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Association between procedure volume and 30-day mortality in stroke patients treated with EVT or IV rt-PA during the introduction period of EVT in Japan

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Abstract: This study aimed to determine whether procedure volume is associated with 30-day mortality following endovascular thrombectomy (EVT) or intravenous recombinant tissue plasminogen activator (IV rt-PA) for stroke during the introduction period of EVT in Japan. Using nationwide claims records, we investigated data from 8,227 patients undergoing EVT and 13,406 and 6,035 patients undergoing rt-PA monotherapy in hospitals with and without EVT capability, respectively, between April 2014 and February 2016 in Japan. Procedure volume was categorized into three groups according to tertiles of the annual number of EVTs or IV rt-PA injections performed in the hospitals. Hierarchical logistic regression demonstrated that the odds ratio (95% confidence interval) of 30-day mortality following EVT was significantly lower in middle- (0.77 [0.62–0.96]) and high- (0.69 [0.53–0.89]) volume hospitals than that in low-volume hospitals even after adjusting for potential confounding factors. The generalized additive mixed models revealed no obvious threshold volume of EVT to reduce the mortality risk. By contrast, mortality risk following IV rt-PA monotherapy did not decrease in hospitals without EVT capability but did with increasing IV rt-PA volume in hospitals with EVT capability (P for heterogeneity 0.003). The risk of 30-day mortality after EVT for acute ischemic stroke decreased linearly according to EVT procedure volume in each hospital. However, the association between IV rt-PA volume and mortality risk was modified by the hospital's EVT capability. Further research is warranted to determine whether the volume-outcome relationship we observed is a temporary phenomenon following EVT or a consistent trend over time.

***Keywords*:** outcome, endovascular thrombectomy, intravenous recombinant tissue plasminogen activator

Introduction

Stroke remains a major cause of death worldwide (*1*). However, recent advances in reperfusion therapy have significantly reduced case-fatality rates following acute ischemic stroke (AIS) (*2,3*). The therapeutic windows for intravenous recombinant tissue plasminogen activator (IV rt-PA) and endovascular thrombectomy (EVT) are limited, with their efficacy and safety being highly time-dependent (*4-7*). Therefore, patients with stroke who may benefit from reperfusion therapy must be transported as early as possible to the nearest stroke center for timely intervention. To ensure access to IV rt-PA and EVT for every patient in need, stroke centers must be strategically located with sufficient experience and technical expertise to achieve prompt and effective recanalization (*8*).

Hospital volume has been linked to stroke outcomes, though results are sometimes inconsistent (*9-14*). Specifically, higher procedure volumes may be associated with better outcomes following reperfusion therapy for AIS. However, whether outcomes following AIS are influenced by the volume of EVT, IV rt-PA, or both remains to be determined (*15-21*). Furthermore, it remains unclear whether the volume-outcome relationship for IV rt-PA administration remains consistent between hospitals with and without EVT capability following the introduction of EVT.

This study aimed to determine whether procedure volume is associated with 30-day mortality risk following EVT or IV rt-PA in patients with AIS and whether the relationship between IV rt-PA volume and post-procedure mortality varies based on a hospital's EVT capability in the post-EVT era. To this end, we collected nationwide claims data for all patients with AIS

who underwent EVT or IV rt-PA across Japan when EVT was being integrated into stroke care systems.

Materials and Methods

Study design, setting, and data source

We obtained nationwide data of consecutive patients with AIS who underwent reperfusion therapy in Japan through the National Database (NDB) of Health Insurance Claims and Specific Health Checkups, one of the largest healthcare claims databases in the world, covering the entire Japanese population. The NDB includes the claims data for over 95% of hospitalized patients in Japan. Anonymized claims data from the NDB were provided for this study by the Ministry of Health, Labour, and Welfare following a review of our study protocol by a government advisory committee (No. 0326–26). The Institutional Review Board of Kyushu University approved this study (No. 28–70), and the requirement for informed consent was waived since all data were anonymized prior to access. Using the NDB, we analyzed data from patients with AIS hospitalized and treated with EVT or IV rt-PA across Japan.

