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# Impact of Coronavirus Disease 2019 on Time Delay and Functional Outcome of Mechanical Thrombectomy in Tokyo, Japan

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*Objectives:* An association has been reported between delays in the onset-to-door (O2D) time for mechanical thrombectomy (MT) and outbreaks of coronavirus disease 2019 (COVID-19). However, the association between other MT time courses or functional outcomes and COVID-19 outbreaks remains unclear. We compared the time courses of stroke pathways or functional outcomes in 2020 (the COVID-19 era) with those in 2019 (the pre-COVID-19 era) in Tokyo, Japan. *Materials and methods:* This retrospective observational study used data from the Tokyo-tama-REgistry of Acute endovascular Thrombectomy (TREAT), a multicenter registry of MT for acute large vessel occlusion in the Tokyo Metropolitan Area. Patients who had undergone acute MT from January 2019 to December 2020 were included. Patients were classified by the year they had undergone MT (2019 or 2020). *Results:* In total, 477 patients were analyzed. O2D time was significantly longer in 2020 (146.0 min) than in 2019 (105.0 min;  $p = 0.034$ ). No significant difference in door-to-puncture time (D2P) time or modified Rankin Scale (mRS) score 0–2 at 90 days was seen between 2019 and 2020. In the subgroup analysis, O2D time was significantly longer in the first half of 2020 compared with 2019. Multivariable logistic regression analysis revealed that the year 2020 was an independent predictor of longer O2D time, but not for mRS score 0–2 at 90 days. *Conclusions:* Although O2D time was significantly longer in the COVID-19 compared with the pre-COVID-19 era, D2P may not be significantly delayed and functional outcomes may not be different, despite the COVID-19 pandemic.

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## Introduction

Several papers from around the world have reported that outbreaks of coronavirus disease 2019 (COVID-19) have led to the following time delays associated with endovascular mechanical thrombectomy (MT) for patients with acute ischemic stroke (AIS): onset-to-door (O2D) time,<sup>1,2</sup> door-to-puncture (D2P) time and door-to-recanalization time.<sup>3</sup> Several speculative factors may explain these delays, such as a collapse of emergency services focused on patients with COVID-19<sup>2</sup> and patients' fear of exposure to COVID-19 through interactions within the health-care system.<sup>2,4</sup>

In Japan, the first patient with COVID-19 was reported on January 15, 2020. During 2020, waves of the COVID-19 pandemic may have led to time delays or changes in functional outcomes after MT. Previous reports have reported reduced numbers of patients admitted for stroke, thrombolysis, and thrombectomy worldwide<sup>5</sup> and in Tokyo.<sup>6</sup> However, whether the status of the COVID-19 pandemic in Japan is correlated with time delays to, or changes in functional outcomes after, MT remains poorly understood.

Therefore, this study aimed to compare the time courses of stroke pathways or functional outcomes in 2020 (the COVID-19 era) with those in 2019 (the pre-COVID-19 era) in Tokyo, Japan using data from the Tokyo-tama-REgistry of Acute endovascular Thrombectomy (TREAT) database.

## Methods

### *Study design and oversight*

This retrospective observational study used prospectively and retrospectively collected data from TREAT (UMIN-CTR: UMIN000026888), a multicenter registry of MT for acute large vessel occlusion (LVO) in the Tokyo Metropolitan Area.<sup>7</sup> The survey covered patients with LVO who underwent acute MT between January 2019 and December 2020. The participating facilities were 18 thrombectomy-capable stroke centers in the Tokyo metropolis. The study protocol was approved by the ethics committee of each participating center. Written, informed consent was obtained from all participants or their legal representative.

### *Patient selection*

The inclusion criteria for this study were: 1) underwent acute MT and 2) was directly transferred by emergency medical services (EMS) from home/scene or another hospital. The exclusion criteria were: 1) missing data about O2D, last-known-well (LKW), or D2P time, 2) missing data about

modified Rankin Scale (mRS) scores at 90 days after MT, 3) pre-mRS score 3–5, and 4) O2D time over 24 h.

