Effect of COVID-19 on emergency admissions for young patients with ischemic stroke: An interrupted time series analysis

COVID-19'un genç hastalarda iskemik inme nedenli acil başvurularına etkisi: Kesintili zaman serisi analizi

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Abstract

Aim: This study aims to evaluate the influence of Coronavirus Disease-19 (COVID-19) on the frequency of emergency admissions for ischemic stroke among both young and general populations at a university hospital in Turkey.

Methods: An interrupted time series analysis was employed in this study, utilizing retrospectively collected data from the Bezmialem Vakıf University Hospital system. The study included patients who visited the hospital emergency department from May 2019 to February 2023 and were diagnosed with ischemic stroke.

Results: 2196 patients with ischemic stroke were admitted to our hospital and 277 of them were young stroke patients. During the pre-pandemic period, there was a noteworthy rise in overall admissions for ischemic stroke ($p<0.001$); however, no significant change was observed in the rate of admissions for young stroke cases ($p>0.05$). The COVID-19 pandemic had an immediate impact on emergency ischemic stroke admissions, leading to a significant decrease in total admission numbers. Upon analyzing the post-COVID-19 period, we observed that COVID-19 did not exert a significant influence on the rate of strokes among the youth population.

Conclusion: The hospital admissions of patients with ischemic stroke have been significantly affected by the outcomes of quarantine measures implemented during the COVID-19 period. However, when the analysis of the post-COVID-19 period was conducted using interrupted time series analysis, a significant impact of COVID-19 on the admissions of young patients with ischemic stroke was not observed.

Keywords: COVID-19; interrupted time series analysis; stroke

Öz

Amaç: Bu çalışma, Koronavirüs Hastalığı-19 (COVID-19)'un Türkiye'deki bir üniversite hastanesinde hem genç hem de genel popülasyonda iskemik inme nedeniyle acil başvuru sıklığı üzerindeki etkisini değerlendirmeyi amaçlamaktadır.

Yöntemler: Bu çalışmada Bezmialem Vakıf Üniversitesi Hastanesi sisteminden retrospektif olarak toplanan veriler kullanılarak kesintili zaman serileri analizi kullanılmıştır. Çalışmaya Mayıs 2019 ile Şubat 2023 tarihleri arasında hastane acil servisine başvuran ve iskemik inme tanısı alan hastalar dahil edilmiştir.

Bulgular: Hastanemize iskemik inmeli 2196 hasta başvurmuş ve bunların 277'si genç inme hastası olduğu görülmüştür. Pandemi öncesi dönemde, iskemik inme nedeniyle hastane başvurularında istatiksel olarak anlamlı bir artış olmakla birlikte ($p<0.001$), genç inmeli olguların başvuru oranlarında anlamlı bir değişiklik gözlenmemiştir. ($p>0,05$). COVID-19 pandemisi acil iskemik inme başvuruları üzerinde ani bir etkiye neden olmuş ve toplam başvuru sayılarında önemli bir düşüşe yol açmıştır. COVID-19 sonrası dönem analiz edildiğinde, COVID-19'un genç popülasyondaki inme oranları üzerinde istatiksel açıdan anlamlı bir etkisi olmadığı görülmüştür.

Sonuç: İskemik inmeli hastaların hastaneye başvuruları, COVID-19 döneminde uygulanan karantina önlemlerinin sonuçlarından önemli ölçüde etkilenmiştir. Ancak kesintili zaman serisi analizi kullanılarak COVID-19 sonrası analizi edildiğinde, genç iskemik inmeli hastaların başvurularında COVID-19'un anlamlı bir etkisi gözlenmemiştir.

Anahtar Sözcükler: COVID-19; inme; veri analizi

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INTRODUCTION

The World Health Organization declared a pandemic on March 11, 2020, marking the significant global spread of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which leads to the development of Coronavirus Disease-19 (COVID-19) disease. This infectious disease has had far-reaching consequences on the healthcare systems worldwide. The emergence of COVID-19 has not only altered the mortality rate and disease burden directly as a communicable disease but also impacted non-communicable conditions such as cerebrovascular diseases, cardiovascular diseases, and dementia, further increasing the overall burden of illness (1).

