Impact of The COVID-19 Pandemic on Emergency Admission For Stroke Patients: A Cohort Study in Japan

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Research

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Abstract

Background: Hospitalization rates have reportedly reduced on account of measures such as the declaration of a COVID-19-related state of emergency. Appropriate treatment of stroke immediately after its onset contributes to improved survival, and delay in hospitalisation after onset affect stroke severity and mortality. This study aimed to determine the impact of the COVID-19 pandemic on emergency hospitalisation of stroke patients in Japan and the associated changes in stroke severity and mortality.

Methods: This was an observational study that used nationwide administrative data. The participants were selected from the data of hospitalised patients diagnosed with stroke. We cross-sectionally observed the background factors of patients during April and May 2020, when COVID-19-related state of emergency was declared, and the same period in 2019. We also modelled monthly trends in the numbers of emergency stroke admissions, of stroke admissions at each level of Japan Coma Scale (JCS), and of deaths within 24 h using interrupted time series regression (ITS).

Results: There was no difference between the pre- and the COVID-19 pandemic periods in the pre-hospital baseline characteristics of patients. No significant change was seen through ITS in the number of emergency stroke admissions between the COVID-19 and the pre-COVID-19 pandemic periods (risk ratio [RR]=0.96, 95% confidence interval [95%CI]: 0.90–1.02, P=0.159). There was a significant difference in the JCS3 of impaired consciousness in emergency stroke patients, which was more severe during the COVID-19 pandemic than pre-COVID-19 pandemic (RR=1.16, 95%CI: 1.04–1.28, P=0.005). There was no change in the mortality rate of patients with COVID-19 compared to those without COVID-19, but there were significantly more deaths within 24 h of admission. (No deaths within 24 h: RR=0.97, 95%CI: 0.88–1.06, P=0.446; deaths within 24 h: RR=2.80, 95%CI: 2.40–3.27, P<0.001).

Conclusions: COVID-19 infection prevalence increased the number of deaths and severity of illness within 24 h of hospitalisation in Japan. However, there was no association between the number of hospital admissions or deaths with baseline characteristics. These results suggest no problems in accepting hospitalised patients during the COVID-19 pandemic, but the delay in visiting the hospital after disease onset may have increased stroke severity.

Background

In December 2019, the first case of the novel coronavirus disease (COVID-19), caused by a severe acute respiratory syndrome, was reported in Wuhan, China [1]. COVID-19 is characterised by rapid spread, and various preventive measures have been implemented worldwide to contain this disease. In Japan, as of 30 August 2020, 67,077 confirmed cases of COVID-19 have been reported [2].

With various countermeasures in place against the infection, hospitalization rates have decreased in overseas emergency hospitals, and a similar decrease in emergency hospital admissions across urban areas of Japan has been reported [3][4][5].

Stroke is the second leading cause of death worldwide, the fourth leading cause of death in Japan, and is a common cause of emergency hospitalisation [6]. Appropriate treatment immediately after the onset of stroke contributes to the survival rate, and especially for treatments with limited indications, the time spent in the hospital from the onset of stroke is important [7][8][9][10]. Therefore, since the delay in hospitalisation from the onset of stroke may affect severity and mortality, it is important to understand the emergency hospitalisation status of stroke patients due to COVID-19 infection.

The Japanese government implemented various strategies to prevent the spread of COVID-19, and from 7 April, 2020 to 25 May, 2020 the government declared a state of emergency. The public was asked to stay home or work remotely, and large-scale events were cancelled or postponed. Additionally, to prevent the spread of infection at medical institutions or when travelling, the Japanese government instructed people to contact medical institutions before seeing a doctor if they had fever or other symptoms [11][12]. At the time of the declaration of the state of emergency was just declared, the rate of infection slowed down temporarily, but after the declaration of the state of emergency, the rate of infection increased again [2].

Previous studies focusing on COVID-19 have shown a highly significant decrease in the number of visits to emergency cardiology departments during lockdown [3][4]. The fear of a pandemic may have led to changes in patient behaviour, such as avoiding hospitalisation, even when symptoms are present. Studies regarding other past infectious disease pandemics have documented the largest outbreak of severe acute respiratory syndrome in 2003, resulting in limited access to care, lower overall hospitalisation rates, and a significant reduction in the use of healthcare services. There was also a decrease in the rate of hospitalisations and emergency room visits due to acute illness among patients with potentially serious conditions [13].

