Online December 14, 2022
Journal of Neuroendovascular Therapy 2023; 17: 37–46
DOI: 10.5797/jnet.oa.2022-0031

Original Article

# Impact of JSS-PCS on the In-Hospital Workflow and Outcomes of Reperfusion Therapy for Acute Ischemic Stroke: Cases of a Metropolitan Secondary Emergency Facility

*Jun Shinoda,[1,2] Saeko Ichimura,[2] Ryuichi Kanai,[2] Takamasa Majima,[1,3] Shumpei Azami,[1,3] Kouji Inoue,[3] and Toshitaka Shirai[3]*

**Objective:** Protected code stroke has been widely introduced in the emergency medical system for acute stroke in the current coronavirus disease 2019 (COVID-19) pandemic. This study aims to confirm the effects of protected code stroke formulated by the Japan Stroke Society (JSS-PCS) on the quality and outcomes of reperfusion therapy for acute ischemic stroke (AIS), followed by evaluating its validity.

**Methods:** The subjects were 109 consecutive patients with AIS who underwent reperfusion therapy between January 2016 and July 2021, excluding in-hospital onset cases. Patients were classified according to the treatment date into the pre-COVID-19 (n = 82) and the with-COVID-19 (n = 27) groups. JSS-PCS was applied to all patients in the latter group. Statistical comparisons were made between groups on time indicators for initial treatment (onset-to-door time, door-to-imaging time [DTI], door-to-needle time [DTN], door-to-puncture time [DTP], door-to-reperfusion time, and puncture-to-reperfusion time [PTR]). The time indicator transition over the entire period was also evaluated by subgroup analysis. Subsequently, the outcomes at discharge were statistically compared between the two periods, followed by a subgroup comparison. Finally, univariate and multivariate analyses examined whether the application of JSS-PCS affected clinical outcomes.

**Results:** Slight delays were revealed in DTI, DTN, DTP, and PTR in the with-COVID-19 group with no statistical significance. The time indicators were delayed once entering the period of the COVID-19 pandemic and then shortened again. The outcomes at discharge tended to worsen slightly in the with-COVID-19 group with no significance. Subgroup analysis depicted a transient deterioration of outcomes early in the pandemic. Applying JSS-PCS did not significantly affect clinical outcomes in univariate and multivariate analyses.

**Conclusion:** Regarding reperfusion therapy at our facility, the introduction and application of JSS-PCS during the COVID-19 pandemic significantly affected neither time indicators nor outcomes. Infection control should be a top priority in the first medical practice for AIS in today's world, where COVID-19 shows no signs of termination.

**Keywords** ▶ JSS-PCS, reperfusion therapy, in-hospital workflow, outcomes, COVID-19

[1]*Department of Stroke, Eiju General Hospital, Tokyo, Japan*
[2]*Department of Neurosurgery, Eiju General Hospital, Tokyo, Japan*
[3]*Department of Neurology, Eiju General Hospital, Tokyo, Japan*

Received: May 11, 2022; Accepted: October 28, 2022
Corresponding author: Jun Shinoda. Department of Stroke, Eiju General Hospital, 2-23-16, Higashiueno, Taito-ku, Tokyo 110-8645, Japan
Email: shinodaj@mbd.nifty.com



## Introduction

The phrase "Time is brain," derived from Benjamin Franklin's aphorism "Time is money," is a slogan endorsed by all stroke specialists around the world.[1)] However, this slogan has been taken down from top priority and replaced by strict infection control since the declaration of the coronavirus disease 2019 (COVID-19) pandemic in March 2020. As a result, many facilities around the world involved in the treatment of acute ischemic stroke (AIS) have developed their original protected code stroke (PCS) to prevent secondary infection to associated staff.[2,3)]