Study patients

This study included patients with AIS who were hospitalized and received reperfusion therapy in Japan from April 2014 to February 2016. During this study, the number of IV rt-PA therapies administered in Japan stabilized, while EVT usage significantly increased (*22*). Patients were categorized into two groups: those who underwent EVT with or without IV rt-PA (EVT group) and those treated with IV rt-PA alone (IV rt-PA group). Meanwhile, hospitals were classified based on their EVT capability, determined by whether they performed EVT during the study period (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Procedure volume

Procedure volume was defined as the annual number of patients treated with EVT or IV rt-PA at each hospital during the study period. We categorized procedure volume into three groups based on the tertile of the annual number of therapies performed at each hospital.

Clinical outcome

The clinical outcome was the 30-day mortality rate following reperfusion therapy for AIS, defined as death from any cause within 30 days of the therapy for the index stroke (*22,23*).

Covariates

We collected patient-level variables, including age, sex, and stroke severity, to adjust for the risk of death in individual patients. Stroke severity was assessed using a claims-based severity index previously developed and validated for hospitalized patients with AIS (*19,24,25*). This index comprised seven variables from the claims database: airway suctioning, bacterial sensitivity test, general ward stay, intensive care unit stay, nasogastric tube use, osmotherapy use, and urinary catheterization. These variables were assessed within one day of admission and used as covariates.

Hospitals were categorized into three levels of stroke care: stroke centers (high level of care), tertiary hospitals (middle level of care), and other types (low level of care). Definitions for these care levels are provided in the Supplemental Methods (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). Using administrative data, we collected information on the density of hospitals across the three-stroke care levels, the density of neuroendovascular specialists, population density, the proportion of rural residents, annual wage levels, and rates of delayed ambulance transport. We also gathered administrative data on regional population demographics, socioeconomic status, and healthcare system. Definitions of these factors and their data sources are detailed in the Supplemental Methods (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Statistical analysis

We compared differences in baseline characteristics among hospitals with varying stroke volumes using the χ^2 test. Logistic regression analysis was used to test trends in characteristics according to stroke volume. The Cochran–Armitage test assessed trends in crude mortality rates by procedure volume. To investigate the association between categorized procedure volume and 30-day mortality, we employed a hierarchical logistic model that accounted for clustering effects within the hospitals. A random intercept model was utilized, assuming the random intercept follows a normal distribution (*26*).

We constructed two multivariable models in addition to adjusting for age and sex. Multivariable model 1 included age, sex, and stroke severity index variables for each patient. Multivariable model 2 included hospital factors (low, middle, or high level of stroke care) and regional factors (demographics: population density and proportion of rural residents; medical services: density of hospitals across the three-stroke care levels, density of neuroendovascular specialists, and rate of delayed ambulance transport; socioeconomic status: annual wage level).

To confirm the association between the number of procedures and 30-day mortality, we conducted an additional analysis using a generalized additive mixed

model with a smoothing spline function applied to procedure volume (*27*). Heterogeneity between hospitals with and without EVT capability was assessed by including an interaction term for procedure volume × subgroup. All statistical analyses were conducted using the R statistical package (*http://www.r-project.org*, version 4.2.0). Further analysis details using the R statistical package are presented in the Supplemental Methods (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). A two-sided P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

During the study period, a total of 8,227 patients underwent EVT, while IV rt-PA monotherapy was administered in 13,406 in hospitals with EVT capability and 6,035 patients in hospitals without EVT capability (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). We compared the baseline characteristics of these patients as well as the stroke care levels in the hospitals where they received reperfusion therapy based on the annual volume of each procedure. Stroke severity was assessed using a claims-based severity index composed of six factors.

The proportions of older patients, females, and those requiring intensive care unit stay and nasogastric intubation tended to increase with higher EVT volume, whereas the proportion of patients requiring osmotherapy decreased as EVT volume increased (Table 1). Additionally, the proportion of stroke centers increased with higher EVT volumes (Table 1).

