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Comparison of COVID-19 patients who underwent thrombectomy with those in the pre-pandemic period in terms of etiology and prognosis

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Abstract. – OBJECTIVE: We aimed at determining the effectiveness of mechanical thrombectomy (MT) in patients with major vessel occlusion and infected with COVID-19, evaluating its clinical outcome and comparing it with non-COVID patients.

PATIENTS AND METHODS: During the pandemic, 729 patients who underwent MT in stroke centers due to Acute Ischemic Stroke (AIS) with large vessel occlusion were evaluated. This study included 40 patients with a confirmed COVID-19 diagnosis by a positive PCR test between March 11, 2020, and December 31, 2020. These patients were compared to 409 patients who underwent MT due to major vessel occlusion between March 11, 2019, and December 31, 2019.

RESULTS: Of the patients with AIS who are infected with COVID-19, 62.5% were males, and all patients have a median age of 63.5 ± 14.4 years. The median NIHSS score of the COVID-19 group was significantly higher than that of the non-COVID-19 groups. Dissection was significantly more in the COVID-19 group. The mortality rates at 3 months were higher in the COVID-19 groups compared to non-COVID-19 groups.

CONCLUSIONS: This study revealed an increased frequency of dissection in patients with COVID-19. COVID-19-related ischemic strokes are associated with worse functional outcomes and higher mortality rates than non-COVID-19 ischemic strokes.

Key Words:

COVID-19, Stroke, Thrombectomy, Prognosis, Dissection.

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Introduction

In December 2019, after identifying the cases of severe acute respiratory syndrome in Wuhan, a city in the Hubei province of China, an increasing number of people worldwide were diagnosed with Coronavirus disease 2019 (COVID-19)[1]. On March 11, 2020, the World Health Organization declared the COVID-19 outbreak as a pandemic.

Venous and arterial thrombotic events have been reported to be due to thrombotic complications mediated by inflammation, endothelial dysfunction, platelet activation, thrombin formation, and platelet activation in COVID-19[2,3]. Cerebrovascular diseases have been seen in 5-6% of patients with severe COVID-19. COVID-19-related ischemic stroke incidence ranges between 0.4% and 2.7%[4,5].

Acute ischemic stroke (AIS) due to proximal vessel occlusion accounts for 21-27% of all stroke cases[5,6]. Early diagnosis and treatment of acute stroke due to large vessel occlusion can improve the clinical outcome.

This multicenter, national study aimed at determining the effectiveness of mechanical thrombectomy (MT) in patients with AIS with major vessel occlusion and infected with COVID-19, evaluating its clinical outcome and comparing it with non-COVID patients.

Patients and Methods

Data Recorded

Patient data were obtained from the Turkish Interventional Neurology Database, which was created by prospective records that are entered by experienced neurointerventionalists. The study was approved by a local governing institutional review board. Additionally, written consent was obtained from 14 comprehensive stroke centers that were voluntarily involved in the study. Records were independently checked by the researchers.

This study included patients with AIS having large vessel occlusions who underwent MT and were diagnosed with COVID-19, proven by laboratory diagnosis [reverse transcription-polymerase chain reaction (RT-PCR) of nasal oropharyngeal swab samples] between March 11, 2020 (the date when the first case was reported in Turkey), and December 31, 2020[6]. These patients were compared with patients who underwent MT due to major vessel occlusions between March 11, 2019, and December 31, 2019.

The presence of symptoms associated with COVID-19 (fever, cough, shortness of breath, and anosmia) was noted. All patients with positive COVID-19 PCR underwent chest computed tomography (CT) and were evaluated regarding their lung involvement.

Age, gender, baseline modified Rankin Score (mRS), stroke risk factors (diabetes, hypertension, smoking, and dyslipidemia), medical history (history of stroke, atrial fibrillation, etc.), time from onset of symptoms of stroke, stroke severity (National Institutes of Health Stroke Scale – NIHSS), baseline blood pressure, and laboratory findings were recorded.

The etiological classification of ischemic stroke was performed following the Trial of ORG 10172 in Acute Stroke Treatment[7]. All patients underwent a head CT scan and CT angiography. The Alberta Stroke Program Early CT Score was recorded. CT perfusion (CTP) was performed in patients 6 to 24 hours after they had felt well for the last time. Patients with mismatch profiles on CTP underwent MT. Patients with an occluded M1 and M2 segment of the middle cerebral artery (MCA) and the intracranial segment of the internal carotid artery (ICA) (T and L occlusion), and those with proximal (ICA-MCA tandem) and vertebrobasilar occlusion were included in the study.