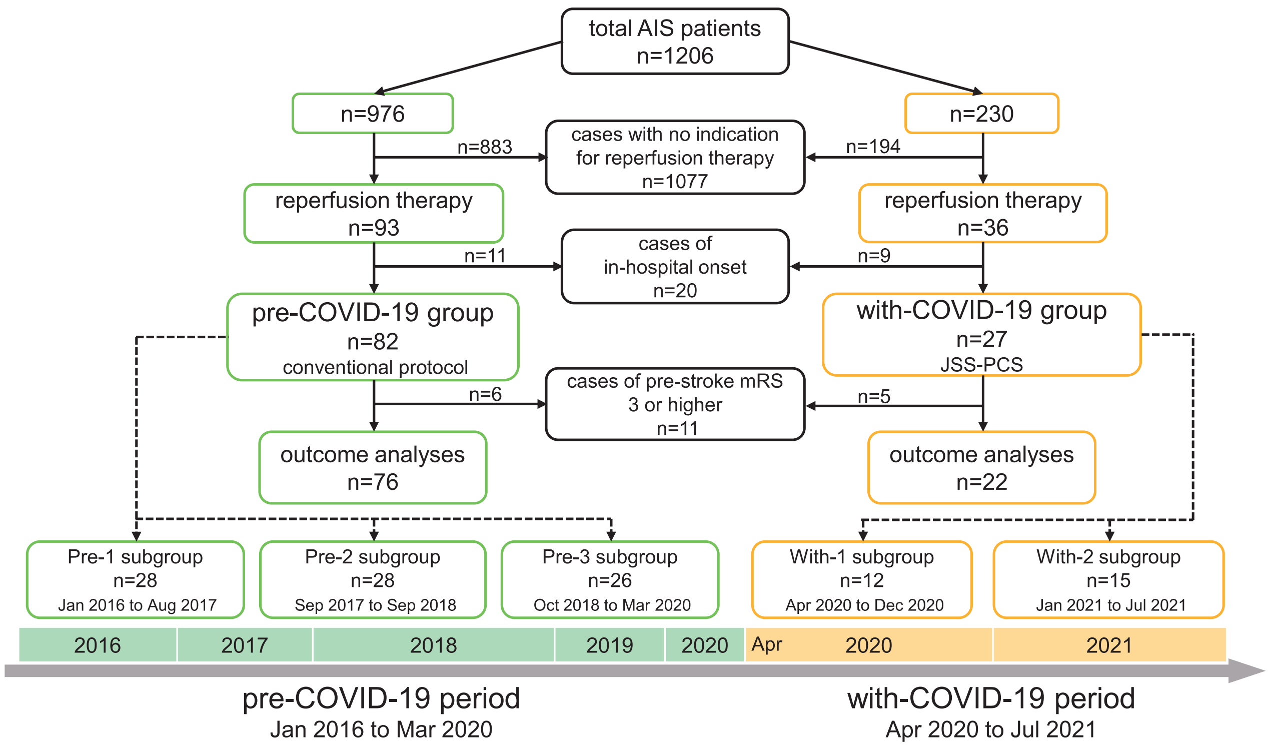


**Fig. 1** Flowchart of patient selection. AIS: acute ischemic stroke; COVID-19: coronavirus disease 2019; JSS-PCS: protected code stroke formulated by the Japan Stroke Society; mRS: modified Rankin Scale

Our facility experienced an unprecedented large-scale nosocomial COVID-19 infection in March 2020. From our sincere reflection on this disaster, strict infection control has been the highest priority issue in emergency medical care. As part of this effort, JSS-PCS, a PCS formulated by the Japan Stroke Society in April 2020,[4,5] has been introduced and utilized for the initial treatment of stroke.

JSS-PCS might be a double-edged sword, although it is well known and widely used in Japan. The introduction of this protocol raises concerns about the elongation of the therapeutic time indicators and worsening outcomes in the reperfusion therapy for AIS, as it puts the highest priority on infection control.

This study compared the time indicators and clinical outcomes of reperfusion therapy for AIS before and after introducing JSS-PCS. Its purpose was to demonstrate the effectiveness and validity of implementing this PCS during the COVID-19 pandemic.

## Materials and Methods

### Study population

Intravenous thrombolysis (IVT), mechanical thrombectomy (MT), and bridging therapy (BT) are referred to as reperfusion therapy. The study population and the process of patient selection are shown in **Fig. 1**. The requirement for written informed consent for study registration was waived due to the study's retrospective nature. The overall verification period was 67 months, from January 2016 to July 2021. Our facility had 1206 patients with AIS during this period, of whom 129 received reperfusion therapy. Of the 129 patients, 20 had in-hospital onset and were excluded from the analysis. The remaining 109 consecutive patients were retrospectively analyzed as a study population. Of the 109 patients, 82 who received these treatments between January 2016 and March 2020 were categorized as the pre-COVID-19 group. The remaining 27 patients treated under strict infection control of JSS-PCS between April 2020 and July 2021 were categorized as the with-COVID-19 group. For further analyses, both groups were subdivided in the order of treatment date into three and two subgroups, respectively. Three subgroups (Pre-1, Pre-2, and Pre-3) derived from the pre-COVID-19 group consisted of 28, 28, and 26 patients, respectively. The with-COVID-19 group was divided into two subgroups (With-1 and With-2), each consisting of 12 and 15 patients.

In outcome analyses, patients with pre-stroke modified Rankin Scale (mRS) score of 3 or more were excluded. From the pre-COVID-19 and with-COVID-19 groups, 76 and 22 patients were subjected, respectively. In a subgroup analysis for clinical outcomes, 26, 26, 24, 9, and 13 patients were derived from Pre-1, Pre-2, Pre-3, With-1, and With-2, respectively.

MRI has been performed in almost all cases of AIS here, although JSS-PCS recommends head CT and CTA as the initial imaging modality for AIS. Thorough disinfection in the MRI room has been provided with adequate ventilation according to our infection control standards. The staff involved in one AIS patient in the emergency room (ER) were two or three doctors including residents, one nurse, zero or one nursing assistant, one or two radiologists, and one clinical laboratory technician. There was no apparent difference in the number of staff before and after the pandemic.

### Patient background

Age, gender, pre-stroke mRS, oral medication, underlying disease, pretreatment neurological findings, pretreatment neuroradiological findings, etiology, and treatment method in each group were statistically compared.

### Comparison of time indicators for treatment

The time indicators for treatment were compared between both groups. Onset-to-door time (OTD), door-to-imaging time (DTI), door-to-needle time (DTN), door-to-puncture time (DTP), door-to-reperfusion time (DTR), and puncture-to-reperfusion time (PTR) were selected as time indicators. The time of the last-known well was defined as the onset time in cases where the accurate onset time is unknown. The values of DTP in patients who did not undergo thrombectomy but puncture were excluded from the analysis.

Furthermore, the transition of these time indicators over the entire period, excluding OTD, was analyzed by statistical comparison among the five subgroups.

### Clinical outcomes at discharge

Outcome at discharge was defined as favorable with mRS of 2 or lower and poor with mRS score of 3 or higher. First, outcomes between pre-COVID-19 (n = 76) and with-COVID-19 (n = 22) groups were compared for all 98 patients and patients who underwent MT or BT. Next, the transition of outcomes was compared among the five subgroups (Pre-1, Pre-2, Pre-3, With-1, and With-2). Subsequently, factors that significantly affected outcomes at discharge in all 98 patients throughout the period were extracted by performing univariate analyses. Finally, multivariate analyses (logistic regression analyses) were performed, of which the common objective variable was the poor outcome at discharge. The JSS-PCS application and factors extracted by the univariate analyses were adopted as explanatory variables.

### Tools for statistical analysis

R (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (2021.09.0 Build 351) were used to perform statistical analysis. In all statistical analyses, *p*-values less than 0.05 were evaluated as having a significant difference.

### Approval of the institutional review board

The research within our submission has been approved by the Ethics Institutional Review Board of Eiju General Hospital.