### *Procedure*

The physician in charge of therapy in the facility determined the therapeutic approach deemed most appropriate. Recanalization status was classified using the modified Thrombolysis In Cerebral Infarction scale.<sup>8</sup>

### *Outcomes*

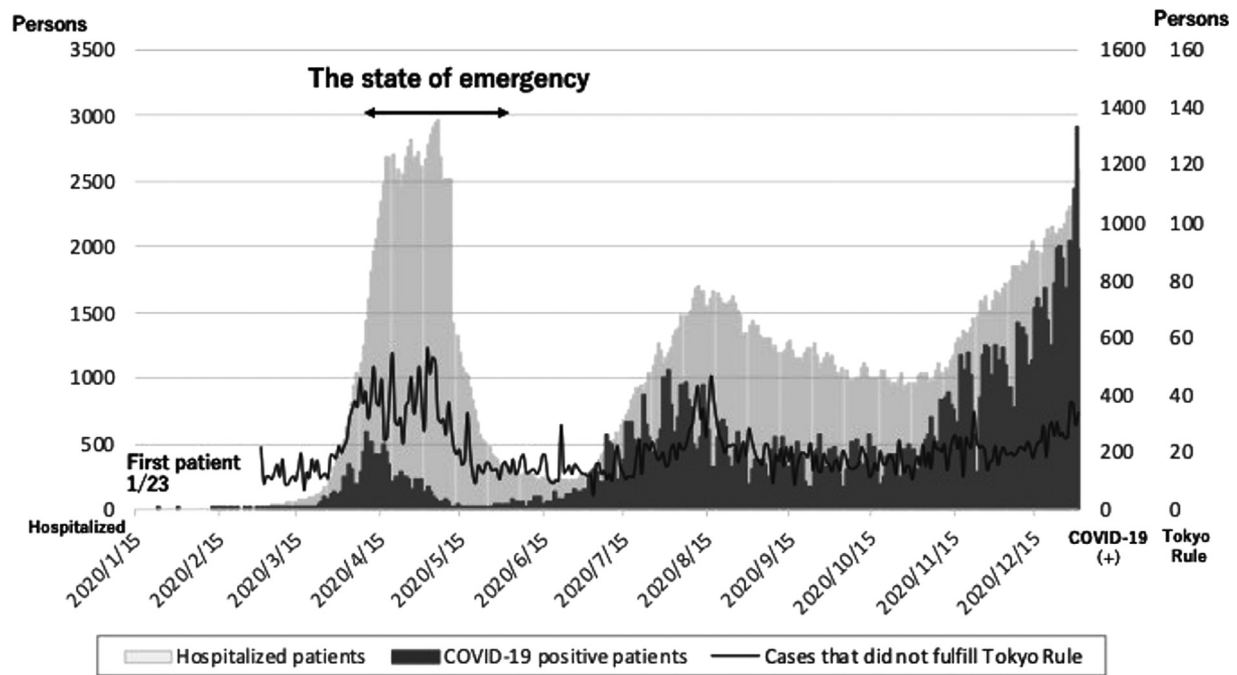
The primary outcomes were O2D time, D2P time, and mRS score at 90 days. Symptomatic intracranial hemorrhage was defined as any intracranial hemorrhage related to worsening of the National Institutes of Health Stroke Scale (NIHSS) score  $\geq 4$  or requiring any additional procedure.

### *Statistical analysis*

Analysis was performed using SPSS 26 software (IBM, Armonk, NY, USA) and R 4.1.0 for measurement of intraclass correlation (ICC) and fixed effect model. The baseline characteristics and outcomes between the cases in 2019 (pre-COVID-19 era) and 2020 (COVID-19 era) were compared using the Mann–Whitney *U*-test for continuous variables and the  $\chi^2$  test for categorical variables. The threshold for significance was  $p < 0.05$ . We estimated ICC to estimate the center effect and used fixed effect model for including center effect in each outcome (O2D, D2P and mRS at 90days). We performed subgroup analysis by comparing baseline characteristics and outcomes between 2019 and 2020 every 3 months. Multivariable logistic regression analysis was conducted to assess independent predictors of O2D time with adjustments for years and previously identified potential predictors<sup>9,10</sup> of mRS scores at 90 days with adjustments for years and previously identified potential predictors of mRS at 90 days.<sup>11–15</sup> To deal with missing data, we used complete case analysis for continuous variables and categorized categorical variables as unknown.

