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Research

Is Ischemic Stroke Declines During the COVID-19 Pandemic?

COVİD-19 Pandemisinde İskemik İnmeler Azaldı mı?

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ABSTRACT

Objective: A decrease in the number of ischemic strokes has been reported during the coronavirus disease-2019 (COVID-19) pandemic period. The aim of this study was to determine the effect of COVID-19 and associated risk factors on the number of ischemic strokes in hospitalizations during the COVID-19 period.

Methods: This cross-sectional study was conducted using hospital records. Data of patients who underwent a COVID-19 real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test between 2020 and 2021 were included. In addition to RT-PCR test results, the diagnosis of ischemic stroke and known risk factors for ischemic stroke (gender, age, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, hypercholesterolemia, congestive heart failure, coronary artery disease, peripheral vascular disease, chronic kidney disease) were evaluated.

Results: According to the inclusion criteria, 25,522 patient records were included in the analysis. There were 123 (0.6%) acute ischemic stroke patients among 19,051 COVID-19-negative patients and 23 (0.4%) among 6471 positive patients. Among the covariates, age and diabetes have a significant effect on acute ischemic stroke. In path analysis, the negative direct effect of RT-PCR positivity on acute ischemic stroke was reversed through the mediator variable effect of diabetes and age. Patients with diabetes and higher age have an increased risk of acute ischemic stroke if they have COVID-19.

Conclusion: Evidence is not satisfactory to determine the effect of COVID-19 on ischemic stroke. Reports of a decrease in the number of hospitalizations due to ischemic stroke are accumulating. This result may be due to the direct effect of COVID-19, the lack of recognition of clinical symptoms, or the decrease in hospital admissions of patients without a severe clinical picture. In the presence of accompanying risk factors such as age and diabetes that will aggravate the stroke clinic, the reducing effect of COVID-19 on the number of ischemic strokes disappears.

Keywords: COVID-19, ischemic stroke, COVID-19 testing, ischemic stroke: diagnosis, ischemic stroke: epidemiology, pandemic

ÖZ

Amaç: Yeni koronavirüs hastalığı-2019 (COVİD-19) pandemi döneminde iskemik inme sayısında azalma bildirilmiştir. Çalışmanın amacı, COVİD-19 döneminde hastaneye yatışlarda COVİD-19 ve ilişkili risk faktörlerinin iskemik inme sayısı üzerindeki etkisini belirlemektir.

Gereç ve Yöntem: Bu kesitsel çalışma hastane kayıtları üzerinden yapıldı. 2020-2021 tarihlerinde COVİD-19 gerçek zamanlı ters transkriptaz-polimeraz zincir reaksiyonu (RT-PCR) testi yaptırmış hasta verileri dahil edildi. RT-PCR test sonuçlarına ek olarak, iskemik inme tanısı, iskemik inme için bilinen risk faktörleri (cinsiyet, yaş, diabetes mellitus, kronik obstrüktif akciğer hastalığı, hipertansiyon, hiperkolesterolemi, konjestif kalp yetmezliği, koroner arter hastalığı, periferik vasküler hastalık, kronik böbrek hastalığı) değerlendirildi.

Bulgular: Dahil etme kriterlerine göre 25.522 hasta kaydı analize dahil edildi. 19.051 COVİD-19 negatif arasında 123 (%0,6), 6471 pozitif hasta arasında 23 (%0,4) akut iskemik inme hastası vardı. Ortak değişkenler arasında yaş ve diyabetin akut iskemik inme üzerinde önemli bir etkisi olduğu belirlendi. Path analizinde, RT-PCR pozitifliğinin akut iskemik inme üzerindeki olumsuz doğrudan etkisi, diyabet ve yaşın aracı değişken etkisi ile tersine çevrilmiştir, diyabetli ve daha ileri yaştaki hastalarda COVİD-19 varsa akut iskemik inme riski artmıştır.

Sonuç: COVİD-19'un iskemik inme üzerindeki etkisine karar vermek için kanıtlar tatmin edici değildir. İskemik inme nedeniyle hastaneye yatış sayısında azalma raporları birikmektedir. Bu sonuç, COVİD-19'un doğrudan etkisi olabileceği gibi, klinik semptomların tanınmaması veya ciddi bir klinik tabloya sahip olmayan hastaların hastaneye başvurularının azalmasından da kaynaklanabilir. İnme kliniğini ağırlaştıracak yaş ve diyabet gibi eşlik eden risk faktörlerinin varlığında COVİD-19'un iskemik inme sayısını azaltıcı etkisi ortadan kalkar.