## Results

### Patient background

**Table 1** shows the backgrounds of patients in the entire study population (n = 109): the pre-COVID-19 group (n = 82) and the with-COVID-19 group (n = 27). There were no significant differences between both groups in age, gender, pre-stroke mRS, oral medication, underlying disease, pretreatment neurological findings, pretreatment neuroradiological findings, etiology, and treatment method. There were no positive cases for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen by polymerase chain reaction screening in the with-COVID-19 group.

### Comparison of time indicators between the two groups

**Table 2** shows a series of time indicators in each group. The median value of each indicator changed in minutes (DTI from 30.5 to 38, DTN from 82.5 to 88, DTP from 153 to 162, DTR from 252 to 232, and PTR from 83 to 84) when entering the COVID-19 pandemic period. There were no statistically significant differences between the two groups in any of these indicators, although slight delays were revealed in DTI, DTN, and DTP. No apparent change was found in the median values of OTD (65 minutes).

### Subgroup analysis for time indicators

The transition of all indicators except for OTD was examined among the five subgroups. The median values of all indicators shortened as time elapsed in the pre-COVID-19 period. However, this tendency reversed, and the median values extended when entering the With-1 at the beginning of the COVID-19 pandemic. Interestingly, all but PTR shortened again during the With-2 period (**Fig. 2**). The Kruskal–Wallis test showed no statistically significant difference among the subgroups in all indicators.

**Table 1** Baseline characteristics of patients during the study period

| | All (n = 109) | Pre-COVID-19 (n = 82) | With-COVID-19 (n = 27) | *p* value |
|---|---|---|---|---|
| Age, median (IQR), years | 75 (68-83) | 74.5 (68-81) | 79 (66.5-84) | 0.500 |
| Female, n (%) | 47 (43.1) | 36 (43.9) | 11 (40.7) | 0.826 |
| Pre-stroke mRS score ≤2, n (%) | 98 (89.9) | 76 (92.7) | 22 (81.5) | 0.136 |
| Medical history | | | | |
| Antiplatelet therapy, n (%) | 9 (8.3) | 5 (6.1) | 4 (14.8) | 0.221 |
| Anticoagulant therapy, n (%) | 11 (10.1) | 9 (11.0) | 2 (7.4) | 0.728 |
| Cerebral infarction, n (%) | 13 (11.9) | 10 (12.2) | 3 (11.1) | 1 |
| Ischemic heart disease, n (%) | 9 (8.3) | 5 (6.1) | 4 (14.8) | 0.221 |
| Af/paroxysmal Af, n (%) | 52 (47.7) | 37 (45.1) | 15 (55.6) | 0.381 |
| Congestive heart failure, n (%) | 8 (7.3) | 6 (7.3) | 2 (7.4) | 1 |
| Chronic kidney disease, n (%) | 18 (16.5) | 13 (15.9) | 5 (18.5) | 0.769 |
| Hypertension, n (%) | 67 (61.5) | 46 (56.1) | 21 (77.8) | 0.067 |
| Diabetes mellitus, n (%) | 19 (17.4) | 11 (13.4) | 8 (29.6) | 0.077 |
| Dyslipidemia, n (%) | 28 (25.7) | 19 (23.2) | 9 (33.3) | 0.317 |
| Neurological and CT/MRI findings | | | | |
| NIHSS, median (IQR) | 10 (6-18.5) (n = 99) | 10 (6-17) (n = 76) | 12 (6-24) (n = 23) | 0.194 |
| DWI-ASPECTS, median (IQR) | 9 (6-10) (n = 107) | 9 (7-10) (n = 80) | 8 (5-10) (n = 27) | 0.237 |
| Infarction in the anterior circulatory region, n (%) | 88 (83.8) (n = 105) | 65 (82.2) (n = 79) | 23 (88.5) (n = 26) | 0.554 |
| Occluded artery on MRA/CTA | | | | |
| ICA, n (%) | 20 (18.3) | 12 (14.6) | 8 (29.6) | 0.092 |
| M1 segment of MCA, n (%) | 25 (22.9) | 19 (23.2) | 6 (22.2) | 1 |
| M2 or distal segment of MCA, n (%) | 10 (9.2) | 7 (8.5) | 3 (11.1) | 0.707 |
| Arteries of posterior circulation, n (%) | 7 (6.4) | 7 (8.5) | 0 (0.0) | 0.190 |
| Etiology | | | | |
| Atherosclerosis (large artery), n (%) | 19 (17.4) | 16 (19.5) | 3 (11.1) | 0.394 |
| Cardiogenic, n (%) | 57 (52.3) | 42 (51.2) | 15 (55.6) | 0.825 |
| ESUS, n (%) | 19 (17.4) | 15 (18.3) | 4 (14.8) | 0.778 |
| Small deep infarcts, n (%) | 11 (10.1) | 6 (7.3) | 5 (18.5) | 0.136 |
| Treatment | | | | |
| IVT, n (%) | 53 (48.6) | 41 (50.0) | 12 (44.4) | 0.662 |
| MT, n (%) | 21 (19.3) | 14 (17.1) | 7 (25.9) | 0.399 |
| BT, n (%) | 35 (32.1) | 27 (32.9) | 8 (29.6) | 0.816 |

Statistical comparisons were performed using the Mann–Whitney U test or Fisher's exact test, appropriately. Af: atrial fibrillation; ASPECTS: Alberta Stroke Program Early CT Score; BT: bridging therapy; COVID-19: coronavirus disease 2019; DWI: diffusion-weighted imaging; ESUS: embolic stroke of undetermined sources; ICA: internal carotid artery; IQR: interquartile range; IVT: intravenous thrombolysis; MCA: middle cerebral artery; mRS: modified Rankin Scale; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale

**Table 2** Comparison of the time indicators for treatment between the pre-COVID-19 and with-COVID-19 groups

| | Pre-COVID-19 | | | With-COVID-19 | | | Mann–Whitney U test | | |
|---|---|---|---|---|---|---|---|---|---|
| | Median (minutes) | IQR (minutes) | n | Median (minutes) | IQR (minutes) | n | *p* value | 95% CI | |
| OTD | 65 | 45–128.8 | 82 | 65 | 43–134.5 | 27 | 0.814 | –22 | 14 |
| DTI | 30.5 | 22–43 | 82 | 38 | 26–47.5 | 27 | 0.207 | –11 | 3 |
| DTN | 82.5 | 69.8–105.5 | 68 | 88 | 81–95 | 20 | 0.312 | –17 | 7 |
| DTP | 153 | 113–196 | 41 | 162 | 120.5–186 | 15 | 0.945 | –34 | 35 |
| DTR | 252 | 215–307 | 41 | 232 | 196–276 | 15 | 0.329 | –21 | 53 |
| PTR | 83 | 61–110 | 41 | 84 | 64–96.5 | 15 | 0.650 | –15 | 28 |

95% CI: 95% confidence interval; COVID-19: coronavirus disease 2019; DTI: door-to-imaging time; DTN: door-to-needle time; DTP: door-to-puncture time; DTR: door-to-reperfusion time; IQR: interquartile range; OTD: onset-to-door time; PTR: puncture-to-reperfusion time

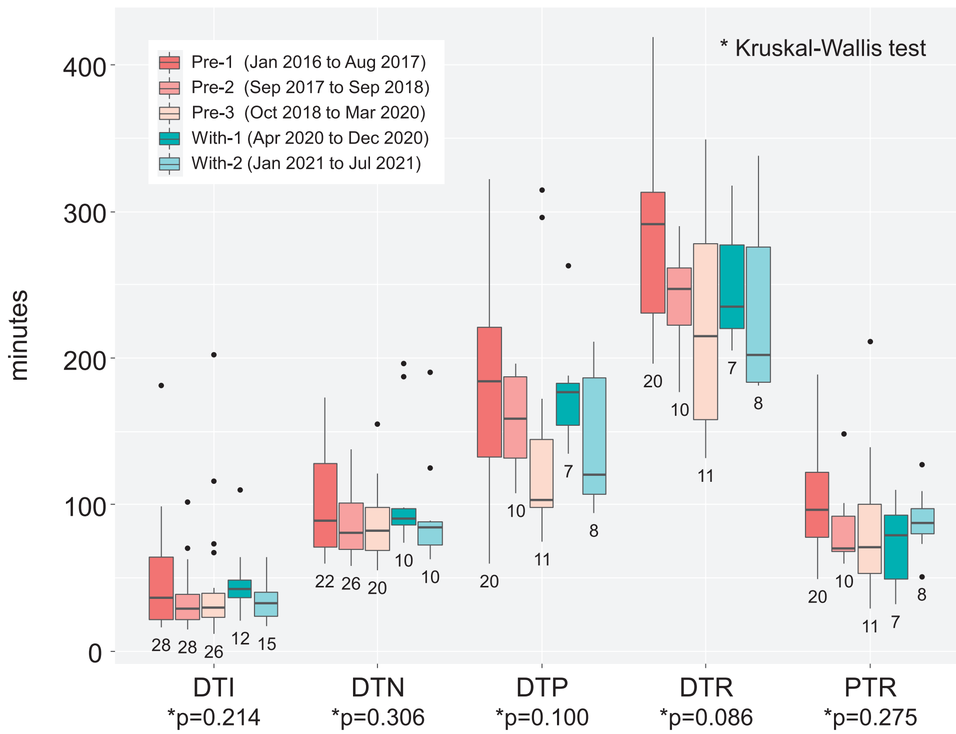


**Fig. 2** Box plot of each time indicator in five subgroups. The numbers below each plot represent the number of cases. DTI: door-to-imaging time; DTN: door-to-needle time; DTP: door-to-puncture time; DTR: door-to-reperfusion time; PTR: puncture-to-reperfusion time

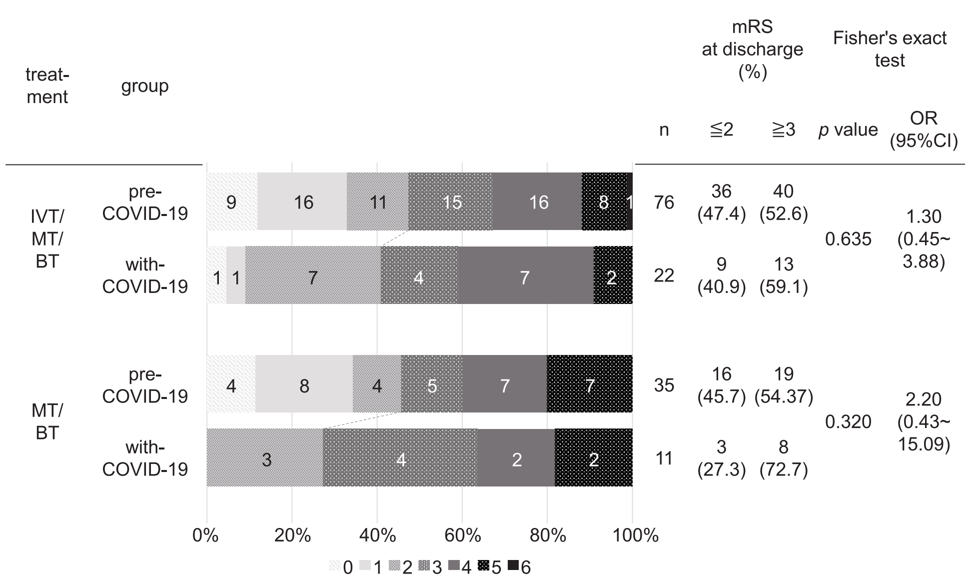


**Fig. 3** Comparison of treatment outcomes between the pre-COVID-19 and with-COVID-19 groups. 95% CI: 95% confidence interval; BT: bridging therapy; COVID-19: coronavirus disease 2019; IVT: intravenous thrombolysis; mRS: modified Rankin Scale; MT: mechanical thrombectomy; OR: odds ratio