Although respiratory disease is the most common and significant manifestation of COVID-19, there have been notable reports of neurological symptoms. According to a Rapid Review conducted by Mark Ellul et al, COVID-19 appears to have a higher propensity for causing thrombotic vascular events, including stroke, compared to other coronaviruses and seasonal infectious diseases (2). A study by Merkler et al found a 7.6 (times) increased risk of stroke in patients with COVID-19 compared to those with influenza (3). Another study by Yang et al discovered that the risk of acute ischemic stroke was 10 times higher in the first three days after COVID-19 diagnosis in individuals aged 65-74 without a history of stroke (4). While some studies suggest a significant increase in the risk of ischemic stroke following COVID-19 diagnosis (5,6), others have reported that acute ischemic events occur less frequently or at a similar frequency as expected in hospitalized COVID-19 patients (7,8).

Epidemiological evidence indicates a significant rise in the occurrence of ischemic stroke among young individuals. The long life expectancy of young stroke patients and the substantial long-term care expenses present considerable challenges for healthcare systems (9). A commentary published in The Lancet highlighted the relationship between COVID-19 and stroke in young populations who lack typical vascular risk factors, sometimes exhibiting only mild respiratory symptoms. The need for comprehensive research in this area was emphasized (10).

Interrupted time series (ITS) analysis is a method of statistical analysis involving tracking a long-term period before and after a point of intervention to assess the intervention's effects. this advanced statistical method can provide important information in terms of seeing the effects of COVID-19. Studies examining the relationship between COVID-19 and stroke with interrupted time series analysis are limited (11-14). These studies in the literature include the period until July 2020 at most and draw attention to the effect of stroke-related hospital admissions during quarantine processes, mostly due to the COVID-19 pandemic. In addition, no study was found that evaluated the effect of COVID-19 in young stroke patients. The aim of this study is to examine the effect of COVID-19 infection on the number of hospital admissions due to stroke in the young population by examining the number of patients admitted to our hospital for stroke between May 2019 and Şubat 2023 with an interrupted time series analysis.

MATERIALS AND METHODS

Patients

This study was carried out retrospectively through the hospital information system of Bezmialem Vakif University. Patients with a diagnosis of cerebrovascular disease were identified from the emergency admission to the hospital between May 2019 and February 2023. The beginning of the COVID-19 epidemic in our country was taken as the intervention point in March 2019. Patients were identified according to the International Classification of Diseases-Tenth Revision (ICD-10) codes: the codes were I63.9, I64, I67.9. The epicrisis and MRIs of these patients were reviewed, and those diagnosed with ischemic stroke by a neurologist were included in the study, hemorrhagic stroke patients were excluded. For this study, the age range of young stroke was taken as 18-50. The study was approved by the Non-Interventional Research Ethics Committee of Bezmialem Vakıf University (date: 24.01.2023, decision no: 2022/404).

We investigated the impact of COVID-19 on stroke admissions by analyzing the total number of stroke patients, the total number of young stroke patients, and the young/total stroke ratio. Our study was exclusively conducted at a single hospital, and it is essential to recognize that hospital policies during the COVID-19

and post-COVID-19 periods may have influenced the admission numbers. Hence, we performed a statistical analysis on the proportion of young individuals among total patient admissions to gain a more comprehensive understanding of the effect of COVID-19 on strokes in this particular age group.

Statistical Analysis

This study used interrupted time series analysis, which is one of the most advanced statistical methods and is rarely used in the health field. Time series models are used to examine time-dependent changes in statistical models and are quite comprehensive. Model selection is made in accordance with the purpose and data. Interrupted time series is among these models. There is a cut-off point in the main idea of the method, this cut-off point can be an intervention, treatment, etc. After this intervention, immediate slope changes are evaluated. Changes are obtained in terms of the slope obtained before the intervention, which is dependent on time, and the coefficient showing the sudden change after the intervention, and the slope after the intervention. Therefore, in this method, the change in a situation over time is evaluated by analyzing a certain period before and after a relevant intervention. The difference in trends between before and after the intervention is analyzed using models where there is no difference in trends. The hypothesis is whether the observations in the pre-intervention and post-intervention periods have different levels or slopes. The distribution of data points before and after the intervention/interference, the presence of confounding factors such as variability in the data, seasonality, and no limitations on the data points (15-18).

