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Short- and long-term mortality after intravenous thrombolysis for acute ischemic stroke

A propensity score-matched cohort with 5-year follow-up

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Abstract

It remains unknown whether intravenous thrombolysis (IVT), thrombectomy, or poststroke antithrombotic medication lower short- and long-term mortality in acute ischemic stroke (AIS). This study aimed to investigate the efficacy of IVT in AIS using propensity score matching, to determine whether IVT could reduce short- and long-term mortality, and to identify risk factors influencing short- and long-term mortality in AIS.

During 2013 to 2014, the nationwide Korea Acute Stroke Assessment registry enrolled 14,394 patients with first-ever recorded ischemic stroke. Propensity score matching was used to match IVT and control cases with a 1:1 ratio. The primary outcome was survival up to 3 months, 1 year, and 5 years, as assessed using Kaplan–Meier estimates and Cox proportional hazards.

In total, 1317 patients treated with IVT were matched with 1317 patients not treated with IVT. Survival was higher in the IVT group (median, 3.53 years) than in the non-IVT group (median, 3.37 years, stratified log-rank test, $P < .001$). Compared with the non-IVT group, thrombolysis performed within 2 hours significantly reduced the risk of 3-month mortality by 37%, and thrombolysis performed between 2 and 4.5 hours significantly reduced the risk of 3-month mortality by 26%. Thrombectomy significantly reduced the risk of 3-month mortality by 28%. Compared with no poststroke medication, poststroke antiplatelet medication was associated with 51%, 55%, and 52% decreases in 3-month, 1-year, and 5-year mortality risk, respectively. Poststroke anticoagulant medication was associated with 51%, 54%, and 44% decreases in the risk of 3-month, 1-year, and 5-year mortality, respectively.

IVT and mechanical thrombectomy showed improvement in short-term survival. To improve long-term outcomes, the use of poststroke antithrombotic medication is important in AIS.

Abbreviations: AIS = acute ischemic stroke, CCI = Charlson Comorbidity Index, CI = confidence interval, HIRA = Health Insurance Review and Assessment Service, HR = hazard ratio, IQR = interquartile range, IVT = intravenous thrombolysis, NIHSS = National Institutes of Health Stroke Scale, tPA = tissue plasminogen activator.

Keywords: emergency medical services, mechanical thrombectomy, mortality, stroke, thrombolytic therapy, tissue plasminogen activator

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1. Introduction

Intravenous thrombolysis (IVT) using tissue plasminogen activator (tPA) for acute ischemic stroke (AIS) can improve patients' functional outcomes.[1–3] However, AIS remains associated with high mortality worldwide, although IVT has become a means of standard management since the National Institute of Neurological Disorders and Stroke trials.[4,5] IVT has a narrow indication as a time-dependent tool, and it remains controversial whether IVT can reduce short- and long-term mortality in AIS.[4] The Third International Stroke Trial also failed to reduce short-term (3-month) and long-term (18-month) mortality.[6] Another observational study evaluated long-term outcomes of IVT using propensity score matching and demonstrated significantly lower mortality in patients receiving IVT than in the control group. However, the median follow-up of that study was only 1.4 years.[7]

The present study aimed to investigate the efficacy of IVT in AIS using propensity score matching and determine whether it could reduce short- and long-term mortality. Propensity score matching is useful in observational studies, as it can decrease the confounding factors of baseline characteristics.[8–11] We also investigated the risk factors influencing short- and long-term mortality in AIS.

2. Methods

We analyzed data collected from 2013 to 2014 by the Acute Stroke Assessment Registry, a nationwide, prospectively collected database including data from 216 preselected hospitals. These nationwide data are collected once every 2 years for a duration of 3 months. South Korea developed the Acute Stroke Assessment Registry to assess the quality of AIS care management and improve the outcomes of patients with AIS in preselected hospitals. Detailed data of patients who visit the emergency department for AIS are collected by skilled medical personnel in preselected hospitals and sent to the Health Insurance Review and Assessment Service (HIRA). Using these data, the HIRA provides feedback to each hospital and assigns a grade. The Acute Stroke Assessment Registry is devoted to improving acute stroke care. We analyzed this AIS data and then tracked the administrative data of these patients with AIS. Thus, these data are reliable and sufficient for observing long-term mortality. The healthcare and medical insurance systems in South Korea cover the entire population. The general population has good physical and financial access to medical services. Thus, this registry is a reliable way to study the long-term mortality of patients with AIS who need ongoing care.