Anahtar Kelimeler: COVİD-19, iskemik inme, COVİD-19 testi, iskemik inme: tanı, iskemik inme: epidemiyoloji, pandemic

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INTRODUCTION

The causative agent of coronavirus disease-2019 (COVID-19), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a new type of coronavirus known as a positive polarity, single-stranded, enveloped RNA virus with the potential to invade neurological tissues (1). Many neurological diseases and neurological complications related to these diseases have been reported. In a case series of 214 patients from China, 36.4% reported neurological complications in addition to systemic symptoms (2).

Neurological complications may result from a systemic response to infection or from the direct effects of the virus. Direct spread of the virus to the nervous system, immune system disorder, renin-angiotensin system, and neurological damage caused by systemic disorder are thought to be effective mechanisms (3).

Cases of ischemic and hemorrhagic stroke have been reported in patients with COVID-19. Stroke pathogenesis is associated with increased fibrinogen, low platelet levels, coagulopathy, and increased D-dimer levels. The cytokine storm observed in COVID-19 infection can cause prothrombotic activation and microvascular thrombosis. In autopsy studies of infected patients, viral inclusions were detected in endothelial cells, and it has been reported that ischemic events may develop directly due to endothelial damage (4).

The frequency of stroke during the pandemic period can be evaluated from two different perspectives: in the whole community and in patients diagnosed with COVID-19. In different series reported so far, the frequency of stroke in COVID-19 cases with a definitive diagnosis and requiring hospital inpatient care varies between 2.8% and 5.4% (2,5).

Most of the cases reported in the literature are diagnosed with ischemic stroke (6). However, the retrospective nature of these studies, limited number of cases, and lack of detailed clinical and neuroradiological features are important points to consider when evaluating these data. Another noteworthy situation is that stroke is seen more frequently in COVID-19 cases with a moderate and severe clinical course. Initial observations have shown that the presence of ischemic or hemorrhagic stroke is associated with poor prognosis during COVID-19 infection (2).

In the general population, it has been reported that the frequency of stroke decreases, especially in admissions to emergency services. Considering the data of the last five years in Italy, which has experienced the devastating effects of the COVID-19 pandemic, in a center where an average of 51 new ischemic stroke cases per month is observed, surprisingly, only six ischemic stroke cases were admitted between February 21 and March 25, 2020. While 21% of the strokes admitted in the pre-pandemic period were ischemic strokes due to large vessel occlusion, only one ischemic stroke due to cardioembolic large vessel occlusion was recorded during the pandemic period (7).

The aim of this study was to determine the number and effects of COVID-19 on ischemic strokes during the pandemic period on the records of our hospital, which is a regional tertiary health center.

METHODS

This study was conducted with the approval of the Clinical Research Ethics Committee of the Çanakkale Onsekiz Mart University (decision no: 2022-03, date: 02.02.2022). The study was conducted on hospital records by including the data of patients who had COVID-19 polymerase chain reaction (PCR) test (positive or negative results, both will be examined).

In this cross-sectional study, data from patients who underwent COVID-19 PCR testing between 2020 and 2021 at Çanakkale Onsekiz Mart University Hospital were included in the review. In addition to the diagnosis of acute ischemic stroke (AIS), patient characteristics and disease diagnoses that pose a risk for this disease were compiled from the patient records, and arrangements and analyses were made in accordance with the purpose of the study.

Research Variables

In this study, the prevalence of AIS and the effect of exposure to COVID-19 on AIS in the determined period were examined. In addition, the possible effects of AIS risk factors and the change in these possible effects due to exposure to COVID-19 have also been examined.

These variables can be classified as

- Output variable: AIS,
- Exposure variable: COVID-19 (as positive or negative according to the RT-PCR result),
- Variables Potentially Affecting AIS and the covariate with COVID-19:

Gender, age, previous cerebrovascular disease (p-CVD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), hypertension (HT), hypercholesterolemia (HCL), congestive heart failure (CHF), coronary artery disease (CAD), peripheral vascular disease (PVD), and chronic kidney disease (CKD).