In patients treated with IV rt-PA monotherapy, the proportion of cases requiring intensive care unit stay, bacterial sensitivity testing, and nasogastric intubation increased, while the proportions of cases requiring airway suctioning, osmotherapy, and urinary catheterization decreased as IV rt-PA volume increased (Table 2). Similar to EVT, the level of stroke care improved with increasing IV rt-PA volumes (Table 2). Regional characteristics varied according to EVT (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*) and IV rt-PA volumes (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Procedure volume and 30-day mortality

During the study period, as EVT was introduced and increasingly utilized across the country, EVT procedure volumes were low in most hospitals across Japan (Supplemental Figure S2A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). For IV rt-PA monotherapy, the highest number of treatments administered in a single hospital with EVT capability ranged from 6 to 10 per year (Supplemental Figure S2B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*), while in hospitals without EVT capacity, it was ≤ 5 per year (Supplemental Figure S2C, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). The mortality rates following EVT or IV rt-PA administration varied among individual hospitals depending on their procedure volumes for EVT (Supplemental Figure S3A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*) and for IV rt-PA in EVT-capable (Supplemental Figure S3B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*) or -incapable hospitals (Supplemental Figure S3C, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Table 1. Baseline characteristics of patients undergoing EVT

	G1, *n* = 2,682	G2, *n* = 2,832	G3, *n* = 2,713	*P*	P_{trend}
Patient factors					
Age, y, mean (SD)	74.5 (12.1)	74.8 (12.9)	75.1 (12.2)	< 0.001	< 0.001
Women, *n* (%)	1,104 (41.2)	1,196 (42.2)	1,191 (43.9)	0.12	0.04
Stroke severity, *n* (%)					
Airway suctioning	766 (28.6)	807 (28.5)	829 (30.6)	0.16	0.11
Bacterial sensitivity test	119 (4.4)	94 (3.3)	122 (4.5)	0.04	0.91
Intensive care unit stay	1,899 (70.8)	2141 (75.6)	2216 (81.7)	< 0.001	< 0.001
Nasogastric intubation	299 (11.1)	313 (11.1)	355 (13.1)	0.03	0.03
Osmotherapy	423 (15.8)	384 (13.6)	265 (9.8)	< 0.001	< 0.001
Urinary catheterization	1,023 (38.1)	1,021 (36.1)	1,073 (39.6)	0.03	0.28
Hospital factors, *n* (%)					
Stroke centers	2,085 (77.7)	2,456 (86.7)	2,463 (90.8)	< 0.001	< 0.001
Non-stroke centers					
Tertiary hospitals	514 (19.2)	360 (12.7)	250 (9.2)		
Other hospitals	83 (3.1)	16 (0.6)	0 (0.0)		

Procedure volume was classified into three groups based on the annual number of patients undergoing EVT: G1 (1–7 pts/y), G2 (8–16 pts/y), and G3 (17–64 pts/y). EVT: endovascular thrombectomy, pts: patients, P_{trend}: P for trend.

Association between procedure volume and 30-day mortality after EVT

The crude 30-day mortality rate following EVT tended to decrease as the number of EVTs performed increased (Table 3). The age- and sex-adjusted odds ratios for 30-day mortality following EVT were significantly lower in middle- and high-volume hospitals than in low-volume hospitals (Table 3). These associations remained significant even after adjusting for various patient, hospital, and regional covariates.

Association between procedure volume and 30-day mortality following IV rt-PA monotherapy

We examined the trend for mortality rates following IV rt-PA administration. In hospitals with EVT capability, there was a significant decrease in the 30-day mortality rate following IV rt-PA monotherapy, whereas no such trend was observed in hospitals without EVT capability (Table 4). In EVT-capable hospitals, the age- and sex-adjusted odds ratios of 30-day mortality were lower in high-volume hospitals than in low-volume hospitals. Conversely, in hospitals without EVT capability, the mortality risk following IV rt-PA administration did not decrease with higher IV rt-PA volumes. Furthermore, EVT capability significantly modified the association between IV rt-PA volume and post-administration mortality, even after adjusting for multiple confounding factors.

