the Ethics Committee of Karabük University in January 2022 (Date: 18.01.2022, Number: 2022-801). Informed consent wasn't received from participants included in the study because of the retrospective study design.

Study Design: Patient age, gender, comorbidities, Glomerular Filtration Rate (GFR), creatinin, blood urea nitrogen (BUN), ferritine, D- Dimer, interleukin-6 (IL-6), C- reactive protein (CRP), neutrophile and lymphocyte counts, COVID-19 RT-PCR results on admission were noted and analyzed. Moreover brain CT, CT angiography, Chest CT (CT; Toshiba Canon Aquilion Start 16 Slices), brain magnetic resonance imagining (MRI; 1.5-Tesla GE Signa HDxt 1.5T MRI) were evaluated. Cardiac comorbidities and etiological tests such as electrocardiogram (ECG), rhythm holter and echocardiography were evaluated. Smoking habits, antiaggregant/ anticoagulant usage prior to stroke was also assessed. Stroke etiology was defined from the ASCOD classification (A, atherosclerotic; S, small vessel disease; C, cardioembolic; O, other defined causes; D dissection) (10). Chest CT images were acquire with 0.625-mm slice thickness with additional 2.5-mm reconstructions on 16-slices. The scanning was from the apices of the lung to the bottom. The images were analyzed by 7 years specialized radiologists blinded to the patient's COVID-19 status, using the COVID-19 reporting and data system (CO-RADS) a previously reported computed tomography-based categorical classification system assessing for the presence or absence of pulmonary findings suspicious for COVID-19. CO-RADS classifies lung findings into 5 groups as it relates to findings consistent with COVID-19 pneumonia: 1 is very low level of suspicion, 2 is low level of suspicion, 3 is equivocal suspicion, 4 is high level of suspicion, 5 is very high level of suspicion (11).

Follow-up: Stroke symptoms were evaluated and scored using the National Institute of Health Stroke Scale (NIHSS) at the time of admission, and discharge. To determine the outcome, the modified Rankin Scale (mRS) scores were checked out during the admission, and discharge period. Pre-stroke status of ambulation and dependency were learned from patients' relatives.

Statistical Analysis: The study was created with descriptive statistics. Categorical variables were expressed as numbers and percentages (%). Categorical variables were evaluated using Fisher's exact test if the frequency was less than 5 in at least one of the cells in 2x2 crosstabs. The continuity-corrected chi-square test was used when frequency was between 5 and 25. In other cases, the Pearson chi-square test was performed. If the frequency was less than 5 in at least one cell, categorical variables were evaluated with the likelihood ratio test; otherwise, they were analyzed using Pearson's chi-square test. While the number of independent groups was two, the significance of group differences was examined using the Mann-Whitney U test. Data were analyzed with the IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) program. Values with $p < 0.05$ were considered significant in the results.

RESULTS

Totally 258 consecutive ischemic stroke cases evaluated. Twenty five patients with stroke (9.66% of all cases) had COVID-19 diagnosis eventually. At baseline, patients with strokes and COVID-19 (SWC) mean age was 68.7 (minimum 35, maximum 89) years. Ten (40%) patients were women, 15 (60%) were men.

Hypertension (56%), diabetes (44%), and atrial fibrillation (44%) were the most comorbid conditions. There were 3 patients in each group who had hyperlipidemia (12%), coronary artery diseases (12%), congestive heart failure (12%). Two patients had stroke and transient ischemic attack (TIA) in their past medical history (8%). None of the patients had malignancy, vasculitis or thrombophilia. Patients had predominantly cardioembolic stroke (52%). Other etiologies were atherosclerotic (36%) and others (12%) according to ASCOD classification, cryptogenic strokes were also included.

From the perspective of COVID-19 PCR results, 18 patients had positive for alpha subtype of COVID-19 (the most known and detected type of COVID-19 at the study period), while 7 of the patients had COVID- 19 negative but their thorax CTs confirm the diagnosis of COVID-19.