## Results

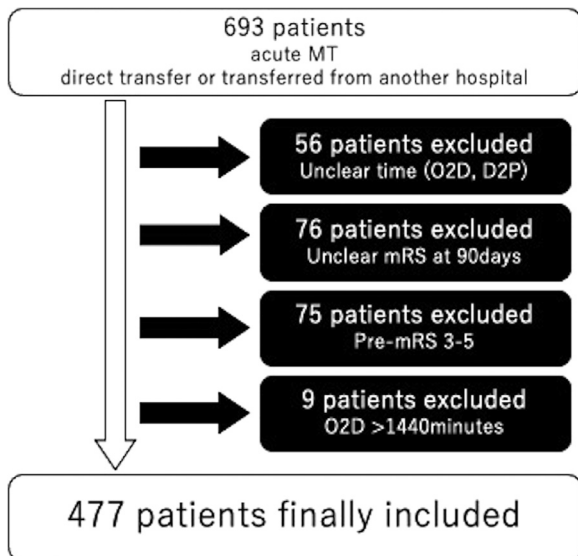
**Fig. 1** shows the numbers of cases in Tokyo, Japan who tested positive for COVID-19, hospitalized patients, and cases who did not fulfill the Tokyo Rule which requires calls to over five institutions or taking over 20 min from the start of hospital selection to find an institution that could accept the patient; this indicates the difficulty of emergency transportations to hospital. The COVID-19 pandemic has been characterized by several waves and



**Fig. 1.** Transition of patients with coronavirus disease 2019 (COVID-19) in Tokyo. The figure shows the number of patients newly diagnosed with COVID-19, hospitalized patients, and cases that did not fulfill the Tokyo Rule for Emergency Medical Care by requiring calls to over five institutions or taking over 20 min from the start of hospital selection to find an institution that could accept the patient (<https://stopcovid19.metro.tokyo.lg.jp/en/>).

peaks. In the peak of the first wave, from April 7 to May 31, 2020, the Japanese government declared a state of emergency and asked people to self-quarantine.

Among 693 patients who met the inclusion criteria between January 2019 and December 2020, 477 were included in the present study (Fig. 2). The patients' baseline and procedural characteristics are shown in Table 1.



**Fig. 2.** Flowchart of the patient selection. D2P: door-to-puncture time, mRS: modified Rankin Scale, MT: mechanical thrombectomy, O2D: onset-to-door time.

NIHSS scores were significantly higher in 2020. Diagnostic modalities for occluded vessels and stroke etiologies significantly differed between 2019 and 2020.

The outcomes are summarized in Tables 2 and 3. O2D time was significantly longer in 2020 (146.0 min) than in 2019 (105.0 min;  $p = 0.034$ ). Although O2D time or LKW time to EMS call time and arrival at the site to departure time did not significantly differ between 2019 and 2020, EMS call to arrival at the site (2019 vs. 2020; 8.0 vs. 9.0 min,  $p = 0.005$ ), door (H1: hospital transferred to first) to departure (H1) time (95.0 vs. 113.5 min,  $p = 0.008$ ), and door (H1) to door (H2: hospital transferred to secondarily for thrombectomy) time (112.0 vs. 133.0 min,  $p = 0.008$ ) were all significantly longer in 2020 than in 2019. Although not significantly different, O2D or LKW to EMS call was longer in 2020 than in 2019. No significant differences were seen in D2P time, mRS score 0–2 at 90 days, or other secondary outcomes between 2019 and 2020. The ICC of each outcome was 0.0169 (O2D), 0.232 (D2P), and 0.0354 (mRS at 90days); large ICC was measured in D2P. The fixed effect model to include the center effect revealed that the coefficients ( $\pm$  standard error: SE) of year and O2D, D2P, and mRS at 90days were  $0.22 \pm 0.093$  ( $p = 0.0183$ ),  $0.018 \pm 0.051$  ( $p = 0.718$ ), and  $-0.34 \pm 0.19$  ( $p = 0.0738$ ).