Volume-outcome relationship between procedure volume and 30-day mortality following EVT or IV rt-PA monotherapy

We examined the volume-outcome relationship between EVT or IV rt-PA volumes and post-procedure mortality using a generalized additive mixed model. The results indicated that the mortality risk decreased as EVT volume increased (Figure 1A). In contrast, the relationship between IV rt-PA volume and mortality risk significantly varied based on the hospital's EVT capability. Specifically, in hospitals with EVT capability, the risk of 30-day mortality following IV rt-PA administration decreased as IV rt-PA volume increased (Figure 1B). However, in hospitals without

Table 2. Baseline characteristics of patients undergoing IV rt-PA monotherapy

	G1, *n* = 6,595	G2, *n* = 6,319	G3, *n* = 6,527	*P*	P_{trend}
Patient factors					
Age, y, mean (SD)	75.1 (11.9)	75.3 (12.0)	75.3 (12.4)	< 0.001	0.12
Women, *n* (%)	2,729 (41.4)	2,622 (41.5)	2,744 (42.0)	0.72	0.44
Stroke severity, *n* (%)					
Airway suctioning	1,299 (19.7)	1,231 (19.5)	1,139 (17.5)	0.001	0.001
Bacterial sensitivity test	171 (2.6)	123 (1.9)	233 (3.6)	< 0.001	< 0.001
Intensive care unit stay	3,107 (47.1)	4,681 (74.1)	4,777 (73.2)	< 0.001	< 0.001
Nasogastric intubation	278 (4.2)	305 (4.8)	440 (6.7)	< 0.001	< 0.001
Osmotherapy	718 (10.9)	548 (8.7)	501 (7.7)	< 0.001	< 0.001
Urinary catheterization	3,330 (50.5)	2,911 (46.1)	2,756 (42.2)	< 0.001	< 0.001
Hospital factors, *n* (%)					
Stroke centers	3,798 (57.6)	5,258 (83.2)	5,751 (88.1)	< 0.001	< 0.001
Non-stroke centers					
Tertiary hospitals	2,420 (36.7)	991 (15.7)	776 (11.9)		
Other hospitals	377 (5.7)	70 (1.1)	0 (0.0)		

Procedure volume was classified into three groups based on the annual number of patients undergoing IV rt-PA monotherapy: G1 (1–10 pts/y), G2 (11–20 pts/y), and G3 (21–101 pts/y). IV rt-PA: intravenous recombinant tissue plasminogen activator, pts: patients, P_{trend}: P for trend.

Table 3. Association between procedure volume and 30-day mortality following EVT

	Event (%)	Age- and sex- adjusted		Multivariable model 1		Multivariable model 2	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
G1, *n* = 2,682	310 (11.6)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
G2, *n* = 2,832	262 (9.3)	0.78 (0.63–0.95)	0.02	0.82 (0.66–1.02)	0.07	0.77 (0.62–0.96)	0.02
G3, *n* = 2,713	221 (8.1)	0.68 (0.53–0.86)	0.001	0.76 (0.59–0.98)	0.04	0.69 (0.53–0.89)	0.005
P for trend	0.002		< 0.001		0.02		0.002

Multivariable model 1 included variables for stroke severity (airway suctioning, bacterial sensitivity test, intensive care unit stay, nasogastric intubation, osmotherapy, and urinary catheterization), as well as patient age and sex. Multivariable model 2 included regional factors (hospital density, EVT specialist density, population density, rural population, wage level, and delayed ambulance transport) and hospital factors (stroke centers, tertiary hospitals except stroke centers, and other hospitals), as well as patient variables in Model 1. EVT: endovascular thrombectomy, OR: odds ratio, CI: confidence interval, pts: patients. Procedure volume was classified into three groups based on the annual number of patients undergoing EVT: G1 (1–7 pts/y), G2 (8–16 pts/y), and G3 (17–64 pts/y).