During a period of 6 months, 20,202 acute stroke patients were admitted to emergency departments. Of these, 18,691 patients were admitted for AIS. Patients with a diagnosis of first-ever stroke were included in this study. Overall, 14,394 ischemic stroke patients were enrolled after excluding 4297 patients with no detailed record of IVT. The dose of tPA was typically calculated to be 0.9 mg/kg, and thrombectomy was performed in patients with failed recanalization after IVT.

We divided the patients into 2 groups: non-IVT group (13,071 patients) and IVT group (1323 patients). The IVT group was subdivided into 2 groups: IVT within 2 hours after symptom onset and IVT between 2 and 4.5 hours after symptom onset. According to the rule of the "50% barrier" in AIS, we used a cutoff value of 2 hours to divide the groups.[12] The health security system in Korea has 2 components (health insurance and medical aid), according to patients' economic status and income. Patients were also divided into those with health insurance and those on medical aid according to economy status. We divided the National Institutes of Health Stroke Scale (NIHSS) score into 5 grades: 1 to 4, 5 to 7, 8 to 13, 14 to 21, and 22 to 42 by neurological status at the emergency department. Vascular risk factors, including smoking (current smoker, ex-smoker, and nonsmoker) and atrial fibrillation, were collected. The Charlson Comorbidity Index (CCI) was determined by ICD-10 code and based on this, patients were divided into 3 groups: 0, 1, and ≥2. The time window for IVT was up to 4.5 hours after the onset of symptoms in this period. The use of emergency medical services before arrival at the hospital, door-to-image time, and door-to-needle time were collected. Mechanical thrombectomy and the use of antithrombotic drugs (antiplatelets, anticoagulants, warfarin, and nonvitamin K antagonist oral anticoagulant) were collected from HIRA data. The use of antithrombotic drugs was defined as patients who had taken medicine for at least 1 week. Survival data were collected from national administrative data with approval from the HIRA, and these data was analyzed with the HIRA. This study was performed under the Joint Project on Quality Assessment Research. Patients' personal information was protected and kept anonymous. This study was approved by the Research Ethics Committee of Soonchunhyang University Hospital (IRB number SCHCH-2018-07-025). The need for informed consent was waived because of the retrospective nature of the study.

2.1. Propensity score matching

Propensity scores were calculated for each patient based on a multivariate logistic regression model. This model included demographic variables (age and sex), stroke severity or comorbidity such as NIHSS and CCI, and economic status defined by health insurance versus medical aid. We matched treated participants with controls in a 1:1 ratio using the greedy nearest neighbor method.[8,13]Figure 1 presents the flowchart of participant selection and propensity score matching set construction. The overall quality of matched samples was assessed by comparing the standardized difference of means and the ratio of variances between the propensity scores of both groups, as well as inspection of propensity scores between groups.

2.2. Statistical analysis

We compared the non-IVT and IVT groups using an independent sample *t* test for continuous variables and the chi-square test for categorical variables. Descriptive data are expressed as percentages and means (standard deviation). The primary outcome of this study was survival up to 3 months, 1 year, and 5 years after symptom onset of first-ever AIS. We reported Kaplan–Meier survival estimates and the difference between survival curves was tested using the log-rank test stratified to matched sets. For the propensity score matching cohort (2634 pairs), robust Cox proportional hazard models were used to estimate the hazard ratio (HR) of AIS associated with thrombolysis and 95% confidence intervals (CI). The model was adjusted for potential confounding factors such as age, sex, onset-to-needle time, health insurance type, arrival mode, NIHSS score, door-to-image time, medical history, CCI, medical facility type, and the use of poststroke antithrombotic drugs (antiplatelet or anticoagulant drugs). A proportional hazards assumption was used to validate

