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Research Article

Evaluation of the Coexistence of Acute Cerebrovascular Disease and Covid-19

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Abstract

Objective: The aim of this study is to investigate the differences between acute cerebrovascular disease (CVD) with COVID-19 and acute cerebrovascular disease (CVD) without COVID-19.

Methods: This was a single-center, retrospective study. Using the database of the University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, In this study was analyzed 84 cases of CVD with COVID-19 and 56 cases of CVD without COVID-19. Statistical comparisons were performed using the Mann–Whitney U test and Pearson Chi-Square test.

Results: There were no significant differences between the two groups in terms of age, gender, or comorbidities ($p > 0.05$). The rates of large vessel occlusion, ischemic stroke, single lesion, anterior circulation lesion, and left hemisphere lesions were high in both groups. But there were no significant differences between the two groups. However, hemorrhagic stroke, multiple territory involvement, and mortality rates were significantly higher in the CVD with COVID-19 group compared to the CVD-only group ($p < 0.05$).

Urea, BUN, AST, CK, CRP, direct bilirubin, ferritin, neutrophil count and percentage, immunoglobulin percentage, INR, PTsec, immunoglobulin, and troponin T levels were significantly higher ($p < 0.05$) in the CVD with COVID-19 group. Meanwhile, GFR, Cl, Ca, albumin, RBC, lymphocyte count and percentage, monocyte percentage, basophil count and percentage, and PT% were significantly lower ($p < 0.05$) in the CVD with COVID-19 group.

Conclusions: The findings indicate that COVID-19 may contribute to more severe neurovascular complications and is associated with increased mortality rates.

Keywords: COVID-19, Cerebrovascular disease, Stroke, Neurovascular complication

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1. INTRODUCTION

Coronavirus disease (COVID-19) was first reported in China in December 2019 and has spread rapidly around the world. COVID-19 is a leading cause of critical pneumonia and death worldwide. Risk factors for severe COVID-19 include cardiovascular disease, diabetes mellitus, hypertension, and old age.[1] The effects of COVID-19 are likely to be increased blood clotting and thromboembolic complications resulting from inflammatory endothelial disruption. The possibility of a link between COVID-19 and acute stroke has been supported by individual case reports and small case series. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with altered blood clotting, systemic inflammatory damage to the endothelium, platelet activation and stasis, and increased thromboembolic complications, including venous and arterial embolism. Beyond pulmonary manifestations, COVID-19 infection is known to cause both direct and indirect cardiovascular and cerebrovascular complications. Although our knowledge of COVID-19 pathogenesis, inflammation, endothelial dysfunction, and coagulopathy is limited, they appear to be of critical importance in COVID-19-associated acute cerebrovascular disease (CVD).[2] Pathogenesis and optimal management of COVID-19-associated ischemic stroke are still unclear, but emerging evidence suggests that cytokine storm-triggered coagulopathy and endotheliopathy are possible mechanisms.[3]

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Acute cerebrovascular disease, especially ischemic stroke, has emerged as a serious complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which leads to coronavirus disease-2019 (COVID-19). Data collected on patients with COVID-19-related stroke has provided us with information such as the tendency for large vessel occlusion, multiple territory involvement, and rarely the involvement of other vessels.[4-7]

The aim of this study is to investigate the differences between acute cerebrovascular disease with COVID-19 and acute cerebrovascular disease without COVID-19.

2. MATERIAL AND METHOD

This was a single-center retrospective study. Using the database of University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, I conducted a retrospective study of 84 cerebrovascular disease (CVD) with covid-19 cases and 56 only CVD cases. The demographic characteristics, medical history, laboratory findings, brain Magnetic Resonance İmaging (MRI) results and outcome were extracted from electronic medical records. All patients CVD with COVID-19 in this study were diagnosed acording to the World Health Organisation (WHO) interim guidline had respiratory symtom, were SARS-CoV-2 Reverse Transcription- Polymerase Chain Reaction (PCR)-PCR positive in throat surab and had viral-like pnömonia on chest Computed Tomography (CT). The diagnosis of acute ischaemic or bleeding stroke was confirmed by brain CT or MRI and clinical symptoms.

To conduct the study, permission numbered 2021.01.211 was obtained from the Ministry of Health and our hospital's ethics committee.

2.1. Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of the variables was measured using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The independent samples t-test was used for the analysis of quantitative independent data that had a normal distribution. The Mann-Whitney U test was used for the analysis of quantitative independent data that did not have a normal distribution. For the analysis of qualitative independent data, the chi-square test was used, and when the conditions for the chi-square test were not met, the Fisher test was applied. SPSS 24.0 software was used for the analyses.