In terms of laboratory findings, there were 9 patients with CRP levels between 5-100 mg/l and 16 patients with >100 mg/l. There was no patient with a normal CRP level of 5 mg/l or less. There were 3 patients with D-dimer level below 1000 ng/ml and 22 cases with 1000 ng/ml and above. IL-6 levels could not be evaluated in 11 patients, but it was above the cut-off value of 4.43 pg/ml in

7 patients and normal in 7 patients. There were 21 patients with ferritin level of 300 mcg/ml and above, and 4 patients with normal levels (45-300 mcg/ml). Considering the neutrophil and lymphocyte counts in cubic millimeters, 1 patient with a neutrophil count below 4000/mm3, 16 patients with a neutrophil count between 4000-11000/mm3, and 8 patients with a neutrophil count of 11000/mm3 and above were present. There were 9 patients with lymphocyte counts below 600/mm3 and 16 patients with a lymphocyte count between 600-3500/mm3. When kidney function tests were evaluated, the mean creatinine values of the patients were 1.088 (0.25-3.18) mg/dl; The mean BUN value was 51.4 (22-96) mg/dl. GFR values were calculated electronically as ml/min/1.73 m2 unit, and there were 7 patients with 90, and above, 13 patients with 60-90, 3 patients with 30-60, and 2 patients with 30 and below. The current cut-off values were the limit values used by both previous studies on the subject, and the biochemistry, and serology laboratories of our hospital adjusted according to the population.

Demographics, comorbidities, laboratory levels, COVID-19 RT- PCR results, admission mRS on admission were presented in Table 1, which correlated with discharged mRS.

Among 25 patients with a confirmed diagnosis of stroke, 22 had COVID-19 related thorax CT findings with a component of GGO (ground-glass opacities) and most with consolidations. All of the involvements were bilaterally and diffuse multifocal. Figure 1 demonstrates pulmonary involvement of the cases with the pie chart.

Nineteen patients (76%) had anterior circulation ischemia, 5 (20%) had posterior circulation ischemia, while 1 patient (4%) had both anterior and posterior circulation ischemia. Large vessel involvement detected in 15 patients (60%) according to infarction aspect, clinical evaluation and finally CT angiography results. Only in one patient CT angiography couldn't be performed due to impaired renal function tests. The mean ASPECT score of the group was 4 (0-9). Two patients had mesencephalic compression in acute stroke period. Decompressive craniectomy were performed in 1 patient while the rest received mannitol as an anti-edema medication.

Intravenous tissue plasminogen activator (iv-tpa) were given to two patients and endovascular

Table 1. Demographic, clinic, radiological and laboratuary parameters and their correlation with mRS.

	mRS 0-3	mRS 4-5	mRS 6
Age			
18-50	1	0	1
51-60	2	0	1
61-70	4	1	3
71-80	2	0	7
81-90	0	1	2
Gender			
Female (10 patients)	3	0	7
Male (15 patients)	6	2	7
HT (14 patients)	4	1	9
DM (11 patients)	6	0	5
AF/PAF/AFLUT			
Present (11 patients)	0	2	9
Absent (14 patients)	9	0	5
Stroke Etiology			
Atherosclerosis (9 patients)	7	0	2
Cardioembolism (13 patients)	0	2	11
Others (3 patients)	2	0	1
Admission NIHSS			
0-4	8	0	1
5-10	1	1	0
11-15	0	0	3
16-25	1	0	7
>25	0	0	3
LVO			
Presence (15 patients)	1	1	13
Absence (10 patients)	8	1	1
Covid-19 PCR test			
Positive	6	2	10
Negative	3	0	4
CRP (mg/l)			
5-100	6	0	3
>100	5	2	11
D-Dimer (mcg/ml)			
<1000	2	0	1
≥1000	7	2	13
IL-6 (pg/ml)			
Normal	1	1	4
High	4	0	3
NA	4	1	7
GFR (ml/dk/1.73m2)			
>90	7	0	0
60-90	2	1	10
30-60	0	1	2
<30	0	0	2
Neutrophil (/mm3)			
<2000	0	0	1
2000-11000	6	2	8
>11000	3	0	5
Lymphocyte (/mm3)			
<600	3	0	6
600-3500	6	2	8
>3500	0	0	0
Ferritin (ng/mL)			
Normal	2	2	0
>300	7	0	14