Table 4. Association between procedure volume and 30-day mortality following IV rt-PA monotherapy

	Event (%)	Age- and sex- adjusted		Multivariable model 1		Multivariable model 2	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
EVT capable hospitals							
G1, *n* = 3042	208 (6.8)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
G2, *n* = 4759	335 (7.0)	1.02 (0.83–1.25)	0.85	1.03 (0.83–1.27)	0.82	0.94 (0.76–1.17)	0.59
G3, *n* = 5605	302 (5.4)	0.76 (0.61–0.94)	0.01	0.78 (0.62–0.97)	0.03	0.70 (0.56–0.88)	0.002
P for trend	0.01		0.01		0.02		0.002
EVT incapable hospitals							
G1, *n* = 3553	257 (7.2)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
G2, *n* = 1560	141 (9.0)	1.26 (0.99–1.62)	0.06	1.43 (1.09–1.88)	0.010	1.31 (1.00–1.72)	0.047
G3, *n* = 922	67 (7.3)	0.99 (0.69–1.42)	0.95	1.29 (0.86–1.93)	0.22	1.19 (0.81–1.75)	0.38
P for trend	0.34		0.40		0.03		0.12
P for interaction	0.03		0.04		0.002		0.003

Procedure volume was classified into three groups based on the annual number of patients undergoing IV rt-PA monotherapy: G1 (1–10 pts/y), G2 (11–20 pts/y), and G3 (21–101 pts/y). Multivariable model 1 included variables for stroke severity (airway suctioning, bacterial sensitivity test, intensive care unit stay, nasogastric intubation, osmotherapy, and urinary catheterization) as well as patient age and sex. Multivariable model 2 included regional factors (hospital density, EVT specialist density, population density, rural population, wage level, and delayed ambulance transport) and hospital factors (stroke centers, tertiary hospitals except stroke centers, and other hospitals), as well as patient variables in model 1. IV rt-PA: intravenous recombinant tissue plasminogen activator, OR: odds ratio, CI: confidence interval, EVT: endovascular thrombectomy, pts: patients.

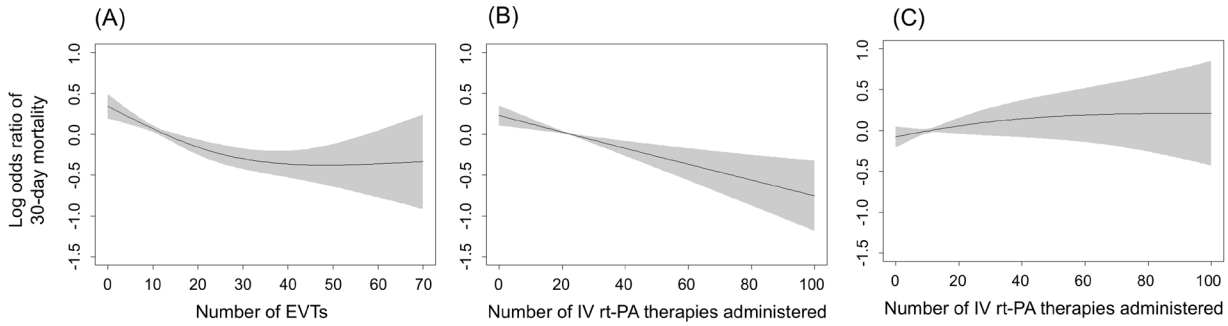

Figure 1. Relationship between procedure volume and 30-day mortality following EVT or IV rt-PA monotherapy. The relationship between procedure volume and 30-day mortality following EVT **(A)** or IV rt-PA therapy in hospitals with **(B)** or without **(C)** EVT capability is shown. The vertical axis represents the log odds ratio of the 30-day mortality, and the horizontal axis shows the annual number of EVTs (A) or IV rt-PA therapies in hospitals with (B) or without (C) EVT capability. The multivariable-adjusted odds ratio was calculated using a generalized additive mixed model. The solid line shows the point estimate, and the dotted lines represent the 95% confidence interval. IV rt-PA: intravenous recombinant tissue plasminogen activator, EVT: endovascular thrombectomy.

