



Care Process of Recanalization Therapy for Acute Stroke during the COVID-19 Outbreak in South Korea

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Background and Purpose We aimed to determine whether the care process and outcomes in patients with acute stroke who received recanalization therapy changed during the outbreak of coronavirus disease 2019 (COVID-19) in South Korea.

Methods We used data from a prospective multicenter reperfusion therapy registry to compare the care process—including the time from symptom onset to treatment, number of treated patients, and discharge disposition—and treatment outcomes between before and during the COVID-19 outbreak in South Korea.

Results Upon the COVID-19 outbreak in South Korea, the number of patients receiving endovascular treatment to decrease temporarily but considerably. The use of emergency medical services by stroke patients increased from 91.5% before to 100.0% during the COVID-19 outbreak ($p=0.025$), as did the median time from symptom onset to hospital visit [median (interquartile range), 91.0 minutes (39.8–277.0) vs. 176.0 minutes (56.0–391.5), $p=0.029$]. Furthermore, more functionally dependent patients with disabilities were discharged home (59.5% vs. 26.1%, $p=0.020$) rather than staying in a regional or rehabilitation hospital. In contrast, there were no COVID-19-related changes in the times from the hospital visit to brain imaging and treatment or in the functional outcome, successful recanalization rate, or rate of symptomatic intracerebral hemorrhage.

Conclusions These findings suggest that a prehospital delay occurred during the COVID-19 outbreak, and that patients with acute stroke might have been reluctant to visit and stay in hospitals. Our findings indicate that attention should be paid to prehospital care and the behavior of patients with acute stroke during the COVID-19 outbreak.

Key Words reperfusion, therapy, stroke, outcome, coronavirus disease 2019.

INTRODUCTION

The world is currently being affected by an ongoing pandemic of a novel coronavirus-related acute respiratory illness called coronavirus disease 2019 (COVID-19). The onset of the COVID-19 outbreak in February 2020 in South Korea prompted the Korea Centers for Disease Control and Prevention (KCDC) to strongly recommend social distancing, minimizing outdoor activity, and the use of personal protective equipment. The KCDC also made daily announcements of the number of confirmed cases of COVID-19 and performed extensive contact tracking and testing when each new confirmed case of COVID-19 was detected. All of these activities were announced daily via the mass media and social network services. In the midst of these announcements, many Koreans were overwhelmed by a fear of COVID-19 and so stayed at home. Given the rapid disease spread, the government designated numerous public relief hospitals and COVID-19 screening centers for the care and testing of COVID-19.

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Recanalization therapies such as intravenous thrombolysis and endovascular thrombectomy (EVT) have been demonstrated to be effective for eligible patients with acute ischemic stroke.^{1,2} These interventions will be effective if the patient presents early to the hospital and receives rapid treatment.³ However, the COVID-19 outbreak may affect the behavior of patients with stroke in terms of the probability of them making hospital visits and the in-hospital care process itself.

To determine whether the behavior of patients with stroke and the in-hospital care process have changed during the COVID-19 outbreak, we compared various related factors between before and during the COVID-19 outbreak in patients who received reperfusion therapy in South Korea using data obtained from a prospective multicenter reperfusion therapy registry.

METHODS

Patients

Data were derived from the Specialized Multi-center Attributed Registry of sTroke—Endovascular or Thrombolytic therapy (SMART-EST) registry (clinicaltrials.gov NCT04066556). The SMART-EST is a prospective multicenter registry containing information on consecutive patients with acute ischemic stroke who have received the standard reperfusion therapy since July 2019 in 18 hospital centers in South Korea. The SMART-EST was the successor to the nationwide multicenter registry project [SElection CRiteria in Endovascular Thrombectomy and thrombolytic therapy registry (clinicaltrials.gov NCT02964052)].⁴

Written informed consent was obtained from patients or their next of kin for inclusion in the registry. The use of the registry was approved by the Institutional Review Board of each participating hospital (4-2019-0486, KBSMC 2019-11-013-001, DSMC 2019-09-011, NHIMC 2019-09-013-003, 19-0158).