Patient Population

The criteria for inclusion in the data file are as follows:

- The patient underwent a COVID-19 PCR test.
- The patient's COVID-19 PCR result was reported as positive or negative.
- The patient was 18-years-old or older.
- Knowing whether the patients have had an AIS.
- Gender, age, and CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD diagnostic information of the patients were present.

The number of patients included in the analysis according to the inclusion criteria was 25,522. The distribution of patient characteristics according to the variables listed above is presented in Table 1.

Statistical Analysis

Data analysis was carried out in two steps.

Step 1: This step is structured in two stages. In the first stage, the relationships between AIS, which is the output variable, and gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD, which may have possible effects, were examined. In the second stage, gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD were accepted as covariate variables, and the relationship between COVID-19 exposure and AIS was examined. These analyses are modeled using logistic regression (8).

Step 2: Path analysis was performed in data analysis in this step. Significant relationships from the logistic regression analysis were used as preliminary information. As detailed in the findings section, the three variables that had a significant impact on AIS were DM, age, and COVID-19. The effect of COVID-19 on AIS was modeled by path analysis of DM and age mediator variables. Path analysis is an approach to model explanatory relationships between observed variables. The defining feature of path analysis models is the absence of hidden variables. Path analysis models are special cases of structural equation models (9). Since the variables in the model are categorical and there is no normal distribution expectation, the estimations were made using the "Asymptotic Distribution Free" method.

RESULTS

COVID-19 and Ischemic Stroke

AIS was diagnosed in 123 (0.6%) of the total 19,051 COVID-19-negative patients. AIS was diagnosed in 23 (0.4%) of 6471 COVID-19-positive patients. The rate of AIS diagnosis in COVID-19-positive patients is significantly lower than that in COVID-19-negative patients.

Analysis

Step 1: The impact of COVID-19 on AIS was modeled by logistic regression. Gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD variables, which may have possible effects on AIS, were taken as covariate variables,

Table 1. Patient characteristics

Gender	Male 13,147 (51.5%)	Female 12,375 (48.5%)
Age	Mean =44.2	Standard deviation =17.3
COVID-19 (RT-PCR)	Negative 19,051 (74.6%)	Positive 6471 (25.4%)
Clinical conditions	**Present n (%)**	**Not-present n (%)**
Acute ischemic stroke	146 (0.6%)	25,376 (99.4%)
Previous cerebrovascular disease	1411 (5.5%)	24,111 (94.5%)
Hypertension	3749 (14.7%)	21,773 (85.3%)
Diabetes mellitus	3529 (13.8%)	21,993 (86.2%)
Coronary artery disease	1179 (4.6%)	24,343 (95.4%)
Congestive heart failure	436 (1.7%)	25,086 (98.3%)
Chronic obstructive pulmonary disease	471 (1.8%)	25,051 (98.2%)
Hypercholesterolemia	3135 (12.3%)	22,387 (87.7%)
Peripheral vascular disease	1732 (6.8%)	23,790 (93.2%)
Chronic kidney disease	444 (1.7%)	25,078 (98.3%)

COVID-19: Coronavirus disease-2019, RT-PCR: Real-time reverse-transcriptase polymerase chain reaction

and the effect of COVID-19 on AIS was remodeled with them. The results are presented in Table 2.

According to the analysis results, COVID-19 disease is effective against AIS [odds ratio (OR): 1.82, p=0.008]. Of the total 19,051 COVID-19-negative patients, 18,928 (99.4%) were AIS-negative, whereas 123 (0.6%) were AIS-positive. Of the 6471 COVID-19-positive patients, 6448 (99.6%) were AIS-negative, whereas 23 (0.4%) were AIS-positive. As COVID-19 reverted to a positive diagnosis, AIS-positive diagnosis showed a decrease 0.2%, and this decrease is significant.

In addition, when modeled with the COVID-19 covariate variables gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD, a small increase from the COVID-19 coefficient (from B=0.600 to B=0.622) but shows the same effect on AIS with a similar significance level (OR: 1.86, p=0.007).