## Clinical outcomes at discharge

Of the 98 patients targeted for outcome analysis, 36 of 76 (47.4%) in the pre-COVID-19 group and 9 of 22 (40.9%) in the with-COVID-19 group had favorable outcomes ($p = 0.635$). In patients with MT or BT, outcomes were favorable in 16 of 35 patients (45.7%) in the pre-COVID-19 group and 3 of 11 patients (27.3%) in the with-COVID-19 group ($p = 0.320$). Neither analysis showed any statistically significant difference between the groups (**Fig. 3**). Outcome analysis among the five subgroups revealed a transient

**Table 3** Subgroup analysis for clinical outcomes at discharge

| Subgroup | mRS at discharge, n (%) ≤2 (n = 45) | mRS at discharge, n (%) ≥3 (n = 53) | *p* value |
|---|---|---|---|
| Pre-1 (Jan 2016 to Aug 2017) | 11 (42.3) | 15 (57.7) | 0.188 |
| Pre-2 (Sep 2017 to Sep 2018) | 13 (50.0) | 13 (50.0) | |
| Pre-3 (Oct 2018 to Mar 2020) | 12 (50.0) | 12 (50.0) | |
| With-1 (Apr 2020 to Dec 2020) | 1 (11.1) | 8 (88.9) | |
| With-2 (Jan 2021 to Jul 2021) | 8 (61.5) | 5 (38.5) | |

Eleven cases with pre-stroke mRS of 3 or more are excluded from the analysis. Statistical intergroup comparison was made using the Fisher's exact test. mRS: modified Rankin Scale

deterioration of clinical outcomes in the With-1 period ($p = 0.188$; **Table 3**). In the with-2 period, treatment outcomes recovered to pre-pandemic levels.

### Univariate analysis for factors affecting clinical outcomes

The background factors for the 98 patients significantly affecting the outcomes were extracted by univariate analysis (**Table 4**). Age (median 70 vs. 77 years, $p = 0.005$), National Institutes of Health Stroke Scale (NIHSS) (median 7 vs. 14, $p < 0.001$), diffusion-weighted imaging-Alberta Stroke Program Early CT Score (DWI-ASPECTS) (median 10 vs. 8, $p < 0.001$), infarction in the anterior circulatory regions (70.7% vs. 92.5%, $p = 0.011$), and the achievement of the thrombolysis in cerebral infarction grade 3 (TICI3) (73.7% vs. 29.6%, $p = 0.006$) were the significant factors. Regarding etiology, there were differences in the distribution of the five stroke subtypes between the two favorable and poor outcome groups ($p = 0.013$). Post hoc comparisons using the Holm method showed significant differences between the two groups in the frequencies of atherosclerosis (large vessels) and embolic stroke of undetermined sources (ESUS) ($p = 0.022$). Arteriosclerosis tended to be distributed more in the favorable outcome group, while ESUS was more in the poor one. JSS-PCS application was not a significant factor for clinical outcomes (20.0% vs. 24.5%, $p = 0.635$).

### Multivariate analysis for poor clinical outcomes

A total of three multivariate analyses (analysis 1 [n = 88], analysis 2 [n = 84], and analysis 3 [n = 46]) were performed, each including JSS-PCS application as an explanatory variable (**Fig. 4**). A value of 1 was given to patients who applied JSS-PCS as an explanatory variable, while 0 was assigned to the rest. Age, NIHSS, DWI-ASPECTS, infarction in the anterior circulatory regions, and achievement of TICI3 were selected as other explanatory variables, which were significant factors in the univariate analyses. The boundary values for age, NIHSS score, and DWI-ASPECTS were between 73 and 74, 9 and 10, and 8 and 9, respectively. The stroke subtype was also selected as an explanatory variable. A value of 0 was assigned to patients classified with atherosclerosis (large vessel) and 2 to those with ESUS. A value of 1 was applied to the rest of the patients. The combination of explanatory variables was adjusted among the three analyses. The factors independently affecting clinical outcomes were NIHSS (analysis 1 and analysis 2), DWI-ASPECTS (analysis 1 and analysis 2), and TICI3 (analysis 3). Although JSS-PCS had odds ratios above 1 in all analyses, the 95% confidence interval always spanned the value of 1. It did not independently affect clinical outcomes, even if adjusted for other explanatory factors.

## Discussion

### Concerns in reperfusion therapy raised by the COVID-19 pandemic

The COVID-19 pandemic has caused serious confusion in acute medical care for stroke worldwide. Decreased admission numbers to stroke units have been reported in multiple countries and institutions.[6–8)]

Regarding reperfusion therapy for AIS, the number of patients with IVT[7)] or MT[9)] has been reported to have decreased. One of the biggest concerns of the COVID-19 pandemic is its adverse effect on in-hospital time indicators such as DTN, DTP, and DTR. These are based on the time spent putting on and taking off personal protective equipment and repeating disinfection operations during the initial treatment in the ER. It is also caused by location preparation as the patient moves through the hospital for imaging and treatment. Concerns about delays in OTD, which is a crucial factor in determining treatment options, have also been raised.