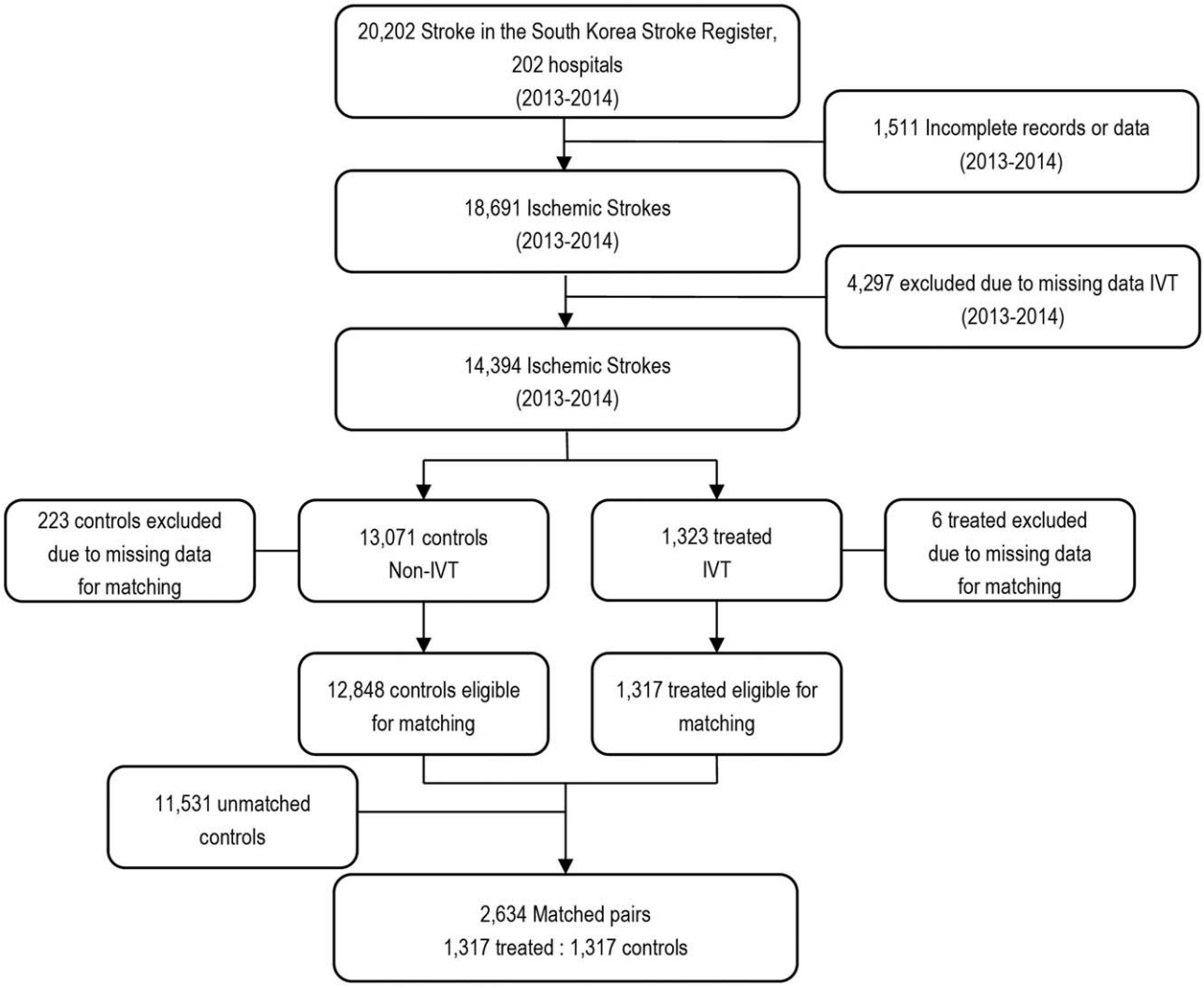

Figure 1. Data attribution flowchart. IVT = intravenous thrombolysis.

the application of Cox proportional hazard models. Data analysis was performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC). A two-sided test with $P < .05$ was considered statistically significant.