The number of confirmed cases of COVID-19 in South Korea has increased dramatically since February 20, 2020. Therefore, for the purpose of this study, we included patients who received reperfusion therapy before and during the COVID-19 outbreak, between October 21, 2019 and April 20, 2020. Five hospital centers that had entered complete data for all consecutive patients who received reperfusion therapy during the study period into the SMART-EST registry participated in this study. All five hospitals were designated as public relief hospitals and COVID-19 screening centers by the government.

Data and time parameters

In addition to demographic information, we obtained data

on treatment time parameters, including the time (in minutes) from symptom onset to the emergency department (ED) visit and the times (in minutes) from arrival at the ED to initial brain imaging, bolus injection of intravenous thrombolytics, femoral puncture for EVT, and final recanalization. When the onset time was unclear, we used the time last-known well as a proxy for the onset time. The location of the culprit lesion was classified as the internal carotid artery, middle cerebral artery, vertebrobasilar artery, or other. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). We also determined the method of transportation to the ED, such as emergency medical services (EMS) or arriving in their own car.

At hospital discharge, we obtained the modified Rankin Scale (mRS) score and the discharge disposition. Successful recanalization in EVT was defined as thrombolysis in cerebral infarction grade 2b or 3 on conventional angiography, whereas successful recanalization in intravenous thrombolysis was defined as an arterial occlusive lesion score of 3 in computed tomography angiography or magnetic resonance angiography at 24 hours. We also determined if patients experienced a symptomatic intracerebral hemorrhage, defined as any type of hemorrhage causing neurological deterioration with an NIHSS score of ≥ 4 or leading to death or surgery within 7 days of stroke onset. Finally, we obtained information on whether a patient was tested for COVID-19 and whether the patient tested positive.

Statistical analyses

Data were expressed as frequency (percentage), median (interquartile range), or mean \pm standard-deviation values. Continuous variables were compared using independent-samples *t*-tests or Mann-Whitney tests, while categorical variables were compared using chi-square tests or Fisher's exact tests, as appropriate. We compared baseline characteristics, time parameters, outcomes, and discharge disposition between before the COVID-19 outbreak (from November 20, 2019 to January 20, 2020) and during the COVID-19 outbreak (from February 19 to April 20, 2020). We also evaluated the number of patients who received reperfusion therapy per month during the 5-month study period. All statistical analyses were performed using the Windows SPSS software (version 23.0, IBM Corporation, Armonk, NY, USA).

RESULTS

There were 151 consecutive patients who received reperfusion therapy during the 5-month study period: 94 before and 57 during the COVID-19 outbreak, respectively. The use of EMS for transport to the ED was more common during the

COVID-19 outbreak (100.0%) than before the COVID-19 outbreak (91.5%, $p=0.025$). The remaining baseline characteristics did not differ between before and during the COVID-19 outbreak (Table 1). All of the 57 patients who were treated during the COVID-19 outbreak were screened for COVID-19, of which 14 were tested for COVID-19, with none of them testing positive.

The number of patients who received reperfusion therapy at the study hospitals decreased considerably when the COVID-19 outbreak began in South Korea. However, the frequency of reperfusion therapy returned to pre-COVID-19 levels during the month after the initial outbreak (Fig. 1). The time from symptom onset to the ED visit was significantly longer during the COVID-19 outbreak (median=176.0 minutes, interquartile range=56.0–391.5 minutes) than before the COVID-19 outbreak (median=91.0 minutes, interquartile range=39.8–277.0 minutes, $p=0.029$). However, the times from ED arrival to initial brain imaging, intravenous thrombolysis, femoral puncture, and final recanalization did not differ between before and during the COVID-19 outbreak (all $p>0.05$) (Table 2).

The rate of successful recanalization, frequency of symp-

tomatic intracerebral hemorrhage, mRS score at discharge, and mortality rate did not differ between before and during the COVID-19 outbreak (Tables 2 and 3). While the functional outcome (mRS score) at discharge did not differ among the 130 survivors, the proportion of patients discharged home (rather than to a rehabilitation facility or another hospital) was significantly larger during the COVID-19 outbreak ($n=32$, 69.6%) than before the COVID-19 outbreak ($n=46$, 54.8%) ($p=0.041$). Sixty-five of the 130 stroke survivors had a disability requiring functional dependence (mRS score=3–5) at discharge. These patients typically require further rehabilitation therapy in regional hospitals after discharge, but the proportion who were transferred to other regional hospitals or nursing homes was significantly smaller during the COVID-19 outbreak (26.1%) than before the COVID-19 outbreak (59.5%, $p=0.020$) (Fig. 2).