3. RESULTS

Data from 84 enrolled CVD with COVID-19 participants were compared with 56 only CVD patients. The mean age of the CVD with COVID-19 group was 69.22±15.73, while the mean age of the CVD group was 64.30±14.55. The age of the participants did not differ significantly ($p>0.05$) between the two groups (Table 2).

Glucose, creatinine, ALT, ALP, NA, K, P, T. Bil, Ind. Bil., WBC, HGB, HCT, rdw, monocyte, PLT, APTT values did not show any significant difference ($p>0.05$) between the two groups (Table 2).

There were significant differences ($p<0.05$) between the two groups in urea, BUN, GFR, AST, CK, CI, Ca, CRP, Albumin, Dir. Bil., ferritin, rbc, lymphocyte, Lymphocyte%, Neutrophil, Neutrophil%, monocyte%, immunoglobulin%, basophil, basophil%, PT%, INR, PTsec, immunoglobulin, TnT values (Table 2).

In the CVD with COVID-19 group, urea, BUN, AST, CK, CRP, Dir. Bil., ferritin, Neutrophil, Neutrophil%, immunoglobulin%, INR, PTsec, immunoglobulin, TnT values were significantly ($p<0.05$) higher than in the CVD group (Table 2).

In the CVD with COVID-19 group, GFR, Cl, Ca, Albumin, rbc, Lymphocyte, Lymphocyte%, monocyte%, Basophil, Basophil%, PT% values were significantly ($p<0.05$) lower than in the CVD group (Table 2).

The gender of the patients did not differ significantly between the groups ($p>0.05$) (Table 2).

Hypertension, diabetes mellitus, coronary artery disease and cerebrovascular disease did not differ significantly ($p>0.05$) between the two groups (Table 1) (Table 3).

In both groups, the rate of large vessel occlusion was higher than the rate of small vessel occlusion, but no significant difference (p>0.05) was found between the groups (Table 1) (Table 3).

In both groups, the rate of anterior circulation lesions was higher than the rate of posterior circulation lesions, but no significant difference (p>0.05) was found between the groups (Table 1) (Table 3).

The lesion rate was higher in the left hemisphere in both groups, but no significant difference (p>0.05) was found between the groups (Table 1) (Table 3).

Table 1.

Demographic data, medical history characteristics and neuroimaging findings of the participants

	CVD with Covid-19 (n=84)		CVD (n=56)		TOTAL (n=140)	
	n	**%**	**n**	**%**	**n**	**%**
gender						
female	45	53,6	24	42,9	69	49,3
male	39	46,4	32	57,1	71	50,7
HT						
(-)	29	34,5	20	35,7	49	35
(+)	55	65,5	36	64,3	91	65
DM						
(-)	42	50	35	62,5	77	55
(+)	42	50	21	37,5	63	45
CAD						
(-)	68	81	43	76,8	111	79,3
(+)	16	19	13	23,2	29	20,7
CVD						
(-)	69	82,1	45	80,4	114	81,4
(+)	15	17,9	11	19,6	26	18,6
vessel occlusion						
large vessel	49	58,3	39	69,6	88	62,9
small vessel	35	41,7	17	30,4	52	37,1
lesion number						
single	70	83,3	53	94,6	123	87,9
multiple	14	16,7	3	5,4	17	12,1
circulation						
anterior	56	66,7	39	69,6	95	67,9
posterior	28	33,3	17	30,4	45	32,1
hemispher						
right	23	27,4	20	35,7	43	30,7
left	47	56	29	51,8	76	54,3
both	14	12,6	7	12,5	21	15
lesion type						
infarct	74	88,1	56	100	130	92,9

Table 1. (Continued)

heamorrhagy	9	5,4	0	0	9	6,4
both	1	1,2	0	0	1	0,7
outcome						
discharge	61	72,6	52	92,9	113	80,7
death	23	27,4	4	7,1	27	19,3

Abbreviations: HT: Hypertension, DM: Diabetes Mellitus, CAD: Coroner Artery Disease, CVD: Cerebrovascular Disease

In both groups, the single lesion rate was higher than multiple lesions, but in the CVD with COVID-19 group, the multiple lesion rate was significantly ($p<0.05$) higher than in the CVD group (Table 1) (Table 3).

Table 2.