According to Japanese regional ambulance activation data, the proportion of emergency calls in the first half of 2020 was lower than that during the same period in 2019 [14][15]. Studies at the regional level have also shown a decrease in the number of emergency stroke admissions [5]. It is possible that the COVID-19 infection has reduced the rate of access to medical care for stroke patients in Japan, which may have an impact on mortality. The purpose of this study was to determine the impact of the COVID-19 pandemic on the admission of stroke patients to emergency hospitals and the resulting changes in stroke severity and mortality throughout Japan.

Methods

Study design

This observational study used nationwide administrative data from patients with a stroke who had been admitted to the emergency department between April 2018 and August 2020.

Patient selection

We extracted data from inpatients who were diagnosed with cerebral infarction (CI), cerebral haemorrhage (CH), and subarachnoid haemorrhage (SH) at the time of admission from April 2018 to August 2020. The International Classification of Diseases 10 diagnostic codes were used for the identification of CI (I63), CH (I61), and SH (I60). Patients aged 20 and older, who visited the emergency room, were included in our study. We excluded patients who stayed in the hospital for over 30 days to exclude non-acute patients. In this study, we used data up to August 2020, which was available until September 2020, and limited the target to patients hospitalised for 30 days or less.

Data source and variables

All data were obtained from the Diagnosis Procedure Combination, which is a national database of acute care inpatients in Japan. Diagnosis Procedure Combination data were used to evaluate the fixed medical payment system. Details of the database are presented elsewhere [16][17][18][19]. The database contains data on hospital ID, patient ID, age, sex, weight and height, diseases, comorbidities according to ICD-10 codes, length of stay (LOS), Barthel index (BI), modified Ranking Scale (mRS) at discharge, admission and discharge destination, Japan Coma Scale (JCS) at admission as a consciousness scale, onset days (four categories: within 3 days, 4–7 days, 8 or more days, asymptomatic), and ambulance use.

We divided patients into the following six groups: 20–44, 45–54, 55–64, 65–74, 75–84, and ≥ 85 years, as the probability of most lifestyle-related diseases increases from approximately 40 years of age [20]. The BMI at admission was categorised based on the modified World Health Organization classification: < 18.4 kg/m^2, 18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, 30.0–34.9 kg/m^2, and > 35.0 kg/m^2, and missing values [21].

The Charlson comorbidity index (CCI) was calculated using Quan’s protocol [22][23]. In the calculation of the CCI, patients’ comorbidity conditions were classified into 17 categories. Each condition had a weighted score of 1, 2, 3, or 6, depending on the mortality risk associated with the case. Individual scores were summed up to obtain the total CCI scores. We divided the total CCI scores into the following four groups: 0, 1, 2, and 3 or more. The JCS is a unique Japanese method of assessing the level of consciousness, similar to the Glasgow scale. The JCS code of 0 denotes a lack of consciousness, while a code of 1–3 denotes the state of being awake without stimuli. A code of 10–30 signifies the ability to be roused by some stimuli, and 100–300 signifies the state of not being roused [24]. We divided the JCS into four groups according to the number of digits: 0, 1, 2, and 3. To determine the impact of the COVID-19 infection, the COVID-19 pandemic period was set to start in April, when the state of emergency was declared. Before and after the April–May period, the number of infected people in the country has been increasing [2].

The requirement for informed consent was waived because of the anonymous nature of the data. Study approval was obtained from the institutional review board of the Tokyo Medical and Dental University.

Statistical methods

Continuous variables were expressed as mean and standard error, and categorical variables were expressed as the number of subjects and percentages. Chi-square and t-test were used to analyse the differences in the characteristics of stroke patients between April and May 2019, and April and May 2020 for discrete and continuous variables. The standard mean difference (SMD) was also calculated to measure the effect sizes of both groups. The baseline characteristics were compared with an absolute standardised difference of ≤ 10% considered to denote negligible imbalances between the COVID-19 pandemic and the pre-COVID-19 pandemic periods [25].