The times from symptom onset to ED visit and from ED visit to final recanalization were longer for the 14 patients who were tested for COVID-19 during the COVID-19 outbreak than for the 43 patients who were not tested (Supplementary Table 1 in the online-only Data Supplement).

Table 1. Comparison of the baseline characteristics of patients upon their arrival at the hospital emergency department between before and during the COVID-19 outbreak

	Total	Before COVID-19 (n=94)	During COVID-19 (n=57)	p
Age, years	69.9±12.7	71.0±11.9	68.2±13.7	0.196
Sex, male	96 (63.6)	60 (63.8)	36 (63.2)	0.934
Hypertension	95 (62.9)	59 (62.8)	36 (63.2)	0.961
Diabetes	59 (39.1)	41 (43.6)	18 (31.6)	0.142
Hyperlipidemia	54 (35.8)	30 (31.9)	24 (42.1)	0.205
Current smoker	36 (23.8)	20 (21.3)	16 (28.1)	0.342
Atrial fibrillation	43 (28.5)	27 (28.7)	16 (28.1)	0.931
Previous ischemic stroke	33 (21.9)	22 (23.4)	11 (19.3)	0.554
Premorbid disability	5 (3.3)	4 (4.3)	1 (1.8)	0.650
Arterial occlusion site				0.372
Internal carotid artery	21 (13.9)	11 (11.7)	10 (17.5)	
Middle cerebral artery	81 (53.6)	49 (52.1)	32 (56.1)	
Vertebrobasilar artery	12 (7.9)	9 (9.6)	3 (5.3)	
Others	4 (2.6)	4 (4.3)	0 (0.0)	
No occlusion	33 (21.9)	21 (22.3)	12 (21.1)	
Transportation method				0.025
Emergency medical services	143 (94.7)	86 (91.5)	57 (100.0)	
Own car	8 (5.3)	8 (8.5)	0 (0.0)	
Treatment modality				0.273
IV thrombolysis	45 (29.8)	31 (33.0)	14 (24.6)	
EVT/IV thrombolysis	106 (70.2)	63 (67.0)	43 (75.4)	
Initial NIHSS score	11.0 (4.0–18.0)	11.5 (5.0–18.3)	10.0 (6.5–14.0)	0.312

Data are n (%), mean±standard-deviation, or median (interquartile range) values.

COVID-19: coronavirus disease 2019, EVT: endovascular thrombectomy, EVT/IV thrombolysis: EVT only or EVT after IV thrombolysis, IV: intravenous, NIHSS: National Institutes of Health Stroke Scale.