Among the variables gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD, whose possible effects were examined and considered as covariate variables, age (OR: 1.08, p<0.0001) and DM (OR: 0.53, p=0.002) has a significant effect on AIS.

Age has a significant effect on AIS. The probability of developing AIS increases with age.

Table 2. Relationships between AIS and COVID-19

Variables	B	OR (95% CI)	p-value
Step 1			
COVID-19	0.600	1.82 (1.17-2.85)	**0.008**
Step 2			
COVID-19	0.622	1.86 (1.19-2.93)	**0.007**
Gender	0.280	1.32 (0.94-1.86)	0.105
Age	0.072	1.08 (1.06-1.09)	**<0.0001**
p-CVD	16.971	23456229.28 (0)	0.986
DM	-0.633	0.53 (0.36-0.79)	**0.002**
COPD	-0.108	0.89 (0.44-1.83)	0.766
HT	-0.141	0.87 (0.57-1.34)	0.519
HCL	0.148	1.16 (0.70-1.92)	0.565
CHF	0.033	1.03 (0.51-2.08)	0.927
CAD	0.034	1.03 (0.59-1.82)	0.909
PVD	0.208	1.23 (0.68-2.23)	0.491
CKD	-0.311	0.73 (0.37-1.46)	0.376

COVID-19: Coronavirus disease-2019, AIS: Acute ischemic stroke, OR: Odds ratio, CI: Confidence interval, p-CVD: Previous cerebrovascular disease, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, HT: Hypertension, HCL: Hypercholesterolemia, CHF: Congestive heart failure, CAD: Coronary artery disease, PVD: Peripheral vascular disease, CKD: Chronic kidney disease

Of the 21,993 DM-negative patients, 21,895 (99.6%) were AIS-negative, whereas 98 (0.4%) were AIS-positive. While 3481 (98.6%) of the total 3529 DM-positive patients were AIS negative, 48 (1.4%) were AIS positive. As patients had a DM diagnosis, the probability of a positive diagnosis of AIS increased by 1.0%.

Step 2: Logistic regression gave an idea about the variables that were significantly correlated with AIS. AIS and COVID-19, age, and DM are associated variables. Among these variables, the explanatory levels were examined by path analysis. In path analysis, it is possible to use internal and external variables and mediator variables. As stated by Baron and Kenny (10), the full mediator effect reduces the relationship between the explanatory variable and the explained variable to zero. The path analysis performed was modeled as shown in Figure 1. Estimates of the modeling in the path analysis are presented in Table 3.

In direct effects, DM and age increased AIS positivity (p<0.05). Again, as a direct effect, as COVID-19 turns positive, AIS becomes negative, and this effect is significant (p<0.05). However, the effect of COVID-19 on AIS was reversed through the mediator variable effects of DM and age. Therefore, as COVID-19 positive, it tends to be AIS positive. In this case, patients with DM and age risk increased their risk of AIS if they received COVID-19.

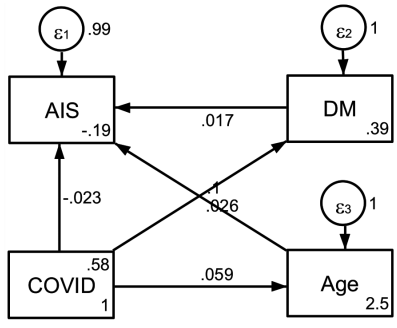

Figure 1. Model of relationships and mediator effect between AIS, COVID-19, age, and DM

COVID-19: Coronavirus disease-2019, AIS: Acute ischemic stroke, DM: Diabetes mellitus

Table 3. Estimates of Path analysis

Effects	Coefficient	p-value
Direct effect		
DM → AIS	0.0047	0.008
Age → AIS	0.0005	<0.0001
COVID-19 → AIS	-0.0041	<0.0001
Indirect effect		
COVID-19 → DM, Age → AIS	0.0012	<0.0001

DISCUSSION

The sociological effects of the pandemic, which are added to the effects of the COVID-19 infection process, bring many unknowns and discussions. Different results have been reported in terms of the incidence of AIS after COVID-19, and the issue has not yet been clarified.