thrombectomy was performed in one. The patient who underwent thrombectomy had also received tpa. While iv- tpa was given in our hospital while for endovascular thrombectomy the patients was transfered to a tertiary healthcare institution. In the remaining patients, hyperacute stroke therapies could not be performed due to temporal incompatibility and other comorbid medical conditions.

There were 9 patients with NIHSS 0-5, 2 patients with 5-10, 3 patients with 10-15, 8 patients with 15-25, and others (3 patients) with >25. Initially, 3 patients had mRS 4-5, 22 patients had mRS 0-3 at admission. Fourteen patients had mRS 6 (death) at hospital period, 2 patients had mRS 4-5, 9 patients had mRS 0-3 at the discharge period. There were 8 patients with NIHSS 0-5, 3 patients with 5-10 at discharged period and the other 14 patients died at the hospital period. We demonstrated them as >25 NIHSS in bar graphs. Changes in NIHSS and mRS during our evaluation were demonstrated in Figure 2, 3 and 4.

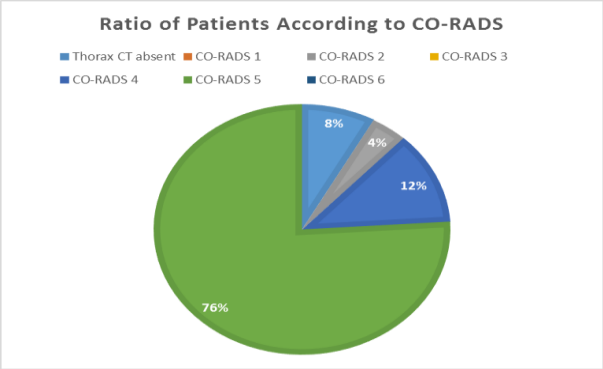

Figure 1. Pulmonary involvement of the ischemic stroke cases according to CO-RADS.

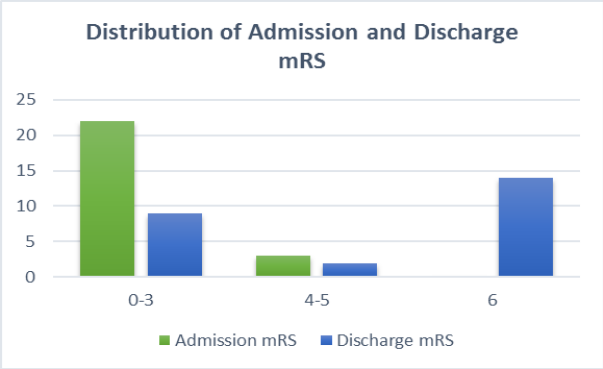

Figure 2. Distribution of admission and discharge mRS.

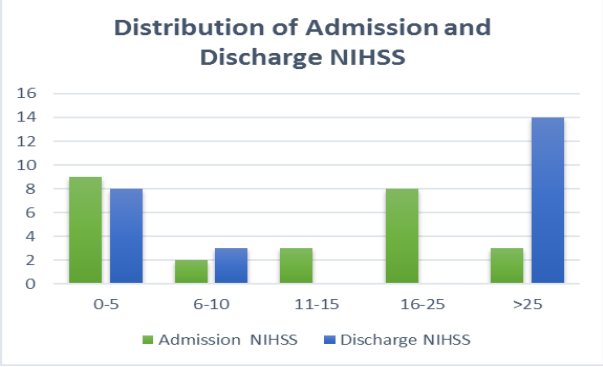

Figure 3. Distribution of admission and discharge NIHSS.