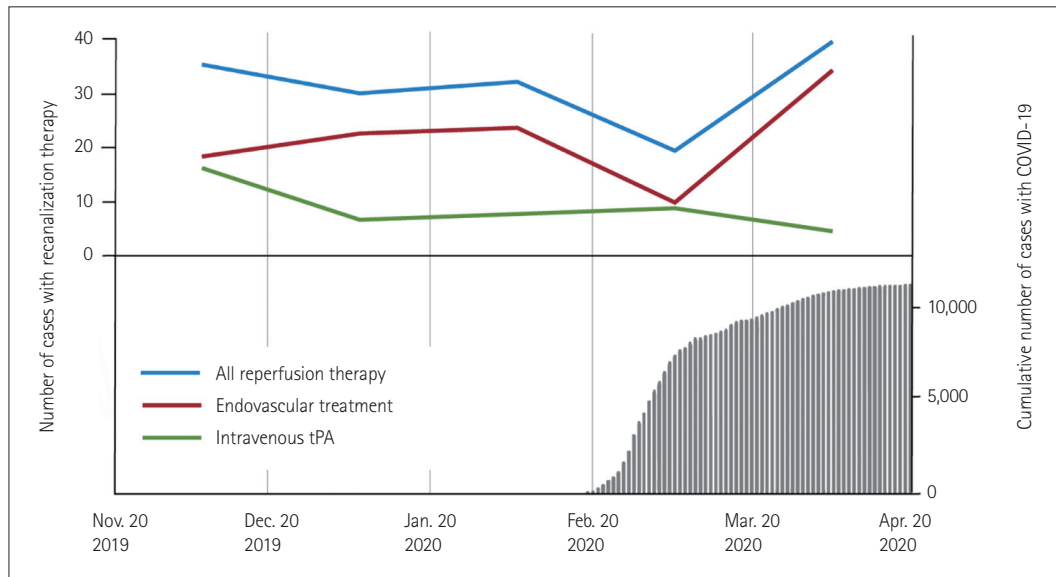


Fig. 1. Secular trends in the number of patients who received reperfusion therapy. The total number of acute stroke cases involving reperfusion therapy is displayed for each month on the left axis. The total number of confirmed cases of COVID-19 in South Korea per day is displayed on the right axis. COVID-19: coronavirus disease 2019, tPA: tissue plasminogen activator.

Table 2. Comparison of times (in minutes) from symptom onset to in-hospital treatments between before and during the COVID-19 outbreak

Parameter	Number	Before COVID-19 (n=94)	During COVID-19 (n=57)	p
Symptom onset to ED arrival	151	91.0 (39.8–277.0)	176.0 (56.0–391.5)	0.029
ED arrival to initial brain imaging	150	18.5 (14.0–27.0)	16.0 (12.0–21.8)	0.068
ED arrival to tPA bolus	86	37.0 (28.0–49.0)	35.0 (21.0–48.0)	0.248
ED arrival to femoral puncture	107	102.0 (78.3–130.3)	94.0 (79.0–114.0)	0.403
ED arrival to final recanalization	82	149.0 (114.5–204.0)	153.0 (112.5–183.5)	0.590

Data are median (interquartile range) values.

COVID-19: coronavirus disease 2019, ED: emergency department, tPA: tissue plasminogen activator.

Table 3. Comparison of patient outcomes at hospital discharge between before and during the COVID-19 outbreak

	Number	Before COVID-19 (n=94)	During COVID-19 (n=57)	p
mRS score=0 or 1	143	24 (25.5)	17 (34.7)	0.250
mRS score=0–2	143	42 (44.7)	23 (46.9)	0.797
Death	143	10 (10.6)	3 (6.1)	0.543
Successful recanalization immediately after EVT	105	55 (88.7)	36 (83.7)	0.460
Successful recanalization at 24 hours	71	37 (84.1)	23 (85.2)	1.000
Symptomatic intracranial hemorrhage	151	6 (6.4)	5 (8.8)	
Discharge route	130			0.041
Rehabilitation department		10 (11.9)	8 (17.4)	
Home		46 (54.8)	32 (69.6)	
Other regional hospital		28 (33.3)	6 (13.0)	

Data are n (%) values.

COVID-19: coronavirus disease 2019, EVT: endovascular thrombectomy, mRS: modified Rankin Scale.

DISCUSSION

In this study we found that during the COVID-19 outbreak, the time from stroke onset to ED arrival and the frequency of EMS use among stroke patients increased and that more

stroke patients were discharged home rather than to another regional hospital, despite having a disability. However, no in-hospital delays were observed from hospital arrival to evaluation and reperfusion therapy.

The findings of this study suggest that there were noticeable

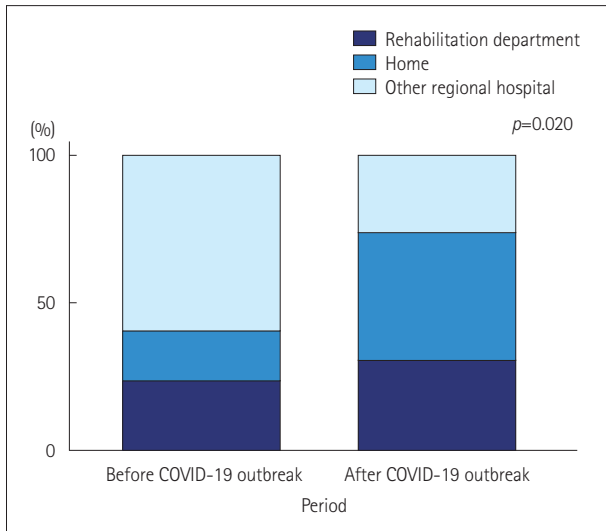


Fig. 2. Comparison of the discharge disposition among patients with functionally dependent disabilities (modified Rankin Scale score=3–5) between before and during the COVID-19 outbreak. COVID-19: coronavirus disease 2019.