A summary of the subgroup analysis is shown in Table 4. Compared with 2019, O2D time was significantly longer from January to March 2020, the beginning of the COVID-19 pandemic in Tokyo (2019 vs. 2020; 84.5 vs. 140.0 min,  $p = 0.025$ ), and from April to June 2020, the

**Table 1.** Patients' baseline characteristics.

		2019 (n = 242)	2020 (n = 235)	p
Age median (IQR)		76.0 (70.0–82.0)	77.0 (68.0–83.0)	0.734
Gender/Male		156 (64.5%)	135 (57.4%)	0.116
LKW		101 (41.7%)	116 (49.4%)	0.094
Previous mRS score	0	195 (80.6%)	168 (71.5%)	0.067
	1	26 (10.7%)	37 (15.7%)	
	2	21 (8.7%)	30 (12.8%)	
Transferred from another hospital		43 (17.8%)	55 (23.4%)	0.128
History	Hypertension	144 (59.5%)	141 (60.0%)	0.912
	Dyslipidemia	66 (27.3%)	70 (29.8%)	0.543
	DM	50 (20.7%)	37 (15.7%)	0.164
	AF	121 (50.0%)	119 (50.6%)	0.889
NIHSS score, median (IQR)		18 (11–23) (n = 241)	19 (14–24) (n = 234)	0.026
Diagnostic modality for occluded vessels	MRA	175 (72.3%)	167 (71.1%)	0.006
	CTA	41 (16.9%)	58 (24.7%)	
	DSA	26 (10.7%)	10 (4.3%)	
Occlusion site	ICA	79 (32.6%)	79 (33.6%)	0.822
	MCA-M1	101 (41.7%)	97 (41.3%)	
	MCA-M2~M3	46 (19.0%)	33 (14.0%)	
	VA-BA	24 (9.9%)	27 (11.5%)	
	ACA	2 (0.8%)	2 (0.9%)	
	PCA	1 (0.4%)	3 (1.3%)	
Etiology	CE	163 (67.4%)	158 (67.2%)	0.021
	LAA	49 (20.2%)	30 (12.8%)	
	Dissection	7 (2.9%)	4 (1.7%)	
	Other	9 (3.7%)	19 (8.1%)	
	Etiology unknown	14 (5.8%)	24 (10.2%)	
	iv-rtPA	Administered	108 (44.6%)	
Not administered	134 (55.4%)	108 (61.7%)		
Unknown	0	1 (0.4%)		
Anesthesia	Local anesthesia	138 (57.0%)	134 (57.0%)	0.218
	Conscious sedatives	92 (38.0%)	79 (33.6%)	
	General anesthesia	11 (4.5%)	18 (7.7%)	
	Unknown	1 (0.4%)	4 (1.7%)	

ACA: anterior cerebral artery; AF: atrial fibrillation; BA: basilar artery; CE: cardioembolism; CTA: computed tomography angiography; DM: diabetes mellitus; DSA: digital subtraction angiography; ICA: internal carotid artery; iv-rtPA: intravenous recombinant tissue plasminogen activator; LAA: large artery atherosclerosis; MCA: middle cerebral artery; MRA: magnetic resonance angiography; mRS: modified Rankin Scale; PCA: posterior cerebral artery; VA: vertebral artery.

peak of the first wave (2019 vs. 2020; 105.0 vs. 155.0 min,  $p = 0.025$ ). In addition, D2P time was significantly longer from October to December 2020, the peak of the third wave (2019 vs. 2020; 62.5 vs. 82.0 min,  $p = 0.022$ ). No significant difference in mRS score at 90 days was found between 2019 and 2020. Since the median time of O2D in total patients was 140.0 min, patients whose O2D  $\geq 140.0$  were classified in longer O2D time group. The results of the multivariable logistic regression analysis of O2D time (Table 5) revealed that LKW time, transferred from another hospital, lower NIHSS score, and year 2020 (odds ratio [OR]: 1.72; 95% confidence interval [CI]: 1.06–2.82;  $p = 0.028$ ) were independent predictors of a longer O2D time. The results of the multivariable logistic regression analysis of mRS score 0–2 at 90 days revealed that year was not associated with mRS score 0–2 at 90 days (Table 6).