3. Results

In total, 14,394 patients with AIS were recruited from March to June 2013 and from June to August 2014. Of them, 1323 (9.2%) received IVT with tPA and 229 had missing data for at least one variable required to calculate the propensity score. These patients were excluded from this study. Of the 2634 remaining subjects, 1317 patients treated with IVT were matched with 1317 patients treated without IVT (Fig. 1). Overall, 286 (10.9%) patients were treated with intra-arterial mechanical thrombectomy. Measures of balance diagnosis indicated that the sample was adequately matched, with standardized difference of mean propensity scores between groups of <.01 (good balance < .25).[12] A comparison of baseline characteristics further supported the good balance of our matched sample (Table 1, http://links.lww.com/MD2/A627). The mean follow-up time was 3.45 years (interquartile range [IQR] = 3.26; range, 0–5.42 years). In total, 923 (35%) patients died during the follow-up period.

3.1. Long-term mortality up to 5 years

Kaplan–Meier estimates showed lower mortality for the IVT group than for the non-IVT group at 5 years (Fig. 2A; log-rank test, $P < .001$). The median survival time was 3.53 years for the IVT group and 3.37 years for the non-IVT group. The absolute risk reduction at 5 years was 7.1% (95% CI, 3.43%–10.70%; number needed to treat: 15). Patients treated with IVT between 2 and 4.5 hours and patients who underwent conservative treatment had significantly higher 5-year mortality than patients treated with IVT within 2 hours (Fig. 2B; log-rank test, $P < .001$). The very old age group (≥70 years) had higher risk of mortality than the young age (<40 years) group (Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A625; log-rank test, $P < .001$). The risk of mortality was significantly higher in the high NIHSS group (≥22) than in the low NIHSS group (Figure S2, Digital Supplemental Content, http://links.lww.com/MD2/A626; log-rank test, $P < .001$).

Table 1

Baseline characteristics of patients with acute ischemic stroke in a 1:1 propensity matched cohort.