behavioral changes in patients who experienced an acute stroke during the COVID-19 outbreak. Many patients with stroke visit hospitals using their own cars in South Korea.⁵ After the first case of COVID-19 in January 20, 2020, the KCDC strongly recommended people to call a regional public health service center when they experienced any symptoms suspicious of COVID-19 or had direct/indirect contact with a confirmed case of COVID-19. Therefore, during the COVID-19 outbreak, people may rely more on government-derived public health services and be more likely to call EMS when they appear to have developed stroke-like symptoms.

The use of EMS transport usually shortens the time from symptom onset to hospital arrival.⁶ However, despite the increased use of EMS, the time from symptom onset to ED arrival increased significantly during the COVID-19 outbreak, which may be ascribed to various factors related to the care system and patients. When being transported from the home to the hospital via the EMS, prehospital delay attributable specifically to the COVID-19 outbreak may occur at any step, including when the staff are donning personal protective equipment or cleaning the ambulance bed, and/or during the screening process performed by EMS personnel.⁷ In addition, some hospitals were closed due to in-hospital COVID-19 outbreaks and some hospitals were fully designated to COVID-19 patient care. Medical resources for controlling this infectious crisis (including medical personnel and infrastructure) were prioritized by the government, and so many ambulances and EMS personnel played a primary role in delivering patients with confirmed or suspected COVID-19 to COVID-19 centers. Although these changes were neces-

sary and inevitable, they may have also contributed to prehospital delay among patients who did not have COVID-19 but who needed EMS, including those with acute stroke. Prehospital delay in acute stroke patients is associated with increased infarction size, neurological worsening, and complications, which subsequently lead to unfavorable outcomes.^{8,9} Therefore, interventions for delivering acute stroke patients at the prehospital level should be considered. For example, it would be beneficial to reduce time delays by choosing the closest hospital, ensuring mutual communication with receiving hospitals, and implementing a prenotification system.⁷

The delayed hospital arrival among patients who were tested for COVID-19 further suggests that patient-related factors are at least partly responsible for the prehospital delay. Patients who are tested for COVID-19 may have had fever, respiratory symptoms, or a recent history of visits to areas with COVID-19 outbreaks. In such cases the EMS personnel would have taken extra preparations to prevent potential disease transmission. Also, the ambulance may have had to bypass the hospital closest to the patient's home since it was not designated as a public relief hospital, further contributing to the delay.

The number of patients who received reperfusion therapy decreased during the analysis period in this study. Some Koreans might be concerned about hospital-acquired COVID-19, given the experiences with a previous outbreak of Middle Eastern respiratory syndrome (MERS) in South Korea.¹⁰ The MERS outbreak began in the ED of a large tertiary hospital in South Korea, and so some patients with acute stroke may have hesitated about visiting the ED of a large hospital when they developed stroke symptoms. During the initial COVID-19 outbreak in South Korea, the number of patients who visited the study hospitals and received reperfusion treatment did indeed decrease considerably. Other factors such as excluding patients with indications outside the strict guidelines¹¹ or a lack of proper transportation^{12,13} could have influenced these findings. Furthermore, the proportion of patients with functional dependence due to a disability who were discharged home also increased significantly during the COVID-19 outbreak. These findings suggest that some patients with stroke may have felt safer staying at home than being admitted to a hospital or rehabilitation center. It is also possible that some regional hospitals were reluctant to accept hospital-to-hospital patient transfers due to the shortage of medical and human resources during the COVID-19 outbreak.