Treatment Procedure

The AIS management during the pandemic was performed following the rules of the local hospital. Patients underwent the procedure with at least one surgical mask. Patients with respiratory distress were intubated in the negative-pressure room in the emergency service. During the intervention, the minimum number of personnel was allowed to the angiography unit, and all staff was asked to wear glasses, visors, high-quality protective face masks (N95/FFP2/FFP3), and aprons[8]. All laboratory-confirmed and clinically suspected cases were followed up in the COVID-19 intensive care units.

Intravenous thrombolytic therapy (tissue plasminogen activator, alteplase of 0.9 mg/kg) was administered to patients who had no contraindications and were admitted within the first 4.5 hours after the onset of symptoms according to the operator's preference.

MT was performed by interventional neurologists, who had at least 5 years of experience in acute stroke endovascular treatment, under local anesthesia, conscious sedation, or general anesthesia.

During the procedure, a large-diameter 9F MERCI balloon guiding catheter or 6F long-sheath was used. Thrombectomy technique with stent retrievers, aspiration technique with large-diameter aspiration catheters or a combination of stent and aspiration techniques (ARTS, SAVE, or SOLUMBRA technique) were used[9,10].

The presence of first-pass recanalization and the number of passes were recorded. In the final angiography, the recanalization status was evaluated using the Thrombolysis in Cerebral Infarction (TICI) scale. TICI 2b-3 recanalization was considered a successful recanalization[11].

New territorial embolism, distal embolism, dissection, vessel rupture, and intracerebral hemorrhage were examined as periprocedural complications associated with MT.

The symptom-to-door time, door-to-imaging time, door-to-groin puncture time, and puncture-to-recanalization time were recorded.

Treatment Outcome Evaluation

The presence of intracerebral hemorrhage (HI1, HI2, PH1, and PH2) was assessed using a follow-up CT taken after 24-36 hours. Symptomatic intracerebral hemorrhage was defined as mortality or worsening at least 4 points in the NIHSS, according to the European Cooperative Acute Stroke study[12,13].

The mRS was calculated at the time of discharge and after 3 months. Patients with mRS of 0-2 in the third month were considered as good clinical outcomes. Despite the successful recanalization rate, patients with mRS of 3-6 in the third month were considered as futile recanalization.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and ratios were used in descriptive data statistics. The distribution of variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data. The Chi-square test was used in the analysis of qualitative independent data and the Fisher test was used when Chi-square test conditions were not met. The Statistical Package for the Social Sciences version 23.0 program (IBM Corp., Armonk, NY, USA) was used in the analyses. In all comparisons, a p-value <0.05 was considered statistically significant.

Results

Study Population

During the pandemic, 729 patients who underwent MT in stroke centers due to AIS with large vessel occlusions were evaluated. This study included 40 patients with a confirmed COVID-19 diagnosis by a positive PCR test between March 11, 2020, and December 31, 2020. These patients were compared to 409 patients who underwent MT due to major vessel occlusion between March 11, 2019, to December 31, 2019.

Demographic Data

Of the patients with AIS who were infected with COVID-19, 62.5% were males, and all patients had the median age of 63.5 ± 14.4 years.

The most common COVID-19 symptoms were fever (16, 40%), cough (25, 62.5%), and dyspnea (25, 62.5%). Stroke was the first symptom in 50% of patients. Ground-glass opacities were observed in 75% of patients who underwent chest tomography. Of the patients with COVID-19 who underwent MT, 41.9% were intubated, which was a percentage significantly higher than that of patients without COVID-19 ($p < 0.001$). All clinical, radiological characteristics and treatment managements of the participants are shown in Table I.

Of the patients with COVID-19, 87.5% had at least one stroke risk factor, whereas 93.2% in patients without COVID-19. This difference was not statistically significant ($p = 0.199$). The risk factor evaluation of patients with COVID-19 revealed that 72.5% had a history of hypertension, followed by diabetes mellitus (37.5%) and atrial fibrillation (35%) (Table I).

No statistically significant difference was found between the COVID-19 and non-COVID-19 groups in terms of demographic data of patients and stroke risk factors (Table I).

Lesion Localization and Etiology

The most commonly affected vascular region was the M1 segment of the MCA in the COVID-19 and non-COVID-19 groups (42.5% and 47.4%, respectively). No significant difference was found between the groups in terms of occlusion localization ($p = 0.217$).