We used an interrupted time series regression (ITS) to model monthly trends in the number of emergency stroke admissions, the number of stroke admissions at each level of the JCS (1, 2, and 3), and the number of deaths within 24 hours or otherwise [26][27]. The Poisson distribution was used as the link function for all models. The month in which the emergency was declared was considered the point in time when the intervention took place, and all subsequent months were considered as post-intervention. We hypothesised a level change model, such that the slope change is not considered in this model. All outcome variables used in the ITS were examined for a unit roof using the Dickey–Fuller test. We included fixed effect terms for the year and season to control for seasonal trends. After checking and adjusting the model for seasonality and trends, autocorrelation and partial autocorrelation were plotted to check for autocorrelation of residuals. We adjusted each model using AIC and adopted one that best fit the model. All tests were 2-tailed, and the threshold for significance was set at $P < .05$. Statistical analyses were performed using R statistical software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Figure 1 shows the total number of eligible patients included in the ITS, the number of patients in April and May 2020 when the state of emergency was declared, and the number of patients during the same period in 2019. A total of 175,166 eligible patients were identified between April 2018 to August and August 2020. When the state of emergency was declared, there were 6,040 hospitalised patients in April and 6,444 in May. For the same period in 2019, 6,197 and 6,828 patients were admitted in April and May, respectively.

Table 1 shows the pre-hospital baseline characteristics of patients admitted in April and May 2019 and 2020. There was no difference between the COVID-19 and the pre-COVID-19 pandemic periods in any of the pre-hospital baseline variables.

Table 1
Baseline characteristics of patients with stroke

Variables		Pre-COVID-19 period		COVID-19 period			
n		13,025		12,484		SMD	P value
Age, N, %						0.025	0.564
	20–44	328	(2.5)	301	(2.4)		
	45–54	936	(7.2)	824	(6.6)		
	55–64	1,498	(11.5)	1,452	(11.6)		
	65–74	3,193	(24.5)	3,067	(24.6)		
	75–84	4,008	(30.8)	3,868	(31.0)		
	85 and over	3,062	(23.5)	2,972	(23.8)		
Sex (Female), N, %		5,711	(43.8)	5,482	(43.9)	0.001	0.926
BMI, N, %						0.044	0.032
	< 18.5	1,408	(11.0)	1,425	(11.6)		
	18.5–24.9	7,088	(55.1)	6,629	(53.9)		
	25–29	2,496	(19.4)	2,441	(19.8)		
	30–34	504	(3.9)	423	(3.4)		
	35 and over	519	(4.0)	504	(4.1)		
	NA	838	(6.5)	879	(7.1)		
CCI, N, %						0.025	0.27
	0	11,196	(86.0)	10,774	(86.3)		
	1	1,585	(12.2)	1,458	(11.7)		
	2	209	(1.6)	226	(1.8)		
	3	35	(0.3)	26	(0.2)		
Cerebral infarction, N, %		9,623	(73.9)	8,847	(70.9)	0.045	< 0.001
Cerebral haemorrhage, N, %		2,768	(21.3)	2,915	(23.3)		

BMI: body mass index; JCS: Japan Coma Scale; BI: Barthel Index; CCI: Charlson Comorbidity Index; SMD: standardised mean difference

Variables		Pre-COVID-19 period		COVID-19 period			
Subarachnoid haemorrhage, N, %		634	(4.9)	722	(5.8)		
Admission pathway, N, %						0.036	0.041
	Home	11,581	(88.9)	11,195	(89.7)		
	Facility	1,028	(7.9)	956	(7.7)		
	Transfer	402	(3.1)	316	(2.5)		
	Else	14	(0.1)	17	(0.1)		
Stroke of onset time, N, %						0.056	< 0.001
	3 days or less	12,103	(93.1)	11,739	(94.2)		
	4–7 days	544	(4.2)	472	(3.8)		
	8 days or more	221	(1.7)	176	(1.4)		
	Asymptomatic	128	(1.0)	72	(0.6)		
Ambulation, N, %		8,266	(63.5)	8,396	(67.3)	0.08	< 0.001
BMI: body mass index; JCS: Japan Coma Scale; BI: Barthel Index; CCI: Charlson Comorbidity Index; SMD: standardised mean difference							

No significant and effective difference was found when comparing the COVID-19 with the pre-COVID-19 pandemic periods in each age group.

In each stroke category, there was a significant but the difference in effect size was not sufficient difference between the COVID-19 and the pre-COVID-19 pandemic periods (COVID-19 period (3 days or less, 4–7 days, 8 days or more, asymptomatic): 12,103, 544, 221, and 128, respectively vs pre-COVID-19 period (3 days or less, 4–7 days, 8 days or more, asymptomatic): 11,739, 472, 176, and 72, respectively; SMD = 0.08, P < 0.001)

In the category of stroke-to-onset days, there was a significant but the difference in effect size was not sufficient difference between the COVID-19 and the pre-COVID-19 pandemic periods (COVID-19 [CI, CH, SH]: 9,623, 2,768, and 634, respectively vs pre-COVID-19 periods (CI, CH, SH): 8,843, 2,915, and 722, respectively; SMD = 0.045, P < 0.001).