In contrast to the prehospital delay during the COVID-19 outbreak, there were no in-hospital delays from ED arrival to initial brain imaging and reperfusion treatment. In each of our study hospitals, every patient arriving at the ED was first screened for COVID-19-related symptoms, body temper-

ature, the recent history of direct or close contact with any COVID-19 patient, and the recent history of visits to areas with COVID-19 outbreaks. During this screening process, patients who were suspected of having COVID-19 were sent to a screening station, tested for COVID-19, and then quarantined until the result of the screening test was available.^{14,15} However, patients with symptoms of acute stroke who were indicated for reperfusion therapy (code stroke) were screened rapidly at most of our study hospitals in order to prevent time delays after entering the ED. Moreover, the primary screening process had already been performed by EDS personnel.

The treatment outcomes did not differ between before and during the COVID-19 outbreak. The Korean Stroke Society has provided statements on optimal stroke care including reperfusion therapy during the COVID-19 pandemic,¹⁶ and many stroke centers including the present study hospitals tried to implement the new protocols for the triage and care of hyperacute stroke patients, such as applying a rapid screening tool to patients with stroke symptoms and performing EVT in a negatively pressurized or properly isolated room by medical staff wearing personal protective equipment before receiving the confirmed result from the COVID-19 test. These aspects of the in-hospital care process for COVID-19-free patients with acute ischemic stroke were not significantly affected by the COVID-19 outbreak, which might explain why the outcomes during the COVID-19 outbreak were similar to those before the outbreak. However, this finding was based on short-term observations, and there are also other potential reasons, such as the possibility that patients treated during the COVID-19 outbreak had favorable characteristics such as a good imaging profile (e.g., good collaterals).

Recent studies of COVID-19 in stroke patients have focused on the prevalence, pathogenesis, and outcomes of stroke in COVID-19 patients, and on developing guidelines or statements for the acute care of patients with stroke who also have COVID-19.¹⁶⁻²⁰ However, a large proportion of patients with acute stroke are COVID-19-free. Our findings indicate that the COVID-19 outbreak may affect the prehospital delivery process and how patients with acute stroke and their families behave after the occurrence of stroke symptoms. In addition to the care provided to stroke patients with confirmed COVID-19, hospital and government policymakers should also be concerned about the behavior of general patients with acute stroke and the prehospital delivery process during the COVID-19 pandemic. Urgent efforts by support networks (i.e., academic stroke society) and policymakers may be required, including the designation of COVID-19-safe stroke centers, providing public education about stroke awareness and the actions to take when stroke symptoms develop, planning for discharge disposition, rehabilitation plans for pa-

tients with disability who are discharged home, and prioritizing stroke patients using EMS.

This study was subject to some limitations. First, the findings were based on data obtained from only a few tertiary hospitals in South Korea over a relatively short time period. The prevalence of COVID-19 and the use of prehospital and in-hospital stroke care systems, including the EMS, may differ between countries. Second, the behavior of people during the COVID-19 outbreak may differ between countries and cultures. These factors mean that our findings are not generalizable. However, a decrease in the number of patients receiving EVT and an increase in the time between stroke onset and treatment have also been observed in other regions and countries.^{11,12,19,21} These previous findings together with our current findings suggest the presence of common problems that need to be addressed in the countries affected by the COVID-19 outbreak.

In conclusion, this study has demonstrated that the COVID-19 outbreak may affect the prehospital delivery process and the behavior of COVID-19-free patients with acute stroke. In addition to managing stroke patients with confirmed COVID-19, attention needs to be paid to the prehospital care and behavior of general patients with acute stroke during the COVID-19 outbreak.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2021.17.1.63>.

Author Contributions

Conceptualization: Young Dae Kim, Ji Hoe Heo. Formal analysis: Hye Sun Lee, Young Dae Kim. Funding acquisition: Young Dae Kim, Hyo Suk Nam. Investigation: all authors. Supervision: Young Dae Kim, Ji Hoe Heo. Writing—original draft: Young Dae Kim, Ji Hoe Heo. Writing—review & editing: Hyo Suk Nam, Sung-Il Sohn, Hyungjong Park, Jeong-Ho Hong, Gyu Sik Kim, Kwon-Duk Seo, Joonsang Yoo, Jang-Hyun Baek, Jung Hwa Seo, JoonNyung Heo, Minyoul Baik, Hye Sun Lee.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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