Dissection was significantly higher in the COVID-19 group ($p = 0.009$). The other etiological causes were similar between both groups (Table I).

Symptom Onset and Data of the Applied Procedures

The median NIHSS score of the COVID-19 group was significantly higher than that of the non-COVID-19 groups [16.5, interquartile range (IQR): 14.3-19] and 16, IQR: 12-18], $p = 0.028$.

The time between symptom-to-arterial puncture and symptom-to-recanalization was longer in the COVID-19 group ($p = 0.021$ and 0.032, respec-

Table I. Characteristics of patients with and without COVID-19 and acute ischemic stroke due to large vessel occlusion.

	COVID-19 (n = 40)	Non COVID-19 (n = 409)	*p*	
Demographic data				
Median age Ort.± s.s, y	63.5 ± 14.4	66.3 ± 13.0	0.210	m
Male sex – No. (%)	25 (62.5)	223 (54.5)	0.333	x^2
Young stroke – No (%)	6 (15)	48 (11.7)	0.608	x^2
Stroke risk factors – No. (%)				
Hypertension	29 (72.5)	325 (79.5)	0.304	x^2
Diabetes mellitus	15 (37.5)	112 (27.4)	0.175	x^2
Smoking	8 (20)	80 (19.6)	0.947	x^2
Alcoholism	1 (2.5)	8 (2)	0.572	x^2
Atrial fibrillation	14 (35)	144 (35.2)	0.979	x^2
Previous ischemic stroke or transient ischemic attack	2 (5)	43 (10.5)	0.268	x^2
Stroke etiology, No. (%)				
Cardioembolism	15 (37.5)	165 (40.3)	0.856	x^2
Large artery atherosclerotic disease	8 20	50 12.2	0.249	x^2
Dissection	5 (12.5)	11 (2.7)	**0.009**	x^2
Unknown etiology	12 (30)	183 (44.7)	0.103	x^2
Symptom associated with COVID-19	32 (80)			
Fever, (%)	16 (40)			
Cough, (%)	25 (62.5)			
Shortness of breath, (%)	25 (62.5)			
Anosmia, (%)	5 (12.5)			
Opacities consistent with a COVID-19 infection on chest computed tomography (%)	30 (75)			
Intubation (%)	13 (41.9)	9 (2.2)	**< 0.001**	x^2
Time from initial COVID-19 symptoms to stroke diagnosis – days				
Stroke diagnosis with COVID-19	20 (50)			
1-7 day	4 (10)			
8-14 day	9 (22.5)			
15-30 day	7 (17.5)			
Stroke characteristics				
NIHSS score on admission, median (IQR)	16.5 (14.3-19.0)	16 (12-18)	**0.028**	m
CT ASPECT score, median (IQR)	8 (7-9.3)	9 (8-10)	0.125	m
Occlusion site – no. (%)				
Extracranial internal carotid artery	8 (20)	38 (9.3)	0.217	x^2
Intracranial internal carotid artery	8 (20)	68 (16.6)		
First segment of middle cerebral artery	17 (42.5)	194(47.4)		
Second segment of middle cerebral artery	3 (7.5)	54 (13.2)		
Vertebrobasilar artery	4 (10)	55 (13.4)		

m = Mann-whitney U test/X^2 = Chi-square test.

tively; Table II). The proportion of rt-PA use was statistically lower in COVID-19 than non-COVID-19 groups (15% *vs.* 20%, $p = 0.041$) (Table II).

The rate of stent-retriever use was statistically lower in the COVID-19 group compared to the non-COVID-19 group ($p = 0.037$).

The laboratory parameters of both groups are shown in Table III. No significant difference was found between the groups in terms of endovascular treatment success, technical characteristics, and procedure-related complications (Table II).

Clinical Outcomes

The 24-hour NIHSS scores were worse in the COVID-19 group compared to the non-COVID-19 group ($p = 0.002$).

The rate of good and poorer outcomes did not statistically differ between the COVID-19 and non-COVID-19 groups (Table IV). The mortality rates at 3 months were higher in the COVID-19 groups compared to non-COVID-19 groups ($p = 0.003$). No significant difference was observed between the causes of mortality (Table IV).

Table II. Treatment procedure.