Comparison of laboratory parameters between the CVD with Covid-19 and CVD groups

	CVD with Covid-19	**CVD**	**Test**	**p***
	n=84	**n=56**	**statististic**	
Age	69,22±15,7	64,30±14,5	t=1,868	p=0,064[a]
glucose	165,80±87,05	149,08±83,44	z=-1,312	p=0,189[b]
urea	63,54±53,5	44,78±31,44	z=-2,425	**p=0,015[b]**
BUN	28,34±22,72	20,92±14,67	z=-2,236	**p=0,025[b]**
creatinine	1,37±1,69	0,97±031	z=-0,555	p=0,579[b]
GFR	67,46±30,56	77,15±24,91	t=-1,975	**p=0,005[a]**
ALT	54,54±294,43	26,32±51,02	z=-1,186	p=0,236[b]
AST	124,31±849,94	26,71±44,94	z=-3,068	**p=0,002[b]**
ALP	94,08±82,43	90,03±46,75	z=-1,072	p=0,284[b]
CK	178,89±264,89	69,88±53,57	z=-2,69	**p=0,009[b]**
CL	99,8±5,26	102,45±3,39	z=-2,663	**p=0,008[b]**
CA	8,68±0,84	8,98±0,56	t=-2,388	**p=0,018[a]**
NA	136,31±6,49	137,83±4,55	z=-1,931	p=0,053[b]
K	4,27±0,69	4,4±0,53	z=-1,129	p=0,259[b]
P	3,41±1,18	3,35±0,71	z=-0,997	p=0,319[b]
CRP	86,88±94,04	18,65±32,47	z=-5,508	**p=0,000[b]**
Albumin	32,06±7,46	37,94±4,10	z=-4,101	**p=0,000[b]**
T.Bil	0,71±1	0,52±0,36	z=-1,412	p=0,158[b]
Dir. Bil.	0,36±0,93	0,21±0,25	z=-2,258	**p=0,024[b]**
Ind.Bil.	0,36±0,27	0,32±0,19	z=-0,443	p=0,658[b]
Ferritin	650,75±1498,37	129,65±137,90	z=-4,243	**p=0,000[b]**
WBC	9,73±4,87	8,56±3	z=-0,987	p=0,324[b]
HGB	11,70±2,29	12,47±2,39	z=-1,761	p=0,078[b]
HCT	35,07±7,05	37,01±6,06	z=-1,680	p=0,093[b]
RDW	14,05±1,85	14,14±2,33	z=-0,253	p=0,800[b]

Table 2. (Continued)

RBC	4,10±0,76	4,43±0,77	t=-2,493	**p=0,014[a]**
Lymphocyte	1,75±2,98	2,22±2,02	z=-4,070	**p=0,000[b]**
Lymphocyte%	16,41±12,59	24,53±11,42	z=-4,405	**p=0,000[b]**
Neutrophil	7,57±4,22	5,75±2,71	z=-2,276	**p=0,023[b]**
Neutrophil%	74,87±15,74	64,46±13,49	z=-4,490	**p=0,000[b]**
Monocyte	0,62±0,35	0,69±0,22	t=-1,418	**p=0,159[a]**
Monocyte%	6,93±4,56	8,31±2,41	z=-3,359	**p=0,001[b]**
Immunoglobulin%	0,69±0,60	0,47±0,48	z=-3,725	**p=0,000[b]**
Basophil	0,09±0,60	0,04±0,02	z=-4,210	**p=0,000[b]**
Basophil%	0,27±0,27	0,47±0,27	z=-4,872	**p=0,000[b]**
PLT	239,71±108,24	254,03±89,90	t=-0,819	**p=0,414[a]**
APTT	27,83±9,52	30,66±40,24	z=-0,865	**p=0,387[b]**
PT%	85,64±18,56	89,70±23,78	z=-2,152	**p=0,031[b]**
INR	1,14±0,26	1,07±0,39	z=-3,580	**p=0,000[b]**
PTsec	15,05±13,07	12,29±4	z=-4,082	**p=0,000[b]**
Immunoglobulin	0,08±0,13	0,05±0,76	z=-3,158	**p=0,002[b]**
TnT	0,70±5,53	0,37±0,07	z=-2,143	**p=0,032[b]**

Abbreviations: mean ± standard deviation, a: Student t Test, b: Mann Whitney U test, BUN: Blood Urea Nitrogen, GFR: Glomerular Filtration Rate, ALT: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, CK: Creatine Kinase, CL: Chlorine, CA: Calcium, NA: Sodium, K: Potassium, P: Phosphorus, CRP: C-Reactive Protein, T.Bil.: Total Bilirubin, Dir. Bil.: Direct Bilirubin, Ind. Bil.: Indirect Bilirubin, WBC: White Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, RDW: Red Cell Distribution Width, RBC: Red Blood Cell, PLT: Platelet, APTT: Activated Partial Thromboplastin Time, PT: Prothrombin Time, INR: International Normalized Ratio, TnT: Troponin T.