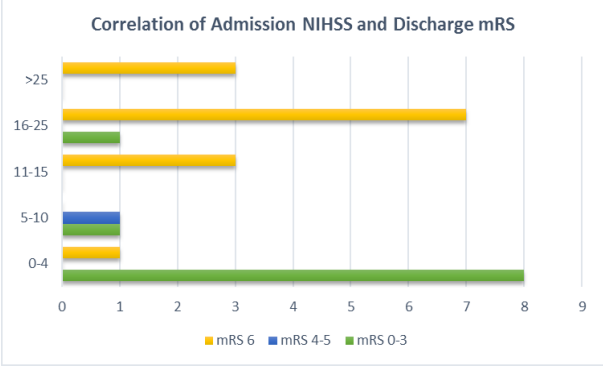

Figure 4. Correlation of admission NIHSS and discharge mRS.

DISCUSSION AND CONCLUSION

The present study evaluated the prevalence, clinical aspects, probable prognostic features of ischemic stroke patients with COVID-19. We found an 9.66% prevalence of COVID-19 positiviness by either PCR or Thorax CT in our ischemic stroke patients. It was observed that most of the patients had hypertension, diabetes and atrial fibrillation co-morbidities at similar percentages, like in other stroke study populations. The NIHSS scores of the patients at the time of admission correlated with the prognosis. In addition, LVO was observed considerably in these patients, and cardioembolism was the most common etiology.

The rate of ischemic stroke in COVID-19 patients in our study was in accordance with similar studies, which have evaluated the prevalence of both ischemic stroke rate in COVID-19 cases and COVID-19 rates in ischemic stroke patients (7,12). The mean age was between 60-70 years (68.7 years). This was similar to other stroke studies(13,14). LVO, large MCA, or posterior system infarcts (low ASPECT scores) were also

noted in the younger population (<55 years) as in previous studies (15). Similar to previous stroke registries our small COVID-19 stroke sample, men were affected more (F/M: 2/3)(7,12). In many stroke studies, it has been emphasized that the prognosis is worse in elderly (>65 years), especially in the female patient population due to the postmenopausal period (7,9,14). In total, 7 of 10 female, 7 of 15 male patients died, and 2 patients were discharged as severely disabled (mRS 4-5). We may state that there is a proportionally higher rate of mortality in women. Comorbid conditions (atrial fibrillation, congestive heart failure, and hyperlipidemia, especially hypertension and diabetes mellitus) were similarly in other non-COVID stroke and COVID-19 stroke studies (9,12,14). Cardioembolism was the most common etiological factor, followed by atherosclerosis rather than cryptogenic stroke similar to some previous studies (13,14).