**Table 4** Factors that affected patients' outcomes at discharge

| | All (n = 98) | mRS ≤2 (n = 45) | mRS ≥3 (n = 53) | *p* value |
|---|---|---|---|---|
| JSS-PCS, n (%) | 22 (22.4) | 9 (20.0) | 13 (24.5) | 0.635 |
| Age, median (IQR), years | 73 (67–80.8) | 70 (62–77) | 77 (68–83) | 0.005 |
| Female, n (%) | 40 (40.8) | 17 (37.8) | 23 (43.4) | 0.681 |
| Medical history | | | | |
| Antiplatelet therapy, n (%) | 8 (8.2) | 2 (4.4) | 6 (11.3) | 0.282 |
| Anticoagulant therapy, n (%) | 9 (9.2) | 4 (8.9) | 5 (9.4) | 1 |
| Cerebral infarction, n (%) | 11 (11.2) | 5 (11.1) | 6 (11.3) | 1 |
| Ischemic heart disease, n (%) | 6 (6.1) | 1 (2.2) | 5 (9.4) | 0.214 |
| Af/paroxysmal Af, n (%) | 45 (45.9) | 18 (40.0) | 27 (50.9) | 0.314 |
| Congestive heart failure, n (%) | 6 (6.1) | 4 (8.9) | 2 (3.8) | 0.409 |
| Chronic kidney disease, n (%) | 13 (13.3) | 5 (11.1) | 81(5.1) | 0.766 |
| Hypertension, n (%) | 57 (58.2) | 24 (53.3) | 33 (62.3) | 0.415 |
| Diabetes mellitus, n (%) | 16 (16.3) | 6 (13.3) | 10 (18.9) | 0.586 |
| Dyslipidemia, n (%) | 27 (27.6) | 13 (28.9) | 14 (26.4) | 0.823 |
| Neurological and CT/MRI findings | | | | |
| NIHSS, median (IQR) | 9.5 (6–16.8) (n = 90) | 7 (5–10) (n = 43) | 14 (7.5–21.5) (n = 47) | <0.001 |
| DWI-ASPECTS, median (IQR) | 9 (6.8–10) (n = 96) | 10 (9–11) (n = 43) | 8 (5–9) (n = 53) | <0.001 |
| Infarction in the anterior circulatory region, n (%) | 78 (83.0) (n = 94) | 29 (70.7) (n = 41) | 49 (92.5) (n = 53) | 0.011 |
| Etiology | | | | |
| Atherosclerosis (large vessel), n (%) | 17 (17.3) | 13 (28.9) | 4 (7.5) | 0.013 |
| Cardiogenic, n (%) | 49 (50.0) | 20 (44.4) | 29 (54.7) | |
| ESUS, n (%) | 18 (18.4) | 4 (8.9) | 14 (26.4) | |
| Small deep infarcts, n (%) | 11 (11.2) | 6 (13.3) | 5 (9.4) | |
| Others, n (%) | 3 (3.1) | 2 (4.4) | 1 (1.9) | |
| Treatment | | | | |
| IVT, n (%) | 52 (53.1) | 26 (57.8) | 26 (49.1) | 0.422 |
| MT, n (%) | 18 (18.4) | 8 (17.8) | 10 (18.9) | 1 |
| BT, n (%) | 28 (28.6) | 11 (24.4) | 17 (32.1) | 0.502 |
| TICI3, n (%) | 22 (47.8) (n = 46) | 14 (73.7) (n = 19) | 8 (29.6) (n = 27) | 0.006 |
| Time indicators | | | | |
| OTN, median (IQR) | 162 (120–202.5) (n = 80) | 147 (115–202) (n = 37) | 165 (128.5–205) (n = 43) | 0.201 |
| OTR, median (IQR) | 343.5 (275–434) (n = 46) | 336 (272–441.5) (n = 19) | 357 (292.5–428.5) (n = 27) | 1 |
| DTN, median (IQR) | 85 (70–104.3) (n = 80) | 79 (69–98) (n = 37) | 89 (74.5–106) (n = 43) | 0.221 |
| DTR, median (IQR) | 239 (212.3–297.5) (n = 46) | 229 (214–297) (n = 19) | 243 (210.5–292.5) (n = 27) | 0.623 |

Statistical intergroup comparison was made using the Mann–Whitney U test or Fisher's exact test, appropriately. Eleven cases with pre-stroke mRS score of 3 or more are excluded from the analysis. Af: atrial fibrillation; ASPECTS: Alberta Stroke Program Early CT Score; BT: bridging therapy; DTN: door-to-needle time; DTR: door-to-reperfusion time; DWI: diffusion-weighted imaging; ESUS: embolic stroke of undetermined sources; IQR: interquartile range; IVT: intravenous thrombolysis; JSS-PCS: protected code stroke formulated by the Japan Stroke Society; mRS: modified Rankin Scale; MT: mechanical thrombectomy; NIHSS: National Institute of Health Stroke Scale; OTN: onset-to-needle time; OTR: onset-to-reperfusion time; TICI3: thrombolysis in cerebral infarction grade 3

### Time indicators in the COVID-19 pandemic

There are several discussions about delays in time indicators for AIS treatment during the COVID-19 pandemic. A prospective multicenter cohort study of cases enrolled in the TRISP registry (20 stroke centers across Europe)[10] reported no significant changes in the time metrics entering the lockdown period. An analysis through a national inpatient stroke registry in the United States, Get With The Guidelines – Stroke,[11] also emphasizes the similarity of time indicators before and during the pandemic.

On the other hand, a comprehensive stroke center in Japan reported significant delays in DTI and door-to-groin