Table 2 shows the mean values of JCS, LOS, number of deaths, and number of deaths within 24 hours, mRS, and number of discharges by COVID-19 pandemic period for post-hospitalization variables. There was a significant effective difference in the JCS disorientation score between the COVID-19 and the pre-COVID-19 pandemic levels, and more patients were hospitalized with severe disorientation during the COVID-19 pandemic (COVID-19 (JCS0, JCS1, JCS2, JCS3): 5,362, 5,090, 1,368, and 1,205, respectively vs pre-COVID-19 periods (JCS0, JCS1, JCS2, JCS3): 4,334, 5,169, 1,448, and 1,533, respectively; SMD = 0.148, P < 0.001). Discharge mRS and mortality were s there was a significant but the difference in effect size was not sufficient difference during and before the COVID-19 pandemic, but there was a significant and effective difference in 24-hour mortality upon admission (COVID-19: 184 vs pre-COVID-19 periods: 518, SMD = 0.167, P < 0.001). There was also a significant and effective difference in the category of discharge destination, with more patients being transferred to other hospitals (COVID-19 (home, facility, hospital, others): 6,637, 747, 4,234, and 1,407, respectively vs pre-COVID-19 periods (home, facility, hospital, others): 5,744, 589, 4,560, and 1,591, respectively; SMD = 0.122, P < 0.001).

Table 2
The mean number of JCS, LOS, Fatalities, Fatalities in 24 h, mRS, and Discharge by COVID-19 pandemic period

Variables		**COVID-19 period**		**Pre-COVID-19 period**		**SMD**	**P value**
JCS, N, %						0.148	< 0.001
	0	5,362	(41.2)	4,334	(34.7)		
	1	5,090	(39.1)	5,169	(41.4)		
	2	1,368	(10.5)	1,448	(11.6)		
	3	1,205	(9.3)	1,533	(12.3)		
LOS, Mean, SD		15.33	(7.6)	15.06	(7.6)	0.036	0.004
Fatalities, N, %		1,403	(10.8)	1,586	(12.7)	0.06	< 0.001
Fatalities in 24h, N, %		184	(1.4)	518	(4.1)	0.167	< 0.001
mRS at discharge, N, %						0.004	< 0.001
	0	1,439	(12.4)	1,202	(11.1)		
	1	3,010	(26.0)	2,590	(23.9)		
	2	2,198	(19.0)	2,072	(19.1)		
	3	1,553	(13.4)	1,394	(12.8)		
	4	2,302	(19.9)	2,423	(22.3)		
	5	1,065	(9.2)	1,177	(10.8)		
Discharge, N, %						0.122	< 0.001
	Home	6,637	(51.0)	5,744	(46.0)		
	Facility	747	(5.7)	589	(4.7)		
	Hospital	4,234	(32.5)	4,560	(36.5)		
	other	1,407	(10.8)	1,591	(12.7)		
LOS: length of hospital stay; JCS: Japan Coma Scale; mRS: modified Ranking Scale							

Figures 2_1 to 2_3 and Table 3 show the results of the ITS for the number of stroke patients from April 2018 to August 2020. There was no significant change in the number of emergency stroke admissions adjusted for ITS between the COVID-19 and the pre-COVID-19 pandemic periods (risk ratio [RR] = 0.96, 95% confidence interval [95%CI]: 0.90–1.02, P = 0.159).

Table 3
Interrupted time series analysis for the number of stroke patients from April 2018 to August 2020

	RR	2.50%	97.5%	P value	
Hospital admissions	0.96	0.90	1.02	0.159	
JCS1	1.03	0.99	1.06	0.607	
JCS2	1.02	0.96	1.08	0.554	
JCS3	1.36	1.26	1.46	< 0.001	**
Deaths within 24 h	2.80	2.44	3.22	< 0.001	***
Deaths except in 24 h	0.97	0.90	1.03	0.287	
***: p < 0.001, ** : p < 0.01, * : p < 0.05.					
JCS: Japan Coma Scale; RR: risk ratio					