It has been emphasized that COVID-19 PCR test may revealed negative results for a number of different reasons (16). In our sample, while the tests were positive in 18 patients, 7 patients had false negative results. On the arrival of all the negative patients, lesions compatible with COVID pneumonic involvement were observed in the thorax CTs taken due to cough and low oxygen saturation (<90%). Except for 5 of the patients whose tests were positive, the rest had a clinical picture of pneumonia at the time of admission. These 5 patients were admitted only with the symptoms of a cerebrovascular disease (hemiparesis/ hemihypoesthesia, dysarthria/ aphasia, etc.). Six of the patients with a positive test had been already diagnosed with COVID and had a stroke during their hospitalization period. All of these 6 patients received enoxaparin sodium subcutaneously during their hospitalization. Two of them received enoxaparin at a venous prophylaxis dose (one injection per day), while the other 4 received at an arterial dose (2 injections per day). It has been emphasized in many studies that the main cause of severe lung, vascular endothelial damage in the COVID-19 process is due to catastrophic immune response (17,18). Interleukins (especially IL-2, IL-6, IL-7), tumor necrosis factor-α (TNF-α), procalcitonin (PCT), CRP, ferritin and fibrin degradation product D-dimer, which is a marker of procoagulation, are markers that are particularly emphasized in this immunopathogenesis (8,9,17,18). As a result of prognostic evaluation of laboratory values, high levels of CRP, D-Dimer and Ferritin appeared as indicators of poor prognosis. The present results are correlated with previous single center studies and multicenter meta-analysis data(19–24). Although the prognosis could not be adequately correlated with the impairment of renal function tests due to sample limitation, it was observed that all 7 patients with a GFR of 90 and above survived with or without mild sequelae. The lymphocyte count of the patients with a mortal course was 3500/mm3 and below, and no significant correlation could be found with the neutrophil counts. On the other hand radiological evaluation also can confirm the prevalence of lung involvement which is regarded as a marker for disease severity, and there may be a direct correlation between the development of stroke with the severity of pneumonia. The evaluations and expert opinions emphasized that iv- tpa and thrombectomy procedures can be applied in appropriate indications, with appropriate isolation conditions (25). Although COVID-19 also causes hemorrhagic stroke, it has been reported that iv-tpa does not cause a significant bleeding risk, when the profit-loss ratio is evaluated. These hyperacute stroke treatment methods, which are carried out as a team effort, have been recommended by many centers, with the healthcare team taking precautions to protect themselves from infection. Iv- tpa was performed in only two of our patients, and iv- tpa and thrombectomy was performed in one of our patients. Two of the patients who received iv- tpa were already hospitalized for COVID-19 pneumonia and were evaluated very early. One of them was discharged with severe disability as mRS 4-5, and the other was with mild disability as mRS<4. The patient who underwent thrombectomy died in the follow-up due to multiorgan failure.

In the previous meta-analyses, men are affected more than women, the average age is 6-7 decades, but young strokes are observed at a substantial rate (24%) (14,15,26). It has been reported that LVO is seen at a higher rate in this young stroke population (15,27). It has been shown that in approximately 40% of patients, the presentation of stroke is the first presentation of COVID-19, and approximately 1/4 of these stroke patients didn't have comorbidities (7,9,14,28). Slightly different from our population,

approximately 40% of patients were treated with mild disability, 30% were severely disabled (mRS 4-5), and approximately 30% were died(14,26). Contrary to our study, the most common etiology of stroke was found to be large artery atherosclerosis, followed by cardioembolism and cryptogenic stroke (7,13–15,26). Anterior circulation strokes and especially large MCA infarcts are frequently observed in these patients (14). It has been emphasized that hyperacute stroke therapies was applied at a higher rate only in developed countries (25,29,30).

Our study is limited by its retrospective design and evaluated small single-center population. Due to the limited number of patients, advanced statistical analyzes could not be performed and univariate analyzes could not be included, especially in terms of prognosis. Because of these reasons, the prognostic factors we predicted remain statistically weak, even if the results are largely consistent with the meta-analysis data. In addition, non-stroke complications that intervene in the COVID-19 pneumonia also affect prognosis and survival.

In conclusion, patients who had COVID-19 with ischemic stroke as an initial manifestation or at the course of COVID-19 pneumonia period have an 9.66% prevalence in our stroke data from a single center registary in one year period. Hypertension, diabetes and atrial fibrillation co-morbidities were the most commonly recorded comorbidities. The NIHSS scores of the patients at the time of admission significantly determined the prognosis. Higher age, women gender, LVO in neuroimagining, high CRP, Ferritin, D-dimer levels, COVID RT-PCR positivity, presence of hypertension and atrial fibrillation co-morbidities correlated with poor outcome. Further clinical studies are needed to define the unknown mechanisms and management strategies of stroke in COVID-19 pathogenesis.

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Ethics

Ethics Committee Approval: The study was approved by Ethics Committee of Karabük University (Number: 2022-801, Date: 18.01.2022).
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