In this study conducted on tertiary hospital records, it was determined that there was a significant decrease in ischemic stroke cases after the diagnosis of COVID-19. According to our results, the number of patients diagnosed with AIS during the pandemic period was significantly lower in patients with COVID-19. While performing the analyses, the decrease was shown to be evident in patients without additional risk factors. This decreasing effect due to COVID infection is not observed when DM and advanced age, which are seen to pose a risk for strokes, are present in the patient population examined. This result suggests that the comorbidity of advanced age and comorbid diseases caused an increase in AIS during the COVID-19 pandemic or that only severe patients were admitted to the hospital during the pandemic period.

According to the definition of the World Health Organization, a stroke is the sudden loss of function of a part of the brain or the entire brain, lasting for 24 h or more (11). Many views have been proposed regarding the pathophysiological mechanisms related to the development of stroke during COVID-19 infection. The uncontrollable cytokine storm observed in severe cases can lead to multi-organ failure. Activation of the microthrombotic pathway, particularly with destructive pathological mechanisms mediated by the endothelial system, may cause stroke. In infected cases, there is a tendency for thrombosis due to increased D-dimer, fibrinogen, and C-reactive protein (CRP) levels. In addition, inflammatory markers and inflammatory cytokines, such as tumor necrosis factor-α, interleukin-2 (IL-2) receptor, and IL-6, were increased. In particular, the role of IL-6 in stroke has not been clarified. Studies have reported that increased IL-6 levels adversely affect the volume of infarcts in the brain and the long-term outcome (12). In a laboratory study, IL-6 was shown to increase angiogenesis after stroke (13).

Viral inclusion structures were detected in the endothelial cells in postmortem examinations of infected patients. Thus, ischemic events may develop because of direct endothelial damage and widespread endothelial inflammation (14). Widespread microvascular thrombosis is seen with prothrombotic activation together with the cytokine storm that also occurs in COVID-19 infection, and D-dimer levels are found to be high in these patients (7). However, there is a decrease in fibrinogen values and thrombocytopenia (4).

Italian researchers have additionally hypothesized a pathophysiologic mechanism behind this decreased stroke occurrence, based on the controversial role of IL-6 in stroke (15). There is experimental evidence that IL-6, which is elevated in severe COVID-19, has a neuroprotective effect and enhance angiogenesis. The alternate explanations proposed are based on the thrombocytopenia encountered even in patients with mild COVID-19 (12). It is likely that low platelets prevent the formation of large clots in the intracranial circulation (16). Lastly, widespread mitigation measures, which have minimized the prevalence of influenza in the community, could have decreased the negative impact of the flu on cardiovascular disease and stroke. Further research into the cause of the observed associations is warranted (17).

In a different study, a reduction of 39% was observed in patients undergoing imaging with a preliminary diagnosis of stroke (18). A study comparing the pandemic period with the same period of the previous year reported a 36.4% decrease in stroke admissions (19). While the number of mild and moderate strokes with TIA decreased during the pandemic period, there was no significant change in the number of severe strokes and intraparenchymal hemorrhages (20).

In a study based on data from 227 hospitals, a decrease was reported in the number of stroke-related therapeutic interventions during the COVID-19 era. This study showed that a decline in stroke admissions resulted in fewer patients being treated with thrombolysis in 2019 than in 2020. Similarly, it has also been shown that patients who are not hospitalized lose their chances of receiving appropriate secondary prevention treatments for carotid revascularization, antiplatelet therapies, lipid-lowering therapies, anticoagulation for atrial fibrillation, and blood pressure management (21).

This decrease in stroke cannot be fully explained by sociodemographic factors. Measures such as restriction of free movement to control the rate of the pandemic, encouraging not going to emergency services except in very urgent situations, and the tendency not to apply to the emergency services due to the fear of being infected can partly explain the decrease in the number of strokes recorded.

Many risk factors have been identified in stroke. Unchangeable risk factors include age, gender, race, low birth weight, genetic factors, and modifiable risk factors include HT, heart diseases, DM, high blood cholesterol and lipids, smoking, asymptomatic carotid stenosis, familial

Mediterranean anemia, hormonal therapy after menopause, diet, obesity, and physical activity (22).