EVT capability, the mortality risk remained unchanged or tended to increase as IV rt-PA volume increased (Figure 1C).

Discussion

The major findings of this study are as follows: During the initial period of EVT adoption in Japan, a higher procedure volume was associated with a lower risk of 30-day mortality following EVT for AIS. However, no specific volume threshold was identified in the relationship between EVT volume and mortality risk. In contrast, the association between the IV rt-PA volume and 30-day mortality risk significantly varied based on the hospital's EVT capability. While hospitals with EVT capability showed a trend of decreasing mortality risk with increasing IV rt-PA volume, this volume-outcome relationship was not observed for IV rt-PA in hospitals without EVT capacity. These findings suggest a volume-outcome relationship for EVT volume in relation to post-procedure mortality during the initial EVT adoption period in Japan, while the volume-outcome relationship for IV rt-PA appears to be influenced by the presence of EVT capability at the hospital during this period.

Procedure volume and outcome after EVT

As endovascular experience accumulates, technical proficiency likely improves, which may explain the improved outcomes observed with higher EVT volumes. Although recent studies have explored the volume-outcome relationship for EVT, their findings remain inconclusive. Higher EVT volumes are associated with lower mortality in Korea (*19*) and the United States (*15,17,20,21*), while one study in the United States found no significant association between intra-arterial procedure volume and in-hospital mortality (*18*). Our findings support a volume-outcome relationship,

indicating that higher EVT volumes are associated with reduced mortality risk when EVT was increasingly adopted across Japan.

Operator experience contributes to safer, more effective endovascular techniques, ultimately increasing procedural success rates and improving EVT outcomes. In this study, while no specific EVT volume threshold for reduced post-procedural mortality was identified, there remains a need for comprehensive education and training programs to increase the number and proficiency of neuro-interventional specialists. From a hospital perspective, improved post-procedural outcomes stem more from efficient processes than structural elements, as the volume-outcome relationship persisted even when controlling for stroke care levels. Higher volumes may foster high-quality care by enhancing more sophisticated, interdisciplinary coordination.

Procedure volume and outcome following IV rt-PA administration

The relationship between procedure volume and mortality risk following IV rt-PA administration for AIS remains inadequately understood. A previous Japanese study conducted between 2010 and 2012 reported no clear volume-outcome relationship for IV rt-PA administration (*16*). However, our findings suggest that this relationship may be influenced by the availability of EVT. Among patients treated with EVT at EVT-capable hospitals, we observed similar trends of decreasing mortality risk with higher EVT volumes, regardless of whether patients were pretreated with IV rt-PA (data not shown). In contrast, the volume-outcome relationship for IV rt-PA administration varied based on whether hospitals were equipped to provide additional EVT.

Although the exact reasons for this shift remain to be determined, several plausible explanations have been proposed. In high-volume hospitals for IV rt-PA with EVT capability, high-risk patients might have been more frequently excluded from the IV rt-PA-only cohort due to subsequent EVT treatment compared with low-volume hospitals. Conversely, high-volume IV rt-PA hospitals without EVT capability might have faced higher mortality risks as they are limited to administering IV rt-PA alone, even for patients who would otherwise be candidates for EVT. In terms of stroke care quality, high-volume hospitals that adopted EVT during the study period were likely early adopters of advanced treatments, with organizational structures and processes that positively impacted patient outcomes. Conversely, high-volume IV rt-PA hospitals without EVT capability might have lagged behind advancements in stroke treatment, continuing to rely on IV rt-PA monotherapy. These differences in practice and capability likely contributed to the observed changes in the volume-outcome relationship based on EVT availability. A detailed investigation into hospital-specific stroke care practices is essential to identify the factors driving this shift in the volume-outcome relationship for IV rt-PA. Such insights could guide improvements in stroke care delivery and patient outcomes.