There was a significant difference in JCS levels only for JCS3, and impaired consciousness in emergency stroke patients was more severe during the COVID-19 pandemic period than pre-COVID-19 pandemic period (RR = 1.36, 95%CI: 1.26–1.56, P < 0.001). The number of deaths was significantly higher within 24 h of hospitalisation, although the mortality rate for more than 24 h after hospitalisation during the COVID-19 pandemic was unchanged as compared to the pre-COVID-19 pandemic period (no fatalities within 24 h: RR = 0.97, 95%CI: 0.90–1.03, P = 0.287), (fatalities within 24 h: RR = 2.80, 95%CI: 2.44–3.22, P < 0.001). Although no unit root was found for all the variables used in the ITS, a harmonic adjustment term was inserted in the ITS model because of seasonal variation. No autocorrelation or partial autocorrelation was observed in the adjusted model.

Discussion

In this study, emergency stroke admissions during the COVID-19 pandemic were more severe, and the number of deaths within 24 h of admission increased. However, there was no change in the number of deaths, hospital admissions, or characteristics such as age, sex, and dependency. This suggests that the COVID-19 pandemic increased the severity of the disease at the time of emergency admission, although it did not change the patient population admitted to the emergency hospital after stroke. This study was the first to focus on the changes in the severity of emergency stroke patients during the COVID-19 pandemic in Japan, with a particular focus on the urgency of stroke.

Further, we found that the number of patients with a high level of consciousness on admission, and deaths within 24 h of admission increased during the COVID-19 pandemic compared to before the COVID-19 pandemic. The severity of stroke patients at the time of emergency admission was also higher during the COVID-19 pandemic. A previous study on emergency admissions of heart failure patients reported a decrease in the severity of hospitalisation during the COVID-19 pandemic. This study showed that the number of hospitalisations decreased because heart failure patients avoided hospitalisation due to fear of COVID-19 infection [4]. The results of this study did not agree with the results of a previous study conducted on the severity of illness at the time of hospitalisation during the COVID-19 pandemic. This may be due to differences between heart failure and stroke in the conditions that lead to hospitalisation, and patients may have been in a condition that could have inhibited hospitalisation.

There was no difference in the onset date at the baseline. In a previous study of emergency hospital admissions during the COVID-19 pandemic in Japan, there was no difference in the time between stroke onset and transport to the emergency hospital [5]. However, another previous study that assessed the impact of the COVID-19 pandemic on the emergency system in Osaka city, Japan, found that, since April 2020, the emergency system in the city has been facing difficulty regarding hospital acceptance of patients transported to hospitals for acute diseases [28]. It is possible that the COVID-19 pandemic may have caused a change in access to health care, but this cannot be examined in this study because there were no data within 3 days of stroke onset, and future studies are needed.

Furthermore, there was no difference in the number of emergency hospital admissions for stroke patients during the pandemic compared to before. This finding is inconsistent with the results of previous studies conducted in Japan. One previous study aimed to clarify the effect of the COVID-19 pandemic on a comprehensive stroke centre in Japan; the results showed that true emergencies appear to be associated with fewer emergency hospital visits and hospitalisations for stroke [29]. There are two reasons for this. First, the previous study was conducted at a single institution and in an area with a relatively high number of COVID-19 cases, which could have been strongly influenced by the pandemic. In this study, we used data covering about half of the total population of Japan, and examined the impact of COVID-19 after the declaration emergency, when COVID-19 infections were increasing in Japan as a whole; thus, the impact of COVID-19 may have changed in different regions of Japan [30]. Second, the observation period in the previous study was for a few months and did not consider annual and seasonal variations. In the present study, the period used was approximately 2 years, and the analysis also considered seasonal variations. Since the number of stroke patients is known to fluctuate seasonally, it was necessary to consider the long-term period, which led to different results between this study and previous studies [31].

A previous study comparing the COVID-19 pandemic and non-pandemic periods in Canada found no changes in the number of emergency stroke admissions, which was found to be similar to the present study. However, the referral rate to stroke prevention clinics decreased, and the number of patients with minor symptoms decreased. Patients with transient ischemic attacks or very mild strokes may have decided to stay at home instead of seeking medical care, according to a previous study [32]. The results of this study thus suggest that emergency hospitalisation for stroke is normal in Japan.

In this study, the level of consciousness information was used to determine the severity of stroke at the time of hospitalisation, but it did not consider information on treatment such as thrombolytic therapy, or tests such as CT and MRI, which may have resulted in biased information because we could not correctly determine the severity of stroke and other patient conditions. However, it is clear from data such as the number of 24-hour deaths in which the severity of stroke was higher at the time of admission, that there has been a change in the course of events leading to hospitalization.