The infarction rate was high in both groups, but the hemorrhage rate in the CVD with COVID-19 group was significantly ($p<0.05$) higher than in the CVD group. There was no hemorrhage in the CVD group (Table 1) (Table 3).

The mortality rate in the CVD with COVID-19 group was significantly ($p<0.05$) higher than in the CVD group (Table 1) (Table 3).

Table 3.

Comparison of demographic data, medical history, neuroimaging findings between the CVD with Covid-19 and CVD groups

	CVD with Covid-19	**CVD**	**Test statistic**	**p***
	n=84	**n=56**		
gender				
female	45(53,6)	24(42,9)		
male	39(46,4)	32(57,1)	x^2=1,543	p=0,214[a]
HT				
(-)	29(34,5)	20(35,7)		
(+)	55(65,5)	36(64,3)	X^2=0,021	p=0,885[a]
DM				
(-)	42(50)	35(62,5)		
(+)	42(50)	21(37,5)	X^2=2,121	p=0,145[a]

Table 3. (Continued)

CAD				
(-)	68(81)	43(76,8)		
(+)	16(19)	13(23,2)	X^2=0,355	p=0,551[a]
CVD				
(-)	69(82,1)	45(80,4)		
(+)	15(17,9)	11(19,6)	X^2=0,071	p=0,790a
vessel occlusion				
large vessel	49(58,3)	39(69,6)		
small vessel	35(41,7)	17(30,4)	X^2=1,841	p=0,175[a]
lesion number				
single	70(83,3)	53(94,6)		
multiple	14(16,7)	3(5,4)	X^2=4,028	**p=0,045[a]**
circulation				
anterior	56(66,7)	39(69,6)		
posterior	28(33,3)	17(30,4)	X^2=0,136	p=0,712a
hemispher				
right	23(27,4)	20(35,7)	X^2=1,256	p=0,534a
left	47(56)	29(51,8)		
both	14(12,6)	7(12,5)		
lesion type				
infarct	74(88,1)	56(100)		
heamorrhagic	9(5,4)	0(0)	X^2=7,179	**p=0,028[a]**
both	1(1,2)	0(0)		
outcome				
discharge	61(72,6)	52(92,9)		
death	23(27,4)	4(7,1)	X^2=8,841	**p=0,003[a]**

Abbreviations: mean ± standard deviation, a: Pearson Chi-Square. HT: Hypertension, DM: Diabetes mellitus, CAD: Coroner Artery Disease, CVD: Cerebrovascular Disease

4. DISCUSSION

Neurological complications of COVID-19 occur in almost one-third of patients. According to various studies, the frequency of cerebrovascular symptoms in patients with positive SARS-CoV-2 test results varies between 1% and 3%.[8] Acute ischemic stroke was the most common symptom. The cause of cerebrovascular complications in COVID-19 patients is probably multifactorial. In addition to coagulopathy, systemic inflammatory response, endothelial dysfunction and microthrombosis, organ failure and impaired cardiac function can be listed.[9] The characteristics of stroke in patients with COVID-19 are occlusion of large vessels, multiple involvement, high damage to the vertebrobasilar system, a cryptogenic structure and a progressive nature that causes high mortality and disability.[10]

The aim of this study is to investigate the differences between acute cerebrovascular disease with COVID-19 and acute cerebrovascular disease without covid-19.

It has been found that advanced age increases the risk of stroke as a complication of COVID-19. Patients who have stroke as a complication of COVID-19 are generally older, with a mean age of 65.5 years. However, some studies have reported stroke as a complication of COVID-19 in younger patients.[10-13,3] In this study, the mean age of the CVD with COVID-19 group was 69.22±15.73, while the mean age of the CVD group was 64.30±14.55. Although the age of the CVD with COVID-19 group

was high and consistent with the literature, the age of the participants did not differ significantly between the two groups (Table 2).