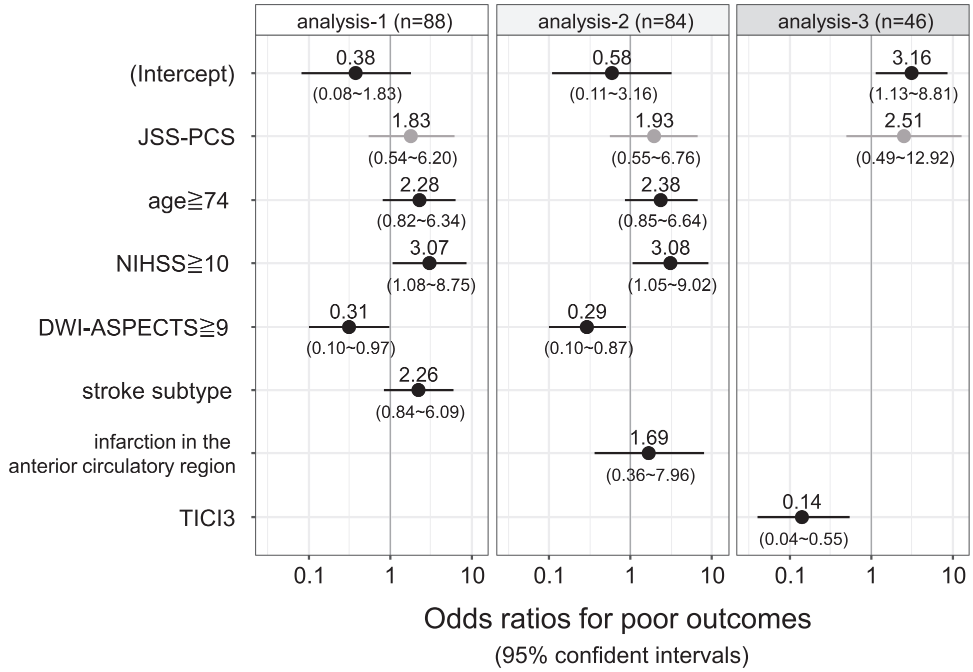


**Fig. 4** Multivariate analysis (logistic regression analysis) with poor outcomes at discharge as the objective variable. The odds ratio of each explanatory variable associated with poor outcomes was calculated for each analysis. The "JSS-PCS" explanatory variable was included in all analyses. ASPECTS: Alberta Stroke Program Early CT Score; DWI: diffusion-weighted imaging; JSS-PCS: protected code stroke formulated by the Japan Stroke Society; NIHSS: National Institute of Health Stroke Scale; TICI3: thrombolysis in cerebral infarction grade 3

puncture time during the pandemic period from a single-center prospective registry.[12] Significant increases in time metrics were also reported from a large comprehensive stroke center in Ontario, Canada.[13] There are several other reports on the adverse effects of the COVID-19 pandemic on treatment time metrics.[6,14–17]

Our study revealed slight delays in DTI, DTN, DTP, and PTR when entering the pandemic phase. In particular, the delays in DTI, DTN, and DTP suggest confusion among the ER staff. However, they did not have enough impact to show statistical significance. There was unexpectedly a 20-minute DTR reduction in the with-COVID-19 group. DTP and DTR are metrics that have passed some time since the emergency visit, of which numerical values have wide variance. Therefore, the adverse effects of confusion in the pandemic phase were considered absorbed within the margin of error. PTR is mainly affected by the difficulty of treatment for each case, such as vascular running, arteriosclerosis, and arterial stenosis. Therefore, the pandemic effect on this index is inferred as limited. OTD did not show an apparent elongation when entering the pandemic. It may indicate the robustness of the local emergency transport system during the pandemic.

Considering the data of our facility together, the presence or absence of delay in time indicators and their degree seems to vary depending on various conditions such as the prevalence of infection in the region, national and regional administration, medical environment, and characteristics of medical facilities.

### Subgroup analyses for time indicators

In the subgroup analysis, median DTP and DTR decreased as time elapsed before the COVID-19 pandemic. For DTI, DTN, and PTR, their median values shortened from the Pre-1 to Pre-2 periods. These are the results of efforts among multiple occupations in the facility to cooperate, streamline treatment workflows, and improve outcomes. However, the time indicators prolonged when entering the With-1, the first half of the with-COVID-19 period. It reflects unfamiliarity and confusion among the ER staff due to the pandemic and the all-new PCS. This confusion may also be owing to the inability to recruit staff due to fear of spreading infection. However, all indicators except for PTR have shortened again in the With-2 period. It shows that the ER staff has adhered to JSS-PCS, gained experience, overcome the initial confusion, and can now carry out their work as smoothly as before. A comprehensive stroke center has also reported initial delays during the pandemic period and subsequent shortening of time indicators due to the adaptation of medical staff.[12] This trend may be a universal one, at least domestically.

### Functional outcomes of reperfusion therapy during the COVID-19 pandemic

Several reports refer to the impact of the COVID-19 pandemic on the functional outcomes of reperfusion therapy for AIS. A study in the Aragon region of Spain reported that the functional outcome at three months during the pandemic was not significantly different from that in the pre-pandemic.[18] A comprehensive stroke center in Japan reported similar results regarding the discharge outcome.[19] On the other hand, clinical outcomes were less favorable on discharge and at three months in a cross-sectional, observational, and retrospective study in which eight countries participated by providing data from the stroke database.[13] Others also reported worsening results.[17] There is such a report of unchanged median values of mRS at three months after treatment despite significant worsening at discharge.[9] As with time indicators, treatment outcomes also seem to vary depending on the macroscopic and microscopic environment surrounding each emergency medical field.

In this study, there was no significant difference in functional outcomes at discharge between pre-COVID-19 and with-COVID-19 groups, although there was a trend toward worsening in the latter group. Subgroup analysis depicted an abrupt deterioration in clinical outcomes after entering the With-1 period. During this period, the in-hospital medical system suffered severe damages due to the nosocomial cluster, such as a series of transfers or retirements of ward staff and strict restrictions on the movement of patients, staff, medical equipment, and materials. In addition, no reperfusion therapy was performed for four months. These conditions in the With-1 period, along with delayed time indicators at the ER, had a considerable negative impact on the quality of medical care and rehabilitation, resulting in worse outcomes during the with-COVID-19 period. During the With-2 period, restrictions on movement within the hospital were eased and ward staff adapted. Improvement of in-hospital circumstances and the shortened time indicator in ER contributed to the improved outcome during this period.

### Significance of JSS-PCS in reperfusion therapy during the COVID-19 pandemic

The sole and primary purpose of JSS-PCS implementation in the COVID-19 pandemic is to prevent secondary infections among emergency medical staff. Therefore, the time indicator prolongation and the accompanying deterioration of treatment outcomes were significant concerns regarding the JSS-PCS introduction.