Conclusions

We found that the prevalence of the COVID-19 pandemic increased the number of deaths and severity of illness within 24 h of hospitalisation in Japan. However, there was no association between the number of hospital admissions and deaths with baseline characteristics. These results suggest that there was no problem in accepting hospitalised patients during the COVID-19 pandemic, but the delay in visiting the hospital after the onset of the disease may have increased the severity of stroke. The results of this study suggest the need to monitor the risk of stroke and changes in patients' conditions before the onset of stroke as the infection spreads. As the COVID-19 infection pandemic becomes more prolonged, the overall severity of the stroke-prone population may also change. The authorities need to encourage patients with high need to come to the hospital and provide appropriate information about high-risk patients in the community.

Abbreviations

CI: Cerebral infarction; CH: Cerebral haemorrhage; SH: Subarachnoid haemorrhage CCI: Carlson comorbidity index; BI: Barthes index; BMI: body mass index; RR: risk ratio; 95%CI: 95% confidence interval; JCS: Japan Coma Scale; LOS: length of hospital stay; mRS: modified Ranking Scale; SMD: standard mean difference

Declarations

TT analysed all the data and was a major contributor to the manuscript preparation. TT, SI, and KF interpreted the data. All authors approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Tokyo Medical and Dental University. The need for informed consent was waived owing to the use of anonymized data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62.
2. **About New Coronavirus Infections** [https://www.mhlw.go.jp/english/new-info/index.html].
3. Tsioufis K, Chrysohoou C, Kariori M, Leontsinis I, Dalakouras I, Papanikolaou A, Charalambus G, Sambatakou H, Siasos G, Panagiotakos D, et al. The mystery of "missing" visits in an emergency cardiology department, in the era of COVID-19.; a time-series analysis in a tertiary Greek General Hospital. Clin Res Cardiol. 2020;109(12):1483–9.
4. Andersson C, Gerds T, Fosbol E, Phelps M, Andersen J, Lamberts M, Holt A, Butt JH, Madelaire C, Gislason G, et al. Incidence of New-Onset and Worsening Heart Failure Before and After the COVID-19 Epidemic Lockdown in Denmark: A Nationwide Cohort Study. Circ Heart Fail. 2020;13(6):e007274.
5. Koge J, Shiozawa M, Toyoda K. Acute Stroke Care in the With-COVID-19 Era: Experience at a Comprehensive Stroke Center in Japan. Front Neurol. 2020;11:611504.
6. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012;380(9859):2095–128.
7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344–418.
8. Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, Bhanji F, Brooks SC, de Caen AR, Donnino MW, Ferrer JM, et al. Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(18 Suppl 2):315–67.

9. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, et al: **Thrombolysis with Alteplase 3 to 4.5 Hours**.
10. **after Acute Ischemic Stroke**. *New Engl J Med* 2008, **359**(13):1317–1329.
11. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol. 2008;7(4):299–309.
12. **Abe to ask all schools to close during March** [https://www3.nhk.or.jp/nhkworld/en/news/20200227].
13. Karako K, Song P, Chen Y, Tang W. Analysis of COVID-19 infection spread in Japan based on stochastic transition model. Biosci Trends. 2020;14(2):134–8.
14. Schull MJ, Stukel TA, Vermeulen MJ, Zwarenstein M, Alter DA, Manuel DG, Guttmann A, Laupacis A, Schwartz B. Effect of widespread restrictions on the use of hospital services during an outbreak of severe acute respiratory syndrome. CMAJ. 2007;176(13):1827–32.
15. **for new coronavirus epidemic affecting self-restraint and health management** https://www.city.chigasaki.kanagawa.jp/koho/1030702/1002784/1039669.html.
16. Hatakeyama K, Ota J, Takahashi Y, Kawamitsu S, Seposo X. Effect of the COVID-19 pandemic on heatstroke-related ambulance dispatch in the 47 prefectures of Japan. Sci Total Environ. 2021;768:145176.
17. Chikuda H, Yasunaga H, Horiguchi H, Takeshita K, Kawaguchi H, Matsuda S, Nakamura K. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. J Bone Joint Surg Am. 2012;94(5):433–8.
18. Okamura S, Kobayashi R, Sakamaki T. Case-mix payment in Japanese medical care. Health Policy. 2005;74(3):282–6.
19. Shinya Matsuda KF, Kiyohide F. Development of Casemix Based Evaluation System in Japan. Asian Pacific Journal of Disease Management. 2010;4(3):55–66.
20. Miyata H, Hashimoto H, Horiguchi H, Fushimi K, Matsuda S. Assessment of hospital performance with a case-mix standardized mortality model using an existing administrative database in Japan. BMC Health Serv Res. 2010;10:130.
21. Deeks A, Lombard C, Michelmore J, Teede H. The effects of gender and age on health related behaviors. BMC Public Health. 2009;9:213.
22. **Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies**. *The Lancet* 2004, 363(9403):157–163.
23. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130–9.