Clinical implications

This study analyzed the use of EVT during its introductory phase in Japan, a period characterized by limited procedural volume, minimal operator experience, and evolving technical approaches (*22*). It is important to consider that the observed volume-outcome relationship may reflect only the early stage of EVT implementation. Therefore, future studies should determine whether this relationship changes across different phases of EVT adoption — initial, widespread, and mature — or persists when experienced mentors and practitioners are available.

In Japan, the healthcare system, characterized by a large number of hospitals and beds but relatively few EVT cases per specialist, likely influences per-facility EVT volumes. The Japanese guidelines for IV rt-PA administration recommend monitoring in stroke care units or similar settings for at least 24 h post-treatment due to the bleeding risks associated with IV rt-PA. Patients are typically closely monitored in stroke care units or high-care units equipped with advanced acute stroke systems. During the early real-world application of EVT, geographic and institutional differences might have contributed to variability in treatment quality. These therapeutic environments for reperfusion therapy may vary significantly between countries. Therefore, it is essential to determine whether the volume-outcome relationship differs internationally.

Study strengths and limitations

This study has several notable strengths. First, the administrative dataset included nearly all patients receiving reperfusion therapy in Japan, reducing selection bias. Second, the volume-outcome relationship was analyzed based on reperfusion therapy type while considering patient, hospital, and regional characteristics.

This study has some limitations. First, due to the claims database, some clinical data relevant to mortality risks, such as baseline neurological severity and recanalization rate, were unavailable. Instead, surrogate variables were used to gauge stroke severity, which have been validated in previous studies (*19,24,25*). Second, patients treated with the "drip and ship" approach were included, although they represented < 3% of the total. Third, EVT volumes in high-volume hospitals were lower than the global standard, and the volume-outcome relationship in other healthcare systems warrants further assessment. Fourth, hospital care quality could not be directly controlled, despite using a hierarchical logistic regression model. Finally, the study was limited to a

specific period in Japan, affecting the generalizability of its findings. Validation studies are needed to confirm the volume-outcome relationship for reperfusion therapy in other contexts.

In conclusion, this study underscores the volume-outcome relationship between EVT or IV rt-PA administration and mortality in patients with ischemic stroke. The linear relationship between EVT volume and post-procedural mortality aligns with the "practice-makes-perfect" hypothesis. Conversely, the volume-outcome relationship for IV rt-PA administration varies based on the hospital's EVT capabilities. Further investigation is needed to determine whether these volume-outcome relationships for EVT and IV rt-PA hold true across different EVT implementation stages and international healthcare systems.