	COVID-19 (n = 40)	Non COVID-19 (n = 409)	*p*	
Treatment with intravenous alteplase – No. (%)	6 (15)	124 (30.3)	**0.041**	x²
Symptom-thrombolysis time (IQR), min	87.5 (67.5-142.5)	150 (50-300)	0.044	m
Median time from symptom to door (IQR), min	163 (92-240)	170 (95-239)	0.973	m
Median time from symptom to arterial puncture (IQR), min	280 (180-360)	216 (152-280)	**0.021**	m
Median time from door to imaging (IQR), min	18 (10-40)	15 (10-20)	0.077	m
Median time from imaging to groin puncture (IQR), min	42.5 (30-57.5)	15 (5-60)	**< 0.001**	m
Median time from arterial puncture to recanalization (IQR), min	47 (23-68)	40 (27-57.5)	0.230	m
Median time from symptom to recanalization (IQR), min	313 (231-403)	265 (195-330)	**0.032**	m
Median number of passes, (IQR)	2 (1-4)	2 (1-3)	0.177	m
First pass effect, No. (%)	15 (37.5)	209 (51.1)	0.101	x²
Use of stent-retriever, No. (%)	25 (62.5)	316 (77.3)	**0.037**	x²
Grade of 2b or 3 on mTICI scale – No. (%)	31 (77.5)	347 (84.8)	0.225	x²
Procedure-related complications, No. (%)				
Distal embolization of thrombus	12 (30)	102 (24.9)	0.483	x²
New territory embolization	1 (2.5)	15 (3.7)	1.000	x²
Arterial perforation	1 (2.5)	2 (0.5)	0.245	x²
Symptomatic intracranial hemorrhage	2 (5)	43 (10.5)	0.408	x²

m = Mann-Whitney U test/X² = Chi-square test.

Table III. Laboratory findings.

	COVID-19 (n = 40)	Non COVID-19 (n = 409)	*p*	
Glucose	142.6 ± 61.4	160.4 ± 80.1	0.107	m
White blood cell, $\times 10^3/\mu L$	10.3 ± 5.1	11.9 ± 7.1	**< 0.001**	m
Platelet $\times 10^4/\mu L$)	23.5 ± 8.1	26.0 ± 10.3	0.156	m
Hemoglobin, g/dL	13.1 ± 6.2	12.5 ± 1.9	0.440	m

m = Mann-Whitney U test/X² = Chi-square test.

Discussion

Our multicenter study, which was largely affected by the coronavirus pandemic, sheds a light on several important findings on the effectiveness and safety of the MT treatment of AIS due to large vessel occlusion in patients with COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a very quick-spreading virus that brings threat worldwide. COVID-19 disease caused by this virus mainly affects the

Table IV. Clinical outcome.

	COVID-19 (n = 40)	Non COVID-19 (n = 409)	*p*	
Median 24 hours NIHSS (IQR)	15.5 (10.3-19.5)	10 (5-17)	**0.002**	m
mRS 0-2 at 90 days, No. (%)	13 (32.5)	193 (47.1)	0.110	x²
mRS 3-6 at 90 days, No. (%)	27 (67.5)	221 (53.9%)	0.138	x²
90-day mortality, No. (%)	15 (37.5)	73 (17.8)	**0.003**	x²
Sepsis associated mortality, No. (%)	4 (26.7)	15 (20.5)	0.600	x²
Malignant brain edema associated mortality, No. (%)	9 (60)	45 (61.6)	0.905	x²
Acute respiratory failure associated mortality, No. (%)	4 (26.7)	15 (20.5	0.600	x²
Early cerebral re-occlusion, No. (%)	0 (0)	17 (4.2)	0.384	x²

m = Mann-Whitney U test/X² = Ki-kare test.

respiratory tract; however, it can result in many tissue and organ damages. Neurological signs may be observed at the disease onset and course. The incidence of neurological complications is higher, especially in severe cases[14].

Our study revealed that 5.4% of the patients who underwent MT during the pandemic period were infected with SARS-CoV-2. The ET-COVID study reported this rate as 11%[6].

Similar to our study, the baseline NIHSS score of patients with COVID with large vessel occlusion who underwent thrombectomy was higher compared to the non-COVID group[6,15,16]. Contrary to a previous study in Barcelona[8], the severity of the initial stroke of patients who were admitted due to ischemic stroke was similar to the previous year. In the current study, patients with COVID-19 related strokes had increased stroke severity at the time of admission, which explains the increased mortality rates and worse clinical outcomes, compared to the non-COVID-19 group despite thrombectomy. High intubation rates due to lung problems may also be associated with increased mortality.