24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
25. Yumoto T, Naito H, Yorifuji T, Aokage T, Fujisaki N, Nakao A. Association of Japan Coma Scale score on hospital arrival with in-hospital mortality among trauma patients. BMC Emerg Med. 2019;19(1):65.
26. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083–107.
27. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46(1):348–55.
28. Hategeka C, Ruton H, Karamouzian M, Lynd LD, Law MR. **Use of interrupted time series methods in the evaluation of health system quality improvement interventions: a methodological systematic review**. *BMJ Glob Health* 2020, 5(10).
29. Katayama Y, Kiyohara K, Kitamura T, Hayashida S, Shimazu T. Influence of the COVID-19 pandemic on an emergency medical service system: a population-based, descriptive study in Osaka, Japan. Acute Med Surg. 2020;7(1):e534.
30. Ota T, Shiokawa Y, Hirano T. Impact of COVID-19 on Stroke Admissions and the Medical Care System in the Tokyo Metropolitan Area. Front Neurol. 2020;11:601652.
31. Hideo Yasunaga KF, Hiroki Matsui HH. Shinya Matsuda: Epidemiology and health services resarch using DPC. Asian Pacific Journal of Disease Management. 2013;7(1·2):19–24.
32. Oberg AL, Ferguson JA, McIntyre LM, Horner RD. Incidence of stroke and season of the year: evidence of an association. Am J Epidemiol. 2000;152(6):558–64.
33. Bres Bullrich M, Fridman S, Mandzia JL, Mai LM, Khaw A, Vargas Gonzalez JC, Bagur R, Sposato LA. COVID-19: Stroke Admissions, Emergency Department Visits, and Prevention Clinic Referrals. Can J Neurol Sci. 2020;47(5):693–6.
34. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet. 2014;384(9958):1929–35.