In interrupted time series, three variables T, ve are used. T is the elapsed time from the start of the study (year, month, etc.), is a dummy variable coded as 0 before the intervention and 1 after the intervention, represents the value of the outcome variable at time t. The model is expressed by the following function.

$Y_t=\beta_0+\beta_1 T+\beta_2 X_t+\beta_3 TX_t$

β_0 represents the starting level at T=0, β_1 represents the change in the outcome variable as time increases (before the intervention), represents the level change after the intervention and represents the slope of the change after the intervention (using the interaction between time and intervention). The dependent variable for the study is the house price index (HPI), T represents the time. is a variable that represents the treatment effect, whether or not there is COVID-19 (15-18).

Quantitative variables are presented as mean, standard deviation, median, minimum, and maximum. All analyses were performed using R Statistical Software (v4. 1.2; R Studio Team 2021) (19,20).

RESULTS

A total of 2196 patients were diagnosed with ischemic stroke among those who applied to the emergency department of Bezmialem Vakıf University between May 2019 and February 2023. 1003 (45.7%) of these patients were female and 1193 (54.3%) were male. The mean age of the patients was 67.22+13.43. 68 patients with ischemic stroke received intravenous Tissue Plasminogen Activator (iv tPA). 277 of the patients experienced ischemic stroke at the age of 50 or younger. They were categorized as the 'young stroke' group. The mean age of young stroke patients was 43.14±7.47 and 54.2% (n:150) were women. When the monthly average numbers are examined, the mean number of strokes is 48.68± 15.37, the mean number of young stroke patients is 14.40±5.40, and the mean value of the ratio of young stroke patients within the overall number of strokes is 0.304±0.10.

The effect of the COVID-19 pandemic was examined for the stroke numbers. When the interrupted time point is taken as March 2020, and the COVID-19 onset time is considered as the interval time, the estimations, standard errors, and p values obtained as a result of the interrupted time series analysis of the data are given in Table 1, Table 2 and Table 3. The time coefficient in Table 1 shows the results of the interrupted time series for all stroke patients. The time coefficient indicates the stroke numbers trend before the pandemic. It's positive and significant, indicating that patient numbers increase over time ($p<0.001$). For each month that passes, the stroke numbers increase by 4.500 points. The COVID-19(intervention) coefficient indicates the immediate decrease in the stroke numbers immediately after the COVID-19. The im-

Table 1. Model results of interrupted time series for stroke numbers.

Coefficients	Estimate	Standard Error	t value	p value
Intercept	31.727	8.205	3.867	**<0.001**
Time	4.500	1.210	3.720	**<0.001**
COVID-19	-30.697	8.359	-3.672	**<0.001**
Time Since COVID-19	-4.766	1.227	-3.885	**<0.001**

COVID-19: Coronavirus Disease-19, p value: significance level, t value: calculated t statistics value

Table 2. Model results of interrupted time series for young stroke numbers.

Coefficients	Estimate	Standard Error	t value	p value
Intercept	13.1818	2.9561	4.459	**<0.001**
Time	0.8182	0.4359	1.877	0.067
COVID-19	-4.9898	3.0117	-1.657	0.105
Time Since COVID-19	-1.0298	0.4420	-2.330	**0.025**

COVID-19: Coronavirus Disease-19, p value: significance level, t value: calculated t statistics value

Table 3. Model results of interrupted time series for the ratio of young stroke cases.