Our study revealed that 41.9% of patients with COVID-19 were intubated, which was similar to other studies[17]. Compared to the data that included the non-COVID-19 group who underwent thrombectomy, the rate of intubated patients and intervention with general anesthesia was quite higher. The conversion from conscious sedation to general anesthesia during the procedure carries risk in terms of aerosol production. Therefore, intubating the patients with COVID-19 with respiratory failure in a negative-pressure room before thrombectomy is logical[18].

Stroke generally occurs within 1-3 weeks after the onset of COVID-19 symptoms. However, similar to other studies[15], stroke was the first presenting symptom in 50% of the patients in our study. A study that evaluated 86 patients with COVID-19 reported COVID-19 as an independent risk factor for in-hospital stroke (odds ratio [2]: 20.9, 95% confidence interval: 10.4-42.0)[14].

Recent studies have investigated the impact of the COVID-19 pre-hospital management on the treatment effectiveness and its consequences on treatment delays for patients with AIS who were eligible for MT. Due to the pandemic, some delays that are associated with the organization of stroke occurred, but the temporal parameters could be reduced by applying certain algorithms[19]. Our study found that the symptom-to-puncture and symptom-to-recanalization periods were longer during the pandemic compared to the pre-pandemic period. This delay in treatment has also been observed at a similar rate in other studies[6]. However, the door-to-imaging time and puncture-to-recanalization time have been similar to those before the pandemic[16]. All the centers that were included in the study were pandemic hospitals that served a crowded group of patients with COVID-19, thus time delays are encountered in both the imaging and treatment processes of patients with acute stroke after March 2020. The use of personal protective equipment and Chest CT imaging are the potential reasons for the delay in symptom-to-puncture and symptom-to-recanalization time[20].

Our study revealed that patients with COVID-19 received less thrombolytic treatment. In Escalard's study, this ratio was similar to the non-COVID group[16]. The hematological effect of COVID-19 remains unclear, which may be related to the less thrombolytic therapy that is given to some patients.

Fewer stent retrievers were used in patients with COVID. The contact aspiration method is technically shorter compared to retractable stents, which may cause the contact aspiration method to be a first choice for compensating the time lost before the procedure in these patients. However, this difference in preference did not affect the success of recanalization.

Our study revealed no significant difference between both groups in terms of full recanalization rate, first-pass effect, and the number of procedures. The complication rate and re-occlusion rates of both groups were similar.

Causes, such as coagulopathy and vascular endothelial dysfunction, may lead to stroke in patients with COVID-19[19]. In our study population, dissection was a significantly more common cause of stroke in patients with COVID-19. Case reports have presented that COVID-19 may be a potential risk factor for dissection[21,22]. Increased cough and arterial wall damage that is triggered by a viral infection may be the underlying mechanisms for dissection[22]. To the best of our knowledge, this is the first study that demonstrated the higher proportion of extracranial cerebral vessel dissection as an etiology of ischemic stroke in patients with COVID-19 who underwent thrombectomy. However, further studies are needed to prove this causality.

The increase in stroke severity in COVID-19-related ischemic strokes as a result of increased large vessel occlusion strokes remains controversial. A study conducted by Ntaios et al[17] showed that ischemic strokes associated with COVID-19 have a worse functional outcome and higher mortality rates than non-COVID-19 ischemic strokes. Our study revealed a worse 24-hour NIHSS score, with a mortality rate of 37.5% higher in patients with COVID-19. Neurovascular pathologies, such as stroke, which increase mortality and morbidity, can be due to a wide range of mechanisms that are associated with SARS-CoV-2. In addition to pathophysiological features of the SARS-CoV-2, including endothelial activation and thrombosis, non-specific effects of inflammation and coagulation dysfunction are also seen in the pre-existing risk factors. Stroke can be caused by the direct effects of the virus, as well as the systemic response to infection[23]. Respiratory distress, acute respiratory distress syndrome, sepsis, shock, and cardiac problems that accompany COVID-19 may contribute to increased morbidity and mortality. Early diagnosis and timely implementation of treatment procedures can reduce mortality and morbidity rates.

Conclusions

This is the first study that revealed an increased frequency of dissection in patients with COVID-19. Our findings suggest that COVID-19-related ischemic strokes are associated with worse functional outcomes and higher mortality rates compared to non-COVID-19 ischemic strokes. Patients with high stroke scores and major vessel occlusions have a worse prognosis. The improvement in pre-hospital and in-hospital organizations and increasing stroke awareness during the pandemic period and timely applied recanalization techniques could increase good clinical outcome rates.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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