## Discussion

The results of this study revealed that O2D time was significantly longer in 2020 than in 2019, but not D2P time or mRS score at 90 days. In the subgroup analysis, O2D time was also significantly longer in the first half of 2020 than in 2019, and D2P time was significantly longer from October to December 2020 than in 2019. According to the multivariable logistic regression analysis, year 2020 was an independent predictor of a longer O2D time; however, it was not associated with mRS 0–2 at 90 days. Previous studies have reported that COVID-19 outbreaks were associated with delays in O2D time.<sup>1,2</sup> The breakdown in emergency services caused by COVID-19 outbreaks and patients' fears of exposure to the disease may be speculative factors explaining the time delays during the COVID-19 era.<sup>2</sup> Another study reported that factors such as a

**Table 2.** Outcomes.

		2019 (n = 242)	2020 (n = 235)	p
<b>Primary outcome</b>				
O2D median (IQR), min		105.0 (51.7–235.2)	146.0 (51.0–360.0)	0.034
D2P median (IQR), min		67.0 (47.0–97.2)	75.0 (53.0–95.0)	0.229
mRS 0–2 at 90 days		109 (45.0%)	87 (37.0%)	0.075
<b>Secondary outcome</b>				
D2N median (IQR), min		62.5 (47.2–87.0) (n = 100)	67.0 (53.0–82.0) (n = 82)	0.410
P2R median (IQR), min		46.0 (31.0–73.5) (n = 190)	47.5 (28.0–72.2) (n = 190)	0.468
O2R median (IQR), min		246.0 (183.0–381.5) (n = 190)	262.0(195.0–480.0) (n = 190)	0.033
Number of passes	Unknown	4 (1.7%)	5 (2.1%)	0.365
	1	121 (50.0%)	104(44.3%)	
	2	48 (19.8%)	62 (26.4%)	
	3	45 (18.6%)	47 (20.0%)	
	>4	24 (9.9%)	17 (7.2%)	
mTICI grade	2b–3	197 (81.4%)	188 (80.0%)	0.383
	0–2a	44 (18.2%)	43 (18.3%)	
	Unknown	1 (0.4%)	4 (1.7%)	
mRS score 0–2 at discharge		83 (34.3%)	62 (26.4%)	0.060
Death at 90 days		24 (9.9%)	35 (14.9%)	0.099
Any ICH	ICH (+)	72 (29.8%)	89 (37.9%)	0.124
	ICH (–)	161 (66.5%)	135 (57.4%)	
	Unknown	9 (3.7%)	11 (4.7%)	
sICH	sICH (+)	7 (2.9%)	12 (5.1%)	0.394
	sICH (–)	226 (93.4%)	212 (90.2%)	
	Unknown	9 (3.7%)	11 (4.7%)	

D2N: door-to-needle time; D2P: door-to-puncture time; D2Picture: door-to-picture time; ICH: intracranial hemorrhage; mRS: modified Rankin Scale; mTICI: modified TICI grade; O2D: onset-to-door time; O2R: onset-to-recanalization time; P2R: puncture-to-recanalization time; sICH: symptomatic intracranial hemorrhage.

**Table 3.** Pre-hospital time courses and time courses of transferred cases (2019 vs. 2020)

Total case		2019 (n = 242)	2020 (n = 235)	p
Pre-hospital time course	Onset/LKW to EMS call, median (IQR), min	36.5 (10.0–167.2) (n = 194)	64.0(8.5–289.5) (n = 185)	0.209
	EMS call to arrival at the site, median (IQR) min	8.0 (6.0–10.0) (n = 192)	9.0 (7.0–12.0) (n = 183)	0.005
	Arrival at the site to departure, median (IQR), min	16.0 (13.0–19.7) (n = 192)	16.5 (13.0–20.0) (n = 180)	0.246
	Departure to door, median (IQR),min	12.0(8.0–15.2) (n = 194)	12.0(9.0–16.0) (n = 178)	0.834
<b>Cases transferred from another hospital</b>		<b>2019 (n = 43)</b>	<b>2020 (n = 55)</b>	
Time course of transferred cases	Door-to-picture in H1, median (IQR),min	26.0(19.5–52.5) (n = 25)	36.0(21.2–54.2) (n = 36)	0.352
	Door (H1) to departure (H1), median (IQR), min	95.0 (61.0–117.0) (n = 25)	113.5 (94.2–153.7) (n = 36)	0.008
	Departure (H1) to door (H2), median (IQR), min	17.0(14.0–22.2) (n = 34)	20.0(13.0–30.0) (n = 47)	0.576
	Door (H1) to door (H2), median (IQR), min	112.0(79.5–135.0) (n = 28)	133.0 (106.0–171.0) (n = 37)	0.008