Variables, n (%)	Total	IVT	Non-IVT	*P* value
Total, number of patients	2634	1317	1317	
Patient level				
Age, mean (SD), yr	67.8 (13.0)	67.2 (12.6)	68.3 (13.3)	.026
18 to 45	147 (5.6)	77 (5.8)	70 (5.3)	.928
46 to 59	544 (20.7)	268 (20.3)	276 (21.0)	
46 to 69	636 (24.1)	319 (24.2)	317 (24.1)	
≥70	1307 (49.6)	653 (49.6)	654 (49.7)	
Male, n (%)	1603 (60.9)	802 (60.9)	801 (60.8)	.968
Female, n (%)	1031 (39.1)	515 (39.1)	516 (39.2)	
Health insurance type, n (%)				
Health insurance	2484 (94.3)	1242 (94.3)	1242 (94.3)	1.000
Medical aid	150 (5.7)	75 (5.7)	75 (5.7)	
NIHSS, mean (SD), score	10.3 (6.3)	10.5 (6.2)	10.2 (6.4)	.228
0 to 4	427 (16.2)	213 (16.2)	214 (16.2)	.998
5 to 7	634 (24.1)	317 (24.1)	317 (24.1)	
8 to 13	759 (28.8)	383 (29.1)	376 (28.5)	
14 to 21	674 (25.6)	334 (25.4)	340 (25.8)	
22 to 42	140 (5.3)	70 (5.3)	70 (5.3)	
Medical history, n (%)				
Smoker				
Current smoker	709 (27.3)	337 (25.9)	372 (28.7)	.255
Ex-smoker	385 (14.8)	193 (14.8)	192 (14.8)	
Nonsmoker	1505 (57.9)	772 (59.3)	733 (56.5)	
Atrial fibrillation/flutter	634 (25.9)	395 (32.2)	239 (19.5)	<.001
Charlson Comorbidity Index, score				
0	2330 (88.5)	1166 (88.5)	1164 (88.4)	.966
1	275 (10.4)	136 (10.3)	139 (10.6)	
2	29 (1.1)	15 (1.1)	14 (1.1)	
Assessment level				
Onset to door time, n (%)				
≤2 h	1087 (48.0)	960 (79.2)	127 (12.1)	<.001
>2 h	1177 (52.0)	252 (20.8)	925 (87.9)	
Mechanical thrombectomy, n (%)	286 (10.9)	225 (17.1)	61 (4.6)	<.001
Arrival mode, n (%)				
EMS	1795 (68.3)	996 (75.7)	799 (60.8)	<.001
No EMS	835 (31.7)	320 (24.3)	515 (39.2)	
Door to image time, n (%)				
≤1 h	2208 (95.1)	1245 (99.5)	963 (89.9)	<.001
>1 h	114 (4.9)	6 (0.5)	108 (10.1)	
Hospital level				
Medical facility type, n (%)				
Tertiary general hospital	1302 (49.4)	697 (52.9)	605 (45.9)	<.001
General hospital	1332 (50.6)	620 (47.1)	712 (54.1)	
Stroke unit				
Yes	1584 (60.1)	840 (63.8)	744 (56.5)	<.001
No	1050 (39.9)	477 (36.2)	573 (43.5)	
Deaths, n (%)				
3-mo	333 (12.7)	160 (12.2)	173 (13.2)	.442
1-yr	526 (20.0)	239 (18.2)	287 (21.8)	.019
5-yr	923 (35.0)	415 (31.5)	508 (38.6)	<.001
mRS at discharge, n (%)				
Good outcome (0–2)	1517 (57.6)	847 (64.3)	670 (50.9)	<.001
Bad outcome (3–6)	1117 (42.4)	470 (35.7)	647 (49.1)	
Poststroke antithrombotic drug				
No medication	92 (3.5)	61 (4.6)	31 (2.4)	<.001
Antiplatelet drug	1356 (51.5)	592 (45.0)	764 (58.0)	
Anticoagulant drug	1186 (45.0)	664 (50.4)	522 (39.6)	

EMS = emergency medical service, IVT = intravenous thrombolysis, mRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation.