Figures

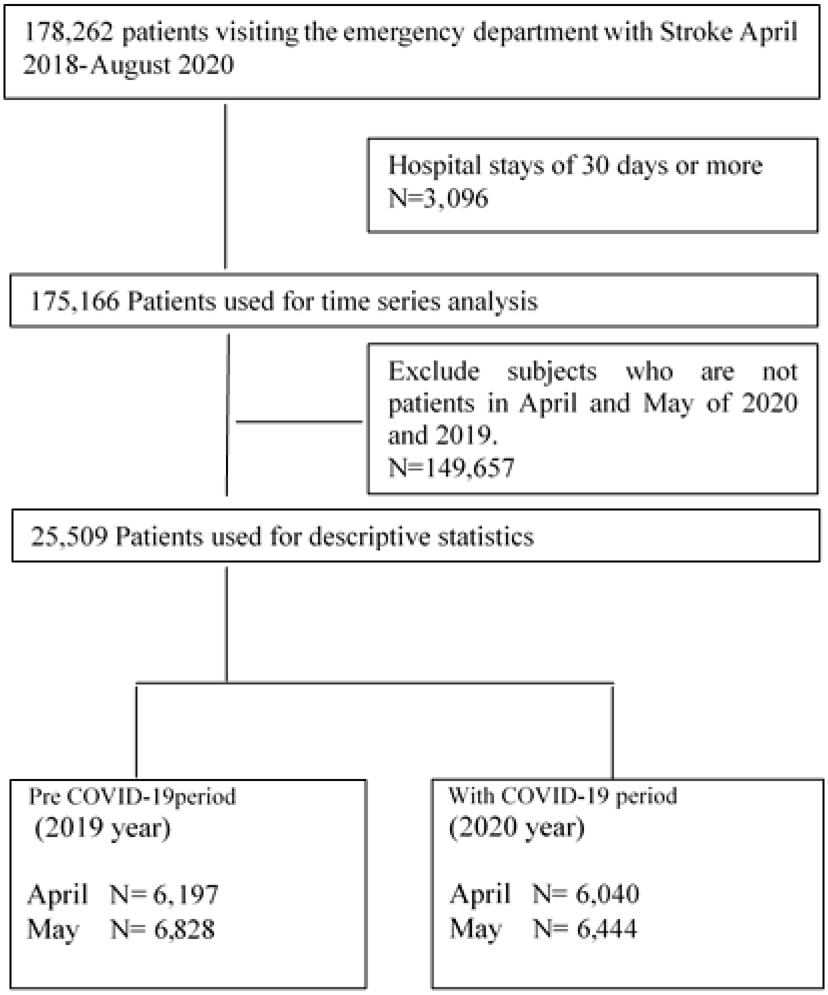

Figure 1

Flow Chart of the Study Cohort

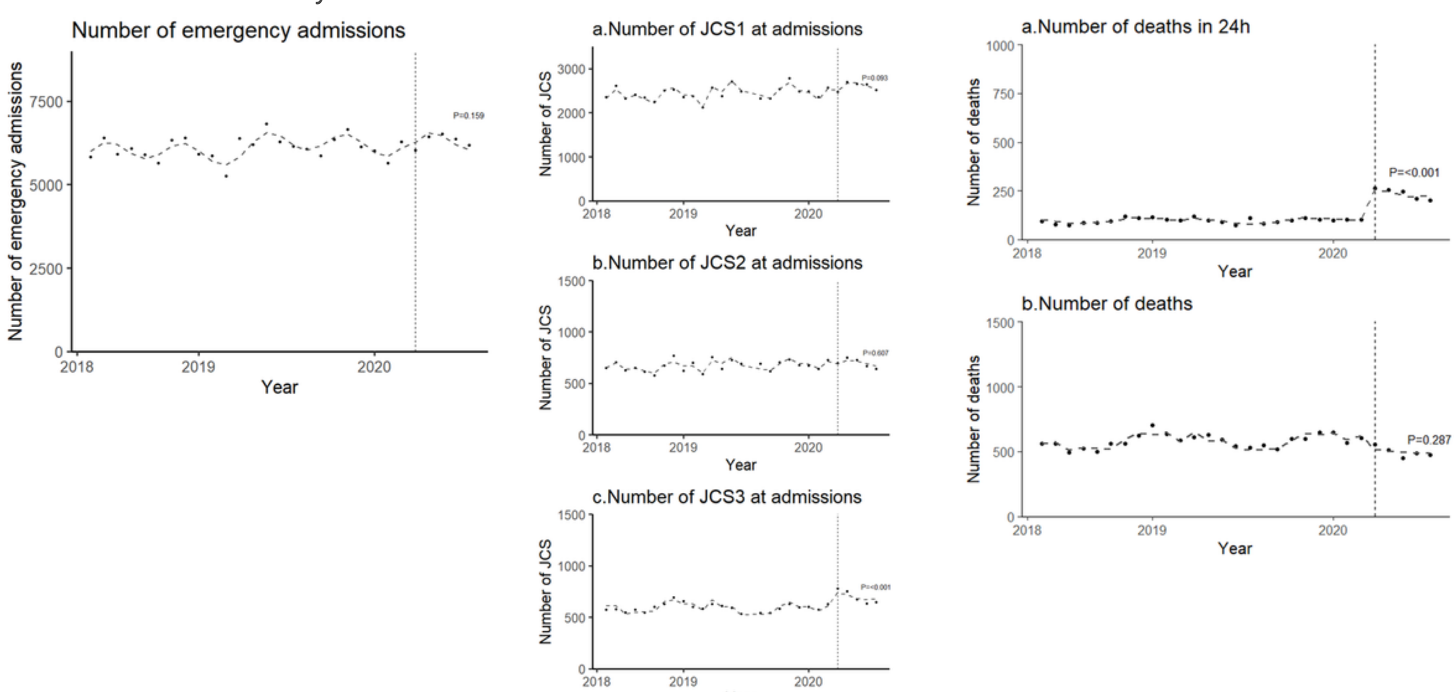

Figure 2

Interrupted Time Series Analysis of Emergency Stroke Admissions in the COVID-19 Pandemic Interrupted Time Series Analysis of Consciousness Levels in Emergency Stroke Admissions in the COVID-19 Pandemic Interrupted Time Series Analysis for 24-Hour and Non-24-Hour Fatalities in Emergency Stroke Admissions in the COVID-19 Pandemic