Interestingly, a significant number of studies report a male predominance for stroke complications in COVID-19 patients. The etiology remains unknown.[3,14] A study conducted in our country, which examined 1040 patients, also found that both the number of men presenting with suspected COVID-19 and the number of confirmed cases were higher in men[15]. In contrast to the literature, although the number of female participants was higher in the CVD with COVID-19 group in this study, the gender distribution did not differ significantly between the two groups.

Most patients who experience stroke as a complication of COVID-19 have one or more preexisting comorbidities. The most common comorbidities reported are hypertension and diabetes mellitus.[13,16] In this study, hypertension, diabetes mellitus, coronary artery disease and cerebrovascular disease did not show significant differences between the two groups.

Ischemic stroke is a more common complication of COVID-19 compared to hemorrhagic stroke.[10,17,18] In this study, the ischemic stroke rate was high in both groups, but the hemorrhage rate in the group that had a stroke as a complication of COVID-19 was significantly higher than in the stroke group (Table 3). There was no hemorrhagic stroke in the only CVD group.

In the literature, the rate of large vessel occlusions have been found to be higher than small vessel occlusions or lacunar strokes in ischemic strokes.[19-22] In this study, in line with the literature, the rate of large vessel occlusions was higher than small vessel occlusions in both groups, but no significant difference was found between the groups (Table 3).

There have also been several reports of hemorrhagic stroke as a complication of COVID-19.[23-25] Patients with hemorrhagic stroke tend to fare worse than patients with ischemic stroke.

In this study, all hemorrhagic strokes were in the CVD with COVID-19 group, and death occurred in 50% of hemorrhagic strokes. Consistent with the literature, patients with hemorrhagic stroke tended to be in worse condition than patients with ischemic stroke.

In the literature, multiple vascular territory infarction was frequent, affecting 27/103 (26 %) of the cases, while small vessel occlusion was reported in only 9/103 (9 %) of cases.[14]

In this study, the single lesion rate was higher in both groups than in multiple lesions, but the multiple lesion rate in the CVD with COVID-19 group was significantly higher than in the CVD group (Table 3).

Acute ischemic stroke in the vertebro-basilar territory was also common, being observed in 6/17 (35%) of patients[6]. Frequent occurrence of posterior circulation stroke has been also confirmed by other authors.[25,5] In this study, the rate of anterior circulation stroke was higher than the rate of posterior circulation stroke in both groups, but no significant difference was found between the groups (Table 3).

The lesion rate was higher in the left hemisphere in both groups, but no significant difference was found between the groups (Table 3). No data on this subject was found in the literature.

The mortality rate in the CVD with COVID-19 group was significantly higher than in the CVD group (Table 3).

In the literature, D-dimer, Fibrinogen, CRP, ferritin, INR, PT, APTT levels were found to be high in patients with CVD with COVID-19.[20,27-29] In this study, urea, BUN, AST, CK, CRP, Dir. Bil., ferritin, Neutrophil, Neutrophil%, immunoglobulin%, INR, PTsec, immunoglobulin, Troponin T(TnT) values were significantly higher in the CVD with COVID-19 group than in the CVD group (Table 2). CRP, ferritin, INR, PT were found to be high, consistent with the literature.

It was observed in the literature that platelet and lymphocyte counts were low.[4,30]

In this study, GFR, Cl, Ca, Albumin, rbc, Lymphocyte, Lymphocyte%, monocyte%, Basophyle, Basophyle%, PT% values were significantly lower in the CVD with COVID-19 group than in the CVD group (Table 2). Only the

lymphocyte value was found to be low, consistent with the literature.

In this study, glucose, creatinine, ALT, ALP, NA, K, P, T. Bil., Ind. Bil., WBC, Hgb, Hct, rdw, monocyte, PLT, APTT values did not show any significant difference between the two groups (Table 2).

This study has some limitations. Since fibrinogen and D-dimer were not measured in the CVD group, these values could not be compared between the two groups.

In conclusion, in this single-center, retrospective study comparing the CVD with COVID-19 group and the CVD without COVID-19 group, there was no difference between the two groups in terms of age, gender, and concomitant diseases. The rates of large vessel occlusion, ischemic, single, anterior circulation and left hemisphere lesions were high in both groups. Hemorrhagic stroke, multiple infarction, and death rates were significantly higher in the CVD with COVID-19 group compared to the CVD group. COVID-19 infection predisposes to stroke, and the mortality of stroke accompanied by COVID-19 is higher than stroke alone.

Article Information Form

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the author.

The Declaration of Ethics Committee Approval

To conduct the study, permission numbered 2021.01.211 was obtained from the Ministry of Health and our hospital's ethics committee.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

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