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References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388:1459-1544.
2. Jauch EC, Saver JL, Adams HP Jr, *et al*. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013; 44:870-947.
3. Powers WJ, Rabinstein AA, Ackerson T, *et al*. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018; 49:e46-e110.
4. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995; 333:1581-1587.
5. Lees KR, Bluhmki E, von Kummer R, *et al*. Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010; 375:1695-1703.
6. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA. 2013; 309:2480-2488.
7. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014; 2014:CD000213.
8. Zhu F, Ben Hassen W, Bricout N, *et al*. Effect of operator's experience on proficiency in mechanical thrombectomy: A multicenter study. Stroke. 2021; 52:2736-2742.
9. Saposnik G, Baibergenova A, O'Donnell M, Hill MD, Kapral MK, Hachinski V; Stroke Outcome Research Canada (SORCan) Working Group. Hospital volume and stroke outcome: Does it matter? Neurology. 2007; 69:1142-1151.
10. Svendsen ML, Ehlers LH, Ingeman A, Johnsen SP. Higher stroke unit volume associated with improved quality of early stroke care and reduced length of stay. Stroke. 2012; 43:3041-3045.
11. Tsugawa Y, Kumamaru H, Yasunaga H, Hashimoto H, Horiguchi H, Ayanian JZ. The association of hospital volume with mortality and costs of care for stroke in Japan. Med Care. 2013; 51:782-788.
12. Hall RE, Fang J, Hodwitz K, Saposnik G, Bayley MT. Does the volume of ischemic stroke admissions relate to clinical outcomes in the Ontario Stroke System? Circ Cardiovasc Qual Outcomes. 2015; 8:S141-S147.
13. Lee KJ, Kim JY, Kang J, *et al*. Hospital volume and mortality in acute ischemic stroke patients: Effect of adjustment for stroke severity. J Stroke Cerebrovasc Dis. 2020; 29:104753.
14. Zhang R, Liu G, Pan Y, Zhou M, Wang Y. Association between hospital volume, processes of care and outcomes after acute ischaemic stroke: A prospective observational study. BMJ Open. 2022; 12:e060015.
15. Adamczyk P, Attenello F, Wen G, He S, Russin J, Sanossian N, Amar AP, Mack WJ. Mechanical thrombectomy in acute stroke: Utilization variances and impact of procedural volume on inpatient mortality. J Stroke Cerebrovasc Dis. 2013; 22:1263-1269.
16. Wada T, Yasunaga H, Inokuchi R, Horiguchi H, Fushimi K, Matsubara T, Nakajima S, Yahagi N. Relationship between hospital volume and early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator. Int J Stroke. 2015; 10:73-78.
17. Saber H, Navi BB, Grotta JC, Kamel H, Bambhroliya A, Vahidy FS, Chen PR, Blackburn S, Savitz SI, McCullough L, Sheth SA. Real-world treatment trends in endovascular stroke therapy. Stroke. 2019; 50:683-689.
18. Asaithambi G, Tong X, Lakshminarayan K, Coleman King SM, George MG. Trends in hospital procedure volumes for intra-arterial treatment of acute ischemic stroke: Results from the Paul Coverdell National Acute Stroke Program. J Neurointerv Surg. 2020; 12:1076-1079.
19. Shim DH, Kim Y, Roh J, Kang J, Park KP, Cha JK, Baik SK, Kim Y. Hospital volume threshold associated with higher survival after endovascular recanalization therapy for acute ischemic stroke. J Stroke. 2020; 22:141-149.
20. Stein LK, Mocco J, Fifi J, Jette N, Tuhrim S, Dhamoon MS. Correlations between physician and hospital stroke thrombectomy volumes and outcomes: A nationwide analysis. Stroke. 2021; 52:2858–2865.
21. Waqas M, Tutino VM, Cappuzzo JM, *et al*. Stroke thrombectomy volume, rather than stroke center accreditation status of hospitals, is associated with mortality and discharge disposition. J Neurointerv Surg. 2023; 15:209-213.
22. Maeda M, Fukuda H, Matsuo R, Kiyuna F, Ago T, Kitazono T, Kamouchi M. Nationwide temporal trend analysis of reperfusion therapy utilization and mortality in acute ischemic stroke patients in Japan. Medicine (Baltimore). 2021; 100:e24145.
23. Maeda M, Fukuda H, Matsuo R, Ago T, Kitazono T, Kamouchi M. Regional disparity of reperfusion therapy

for acute ischemic stroke in Japan: A retrospective analysis of nationwide claims data from 2010 to 2015. J Am Heart Assoc. 2021; 10:e021853.
24. Sung SF, Hsieh CY, Kao Yang YH, Lin HJ, Chen CH, Chen YW, Hu YH. Developing a stroke severity index based on administrative data was feasible using data mining techniques. J Clin Epidemiol. 2015; 68:1292-1300.
25. Sung SF, Hsieh CY, Lin HJ, Chen YW, Chen CH, Kao Yang YH, Hu YH. Validity of a stroke severity index for administrative claims data research: a retrospective cohort study. BMC Health Serv Res. 2016; 16:509.
26. Ross JS, Normand SL, Wang Y, Ko DT, Chen J, Drye EE, Keenan PS, Lichtman JH, Bueno H, Schreiner GC, Krumholz HM. Hospital volume and 30-day mortality for three common medical conditions. N Engl J Med. 2010; 362:1110-1118.
27. Lin X, Zhang D. Inference in generalized additive mixed models by using smoothing splines. J R Stat Soc Series B Stat Methodol. 1999; 61:381-400.

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