EMS: emergency medical service, H1:hospital transferred at first, H2: hospital secondary transferred for thrombectomy, LKW: last known well, NA: not available.

lower NIHSS score were predictors of delays in O2D time.<sup>10</sup> In the present study, although NIHSS scores tended to be higher in 2020 than in 2019, O2D time was

significantly longer in 2020, suggesting an association between COVID-19 outbreaks and delays in O2D time, especially in the first half of the year. The present study



**Table 4.** Outcomes of the subgroup analysis

		2019	2020	<i>p</i>
<b>January to March</b>	number	66	74	-
	O2D, median (IQR), min	84.5 (51.0–160.7)	140.0(47.7–408.5)	0.025
	D2P, median(IQR),min	66.5(47.7–93.5)	69.0(51.0–94.5)	0.832
	mRS 0–2 at 90 days	35 (53.0%)	29(39.2%)	0.101
<b>April to June</b>	number	60	61	
	O2D, median (IQR), min	105.5 (51.5–224.0)	155.0 (52.5–485.0)	0.025
	D2P, median (IQR), min	66.5(47.2–96.5)	67.0 (52.0–90.5)	0.832
	mRS 0–2 at 90 days	26(43.3%)	23(37.7%)	0.528
<b>July to September</b>	number	56	51	
	O2D, median (IQR), min	105.5 (50.2–224.0)	154.0 (52.0–258.0)	0.521
	D2P, median (IQR), min	71.0 (49.5–103.0)	68.0 (53.0–91.0)	0.609
	mRS 0–2 at 90 days	24 (42.9%)	16 (31.4%)	0.220
<b>October to December</b>	number	60	49	-
	O2D, median (IQR), min	143.5 (53.0–301.2)	111.0 (48.5–316.5)	0.918
	D2P, median (IQR), min	62.5 (42.0–100.2)	82.0 (63.0–109.0)	0.022
	mRS 0–2 at 90 days	24 (40.0%)	19 (38.8%)	0.896

D2P: door-to-puncture time; min: minutes, mRS: modified Rankin Scale; O2D: onset-to-door time.

**Table 5.** Results of multivariable logistic regression analysis for longer onset-to-door (O2D) time

	OR	95%CI	<i>p</i>
LKW	17.8	10.4–30.3	< 0.001
Transferred from another hospital	21.2	9.98–45.1	< 0.001
Male	1.17	0.70–1.93	0.537
Pre-mRS 1	0.39	0.18–0.83	0.015
Pre-mRS 2	1.51	0.66–3.46	0.328
Lower NIHSS	0.95	0.92–0.97	0.001
2020	1.72	1.06–2.82	0.028

CI: confidence interval; LKW: last-known-well; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; OR: odds ratio.

also revealed that (1) EMS call to arrival at the site door (H1) to departure (H1) and door (H1) to door (H2) times were significantly longer in 2020, that (2) O2D time or LKW time to EMS call was longer in 2020, although this difference was not significantly different, and that (3) there was no difference in EMS arrival at the site to departure. These findings suggest that the delays in O2D time in 2020 might have been caused by patients' refraining from going to hospital as opposed to the difficulty of searching for a hospital with open beds. From April 7 to May 31, 2020, the Japanese government declared a state of emergency and asked people to self-quarantine, which might have delayed the decisions of patients to make emergency calls or go to the hospital. At the beginning of the pandemic, less information was available about COVID-19 and guidelines for emergency medicine during the pandemic, which might have caused confusion in medical settings or EMS. In addition, medical staff