In the present study, the prolongation of the time indicators was transient, and no significant overall delay was observed. Treatment outcomes certainly tended to worsen after implementing JSS-PCS. However, the exacerbation was temporary early in the pandemic, after which outcomes improved as in-hospital conditions refined. There was no statistically significant deterioration during the pandemic as a whole. Moreover, JSS-PCS, unlike NIHSS and DWI-ASPECTS, was not a significant factor affecting patient outcomes in univariate and multivariate analyses.

From the results of this research, JSS-PCS is considered to have achieved more than its original purpose. The efficacy and validity of introducing this protocol during the COVID-19 pandemic have been demonstrated at our facility.

There is no doubt that shortening the treatment-related time indicators is an essential issue in the initial treatment of AIS. However, in today's world, where COVID-19 has not yet shown signs of termination, measures to prevent the spread of infection are the top priority.

### Limitations

Data analysis at only one domestic facility, a retrospective observational design, and a small number of patients are the limitations of this study. Furthermore, the absolute values of each time indicator, such as DTI, DTN, and DTP, are larger than those of neurosurgery or stroke hospitals and so-called high-volume centers. As a regional core hospital, our facility must also meet a wide range of needs for emergency diseases other than stroke. Therefore, preparing an in-hospital environment only for specialized reperfusion therapy is problematic. There is no doubt that these conditions considerably influence these time indicators.

## Conclusion

The introduction and application of JSS-PCS during the COVID-19 pandemic significantly affected neither time indicators nor outcomes regarding reperfusion therapy at our facility. Measures to prevent the spread of infection should be prioritized in today's world, where COVID-19 has not yet shown signs of termination.

## Acknowledgments

We would like to thank enago (https://www.enago.jp) and Grammarly (https://app.grammarly.com/) for English language editing.

## Disclosure Statement

The authors declare no conflicts of interest.

## References


1) Gomez CR. Editorial: time is brain! *J Stroke Cerebrovasc Dis* 1993; 3: 1–2.
2) Khosravani H, Rajendram P, Notario L, et al. Protected code stroke: hyperacute stroke management during the Coronavirus Disease 2019 (COVID-19) pandemic. *Stroke* 2020; 51: 1891–1895.
3) Srivatanakul K, Asai S, Hirayama A, et al. A protocol of infection control for mechanical thrombectomy in possible COVID-19 patients: Tokai University COVID-19 manual. *JNET J Neuroendovasc Ther* 2020; 14: 157–161.
4) Japanese Stroke Society PCS Working Group. Protocol for stroke management during COVID-19 pandemic: protected code stroke, Japan Stroke Society edition (JSS-PCS). *Jpn J Stroke* 2020; 42: 315–343. (in Japanese)
5) Hirano T. [Protected code stroke during the COVID-19 pandemic]. *Brain Nerve* 2020; 72: 1073–1077. (in Japanese)
6) Montaner J, Barragán-Prieto A, Pérez-Sánchez S, et al. Break in the stroke chain of survival due to COVID-19. *Stroke* 2020; 51: 2307–2314.
7) Miękisiak G, Pettersson SD, Szarek D, et al. Acute stroke care during COVID-19: national data. *Infect Dis Rep* 2022; 14: 198–204.
8) Yoshimoto T, Yamagami H, Sakai N, et al. Impact of COVID-19 on the volume of acute stroke admissions: a nationwide survey in Japan. *Neurol Med Chir (Tokyo)* 2022; 62: 369–376.
9) Geng D, Xu X, Luan X, et al. Differential influence of the COVID-19 pandemic on mechanical thrombectomy and bridging therapy for acute ischemic stroke. *Front Neurol* 2022; 13: 852423.
10) Altersberger VL, Stolze LJ, Heldner MR, et al. Maintenance of acute stroke care service during the COVID-19 pandemic lockdown. *Stroke* 2021; 52: 1693–1701.
11) Srivastava PK, Zhang S, Xian Y, et al. Treatment and outcomes of patients with ischemic stroke during COVID-19: an analysis from Get With the Guidelines-Stroke. *Stroke* 2021; 52: 3225–3232.
12) Yoshimoto T, Shiozawa M, Koge J, et al. Evaluation of workflow delays in stroke reperfusion therapy: a comparison between the year-long pre-COVID-19 period and the With-COVID-19 period. *J Atheroscler Thromb* 2022; 29: 1095–1107.
13) Katsanos AH, de Sa Boasquevisque D, Al-Qarni MA, et al. In-hospital delays for acute stroke treatment delivery during the COVID-19 pandemic. *Can J Neurol Sci* 2021; 48: 59–65.
14) Kerleroux B, Fabacher T, Bricout N, et al. Mechanical thrombectomy for acute ischemic stroke amid the COVID-19 outbreak. *Stroke* 2020; 51: 2012–2017.
15) Plumereau C, Cho TH, Buisson M, et al. Effect of the COVID-19 pandemic on acute stroke reperfusion therapy: data from the Lyon Stroke Center Network. *J Neurol* 2021; 268: 2314–2319.
16) Shokri H, Nahas NE, Basiony AE, et al. Did COVID-19 impact stroke services? A multicenter study. *Neurol Sci* 2022; 43: 1–8.
17) Siegler JE, Zha AM, Czap AL, et al. Influence of the COVID-19 pandemic on treatment times for acute ischemic stroke: the Society of Vascular and Interventional Neurology Multicenter Collaboration. *Stroke* 2021; 52: 40–47.
18) Tejada Meza H, Lambea Gil Á, Villar Yus C, et al. Three-month functional prognosis of patients hospitalised due to acute ischaemic stroke in Aragon: regional analysis of the impact of COVID-19. *Neurología* 2021; 36: 531–536.
19) 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* 2021; 11: 611504.