Coefficients	Estimate	Standard Error	t value	p value
Intercept	0.393	0.063	6.176	**<0.001**
Time	-0.011	0.009	-1.216	0.230
COVID-19	0.103	0.064	1.599	0.117
Time Since COVID-19	0.007	0.009	0.780	0.440

COVID-19: Coronavirus Disease-19, p value: significance level, t value: calculated t statistics value

mediate effect was negative and statistically significant. The Time Since Treatment coefficient indicates that the trend has changed after the intervention. The sustained effect is negative and statistically significant. The coefficient indicates that for each month that passes after the intervention, stroke numbers decrease by 4.766 points on the index (p<0.001). So it can be said that COVID-19 affects stroke numbers (Table 1). The time-dependent changes in the total number of patients with ischemic stroke are shown in Figure 1.

The time coefficient in Table 2 shows the results of interrupted time series for young stroke patients. The time coefficient indicates the stroke numbers trend before the pandemic. It's positive but it was not statistically significant (p=0.067). The immediate effect of COVID-19 on younger stroke numbers was not statistically significant (p=0.105). The Time Since Treatment coefficient indicates that the trend has changed after the intervention. The sustained effect is negative and statistically significant. The coefficient indicates that for each month that passes after the intervention, younger stroke numbers decrease by 1.029 points on the index (p=0.025). So it can be said that COVID-19 affects the younger stroke numbers (Table 2). The time-dependent changes in the total number of young patients with ischemic stroke are shown in Figure 2.

The time coefficient in Table 3 shows the results of interrupted time series for the young stroke ratio. It was found that the time, COVID-19, and time since COVID-19 coefficients were not statistically significant (p>0.05). As a result of this, it was found that COVID-19 did not affect the young stroke ratio (Table 3).

DISCUSSION AND CONCLUSION

This research investigated the impact of COVID-19 on ischemic stroke using interrupted time series analysis. The study analyzed the total number of ischemic stroke admissions, the total number of young ischemic stroke admissions, and the proportion of young patients in total ischemic stroke admissions to a university hospital emergency services between May 2019 and February 2023. The main findings of the study were as follows: (1) While total ischemic stroke admissions increased

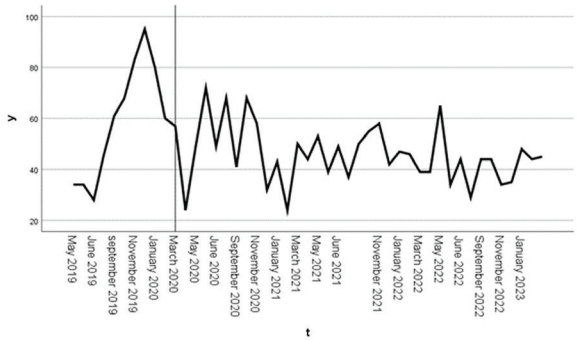

Figure 1. Time series of stroke numbers for all patients.

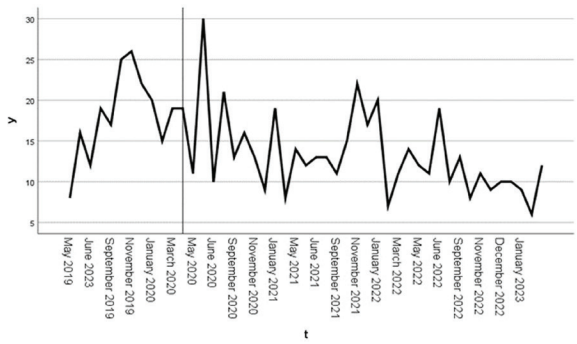

Figure 2. Time series of stroke numbers for young patients.

significantly in the pre-pandemic period, there was no change in young stroke admissions. (2) COVID-19 had an immediate effect on emergency ischemic stroke admissions, and the total admission numbers have decreased significantly. (3) No significant effect of COVID-19 on the youth stroke rate was found.