**Table 6.** Results of multivariable logistic regression analysis for mRS score 0–2 at 90 days

	OR	95% CI	<i>p</i>
Older age	0.95	0.93–0.97	< 0.001
Pre-mRS 1	0.48	0.23–1.00	0.053
Pre-mRS 2	0.31	0.12–0.78	0.013
Higher NIHSS	0.90	0.87–0.93	< 0.001
DM	0.39	0.20–0.77	0.007
ICA occlusion	0.71	0.41–1.22	0.218
iv-rtPA	1.51	0.87–2.61	0.135
O2D	0.99	0.99–1.00	0.045
D2P	1.00	0.99–1.00	0.939
P2R	0.98	0.97–0.99	< 0.001
mTICI $\geq$ 2b	9.62	0.92–100.2	0.058
Any ICH	0.29	0.17–0.80	< 0.024
Year (2020)	0.86	0.52–1.42	0.558

CI: confidence interval; DM: diabetes mellitus; D2P: door to puncture time; ICA: internal carotid artery; ICH: intracranial hemorrhage; iv-rtPA: intravenous recombinant tissue plasminogen activator; mRS: modified Rankin Scale; mTICI: modified TICI grade; NIHSS: National Institute of Health Stroke Scale; O2D: onset-to-door time; OR: odds ratio; P2R: puncture-to-recanalization time.

suddenly had to wear unfamiliar personal protective equipment, which could help explain the delay in door (H1) to door (H2) time.

The difference in D2P time in the subgroup analysis from October to December 2020, during the peak of the third wave, cannot fully be explained by other predictors (e.g., transfer, iv-rtPA, diagnostic modality for occluded vessels, anesthesia) since these factors did not indicate any imbalances; and although CTA may require less time than MRA, the diagnostic modality for occluded vessels (MRA or CTA) was not found to be a predictor of D2P

time in a previous study<sup>16</sup>; thus, it could be explained by the different protocols and systems in each hospital, information on which was not collected in the present study. However, D2P time was not significantly different for the entire study period, so we may conclude that the COVID-19 pandemic did not affect the initial management in each hospital.

The impact of COVID-19 on functional outcomes after MT remains unclear. Despite higher NIHSS scores in 2020, mRS score 0–2 at 90 days did not differ between 2019 and 2020. Patients with a severe case of COVID-19 sometimes present with large-vessel stroke,<sup>17</sup> and a previous report suggested that such patients may be at increased risk of AIS and in-hospital mortality.<sup>18</sup> In Tokyo, although we did not have complete data throughout 2020, COVID-19-related stroke was found in only 0.03% of the patients enrolled in TREAT from February to July 2020.<sup>6</sup> Fewer patients have been diagnosed with COVID-19 Japan than in the United States and other European countries (Fig. 1), and this could be related to the smaller number of patients with severe COVID-19-related stroke, which would have less impact on functional outcomes. Although the present study could not enroll all stroke patients in all hospitals in Tokyo, it seems reasonable to conclude that MT could still be performed safely and effectively in Tokyo, despite the pandemic.

Our study has several limitations. First, we did not include patients treated by best medical treatment, which could have led to a selection bias. In addition, we could not estimate the O2D time of these patients, which would cause a difference from the real-world O2D time for patients with AIS in Tokyo. Second, we excluded about 30% of the eligible patients based on the exclusion criteria, and thus, our study sample could differ from real-world data. Third, we did not collect the AIS protocol in each hospital, which relates to D2P time, or the presence of COVID-19, which relates to functional outcomes. Finally, this was a multicenter study conducted in the Tokyo Metropolitan Area, which could limit the generalizability of the results to other populations.

## Conclusions

The results of this study indicated that O2D time was significantly longer in 2020 than in 2019 and may have been affected by the COVID-19 pandemic. However, D2P time and mRS score 0–2 at 90 days were not significantly different between 2019 and 2020. Although we could not enroll all stroke patients in Tokyo in the present study, we can reasonably conclude that despite the COVID-19 pandemic, the initial management of patients with AIS was effective and MT was well performed.

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## Declaration of Competing Interest

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