Dysregulation of the natural immune response in the background of chronic diabetes, endothelial dysfunction, and impaired barrier structure cause proinflammatory hypercoagulability, the formation of infections, and their more severe course (23). When cellular mechanisms triggered by COVID-19 and diabetes-specific pathological changes come together, the likelihood of a cytokine storm resulting in organ damage in individuals with diabetes increases exponentially.

IL-6, fibrinogen, ferritin, D-dimer, and CRP levels were found to be significantly higher in individuals with diabetes infected with COVID-19 than in non-diabetic subjects (24). A report of 72,314 cases of COVID-19 published by the Chinese Center for Disease Control and Prevention showed that mortality in people with diabetes (7.3%) is about three times higher than that in people without diabetes (2.3%) (25). This may explain why stroke risk factors such as diabetes are indicators of poor prognosis in patients with COVID-19 infection and an increase in AIS in COVID-19.

Infections are the primary cause of death in 1/3 of individuals aged 65 years and over and contribute to death in many older adults. They also have a significant impact on morbidity in older adults, exacerbating underlying diseases and leading to increased secondary risk and functional decline in the elderly (26). As the immune system ages, increased susceptibility to infections, cancer, and autoimmune disorders occurs. In a national study of 88,747 US veterans tested for SARS-CoV-2 infection between February 28 and May 14, 2020, those testing positive had a 4.2-fold risk of mechanical ventilation and a 4.4-fold risk of death compared with those testing negative. Among those who tested positive for SARS-CoV-2, older age was the strongest risk factor associated with hospitalization, mechanical ventilation, and mortality (27).

In studies conducted in China, the most common comorbidities in patients with COVID-19 were found to be HT (23.2%) and DM (10.9%) (28,29). Yang et al. (30) reported in a meta-analysis that the most common comorbidities were HT, DM, cardiovascular diseases, and respiratory system diseases. In this study, it was stated that the advanced age group and comorbidity of the patients may be associated with the serious disease picture (30).

In the English National Audit cohort, the risk ratio of COVID-19 death for type 1 diabetes was 3.51 and that for type 2 diabetes was 2.03. When adjusted for age, sex, and diabetes duration, people who developed fatal or critical care unit-treated COVID-19 on average had worse profiles for almost every clinical measure examined; they were more likely to have other comorbidities and evidence of diabetic microvascular disease (31).

In this study, the risk of COVID-19 and comorbid risk factors for AIS were evaluated. The fact that individuals with COVID-19 are older and the comorbidity of pre-existing DM disease is an unfavorable predictive factor for the occurrence of AIS in patients with COVID-19.

CONCLUSION

In terms of stroke, both the social effects of the pandemic and the process of COVID-19 infection bring many unknowns. There are insufficient evidence to determine whether there are fewer or more stroke patients due to COVID-19. The current results of these studies are contradictory. However, patients with COVID-19 may develop a new stroke, and the presence of other systemic and neurological symptoms of COVID-19 may complicate the diagnosis of stroke. Stroke symptoms are often noticed by another family member, friend, or someone outside the home before they are noticed by the patient himself. During the pandemic period, clinical findings may have been missed in patients with AIS, and applications may have decreased or been delayed because of strict measures to stay at home, individuals' avoidance of contact for fear of being infected, or living alone.

In this study, it was determined that COVID-19 infection decreased hospital admissions in AIS. It has been suggested that the older age of individuals with DM and COVID-19 as a comorbid disease causes AIS or that hospital admission increases because of more severe clinical findings and hospital care is required in this group.

The main limitation of our study seems to be that the study was conducted on data from a single center, the hospital worked as a private pandemic hospital during the COVID-19 pandemic, and the decrease in the number of applications other than COVID-19 patients during this period. Comprehensive studies and aggregate analyses are expected to yield definitive conclusions on the subject.

ETHICS

Ethics Committee Approval: This study was conducted with the approval of the Clinical Research Ethics Committee of the Çanakkale Onsekiz Mart University (decision no: 2022-03, date: 02.02.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: Ö.O., E.M.Ş., Ç.T., Design: Ö.O., E.M.Ş., Ç.T., Data Collection or Processing: Ö.O., E.M.Ş., Analysis

or Interpretation: Ö.O., E.M.Ş., Ç.T., Literature Search: Ö.O., E.M.Ş., Ç.T., Writing: Ö.O., E.M.Ş., Ç.T.

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