The effects of stroke on young adults are extremely severe due to the long-term consequences on their quality of life and ability to be productive. (21). In our research, approximately 30% of the total stroke admissions consisted of young people under the age of 50. Similar to our study, the literature also highlights the significant contribution of young adults to the overall stroke population (22). It is challenging to compare different geographical regions in terms of the incidence of stroke among young individuals due to variations in how the data is reported (23). In studies to identify young stroke patients, the upper cut-off value varies between 45-60 (9). Some epidemiological studies indicate a potential increase in global stroke rates among young individuals (24,25). Emergency admissions to our hospital for the pre-COVID-19 period do not support this situation. Although the young population accounted for a considerable portion of the overall stroke data before the COVID-19 period, it did not exhibit an upward trend in our data.

Various studies conducted in many different parts of the world have observed a significant impact of the COVID-19 pandemic on stroke outcomes (12,26-29). A systematic review that assessed 81 studies conducted in 20 countries revealed a median decrease of 28% in hospital admissions during the initial wave of the pandemic (30). Likewise, in our study, we observed a significant decline in hospital admissions of patients with ischemic stroke due to COVID-19, with a reduction of approximately 30-fold. A study carried out in Iran highlighted that the reduced number of admissions for mild strokes might be attributed to the fear of contracting COVID-19 (11). In conclusion, it has been pointed out that this fear-induced change in stroke care leads to a decrease in thrombolysis treatment and an increase in disability after discharge, and long-term studies are needed.

Furthermore, apart from these acute observations, several interrupted time series analyses from France, and Italy have incorporated the periods before and after the onset of COVID-19 in their analysis, thus providing a more comprehensive dataset (14,31). After a significant decline in the quarantine period, Mariet and colleagues reported that hospitalization volumes have recovered, returning to what was seen in 2019 (31). Similar to our results, Wang et al. observed a gradual increase in their data following an initial decline. Nevertheless, they highlighted that it took until the end of July 2020 for the levels to fully recover to those seen before the pandemic (14). In New York, between March 23 and April 7, 2020, there were reports of five patients under the age of 50, without any vascular risk factors but with a positive COVID-19 test, experiencing large vessel stroke. This was identified as a seven-fold increase in the incidence of large vessel stroke among young individuals compared to the previous year (32). In the literature, the need for comprehensive research on the effect of COVID-19 on the risk of ischemic stroke in young people has been emphasized (10). A subgroup analysis of a study demonstrated a substantial decline in the rates of inpatient and unplanned care admissions, specifically among patients below the age of 60, when compared to older

age cohorts (14). We observed a contrasting situation in our study. Despite a four-fold decrease in hospital admissions of young individuals with ischemic stroke during the COVID-19 period, the difference was not statistically significant. Furthermore, when we analyzed the post-COVID-19 period using interrupted time series analysis, we found no significant impact of COVID-19 on the number of hospital admissions for young individuals with ischemic stroke. Our study sets itself apart from these previous studies by encompassing a longer time frame after the onset of the COVID-19 pandemic and specifically targeting the population of young stroke patients.

A significant limitation of our study is its reliance on data from a single hospital. In order to address this limitation, we emphasized analyzing the ratio of young patients with ischemic stroke to the total number of admissions with ischemic stroke. Another limitation of our study is the limited availability of data from the pre-COVID period. Consequently, our research primarily focuses on the post-COVID period.

The COVID-19 pandemic has undoubtedly left a profound impact on healthcare service delivery worldwide, and its consequences have notably affected hospital admissions for patients with ischemic stroke during the pandemic period. The implementation of quarantine measures and the widespread effects of the pandemic played a significant role in altering the landscape of healthcare utilization. Nevertheless, this study's findings, utilizing interrupted time series analysis, showed no significant impact of COVID-19 on young patients' applications for ischemic stroke during both COVID and post-covid periods. These findings suggest that while the pandemic has undoubtedly presented unprecedented challenges, certain segments of the population, such as young patients seeking medical attention for ischemic stroke, may have adapted or experienced minimal disruption in their access to healthcare services. However, it is crucial to continue to monitor and evaluate the long-term effects of COVID-19 on stroke risk in both the youth and the general population.

Conflict-of-Interest and Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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