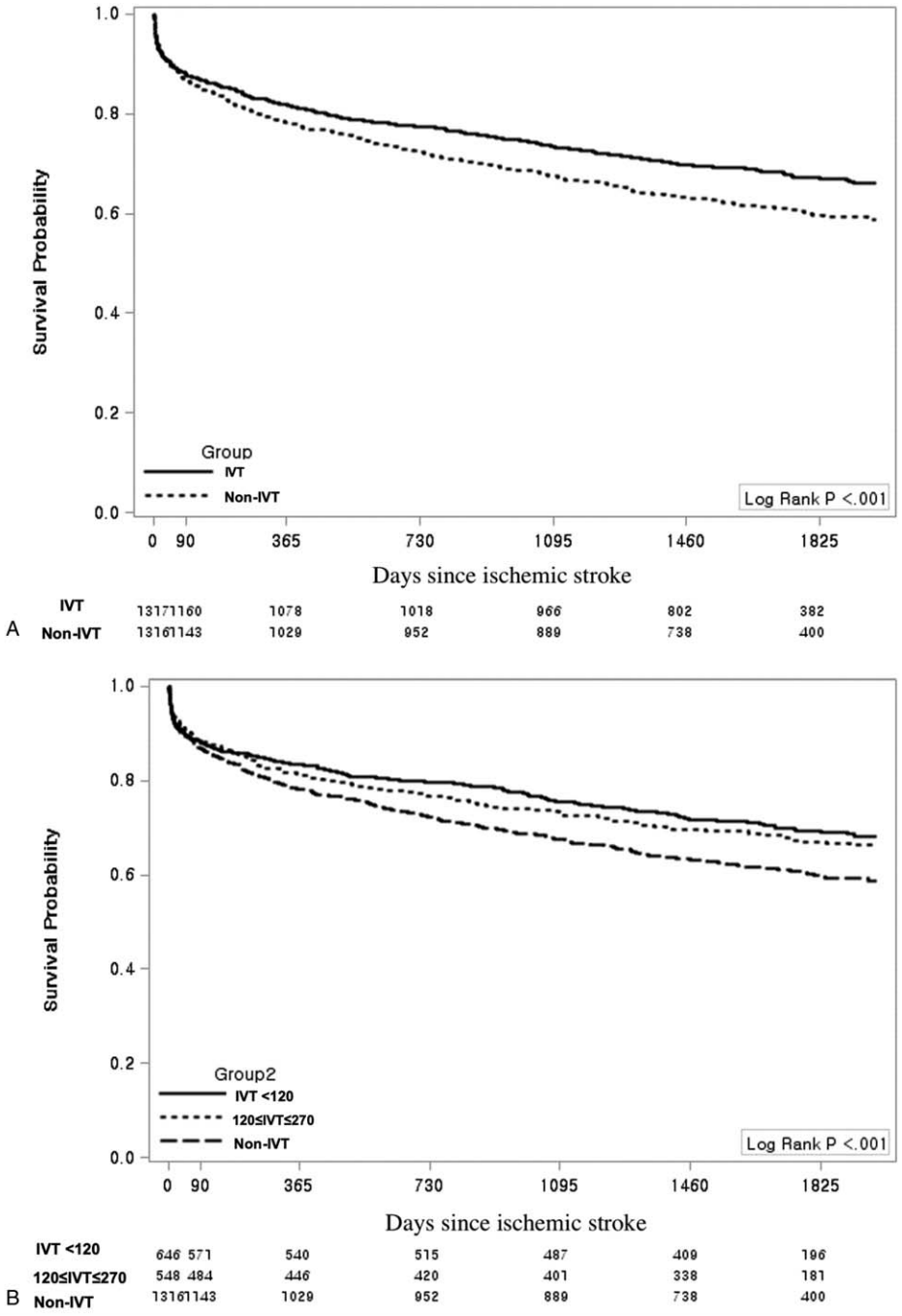

Figure 2. Kaplan–Meier curve of acute ischemic stroke patients for 5 years. (A) Survival rate between IVT group and non-IVT group. (B) Survival rate of patients who received IVT within 2 hours and IVT between 2 and 4.5 hours compared with non-IVT group. IVT = intravenous thrombolysis.

3.2. Risk factors for mortality

Table 2 shows the Cox analysis of factors influencing mortality. After adjusting for age, sex, onset to treatment time, health insurance, arrival mode (emergency medical services), NIHSS score, door-to-image time, medical history, CCI, medical facility type, and poststroke use of antithrombotic drugs (antiplatelet or anticoagulant drugs), the IVT group treated between 2 and 4.5 hours showed a 26% (HR, .74; 95% CI, .60–.92) decrease in 3-month mortality, and the IVT within 2 hours group showed a 37% (HR, .63; 95% CI, .51–.79) decrease in 3-month mortality compared to the non-IVT group. Mechanical thrombectomy was associated with a 28% (HR, .72; 95% CI, .52–.99) decrease in 3-month mortality. Both IVT and mechanical thrombectomy tended to reduce the risk of 1- and 5-year mortality; however, the reduction was not statistically significant ($P > .05$). The very old age group (≥70 years) showed significantly higher risk of 3-month (HR, 16.08; 95% CI, 5.13–50.47) and 1-year (HR, 13.16; 95% CI, 4.74–36.55) mortality than the young age group (18–45 years). However, age was not associated with 5-year mortality (HR, 1.35; 95% CI, .64–2.87). There was no statistically significant difference in mortality between being in the health insurance and medical aid groups, according to the economic

Table 2

Cox analysis of factors influencing 3-month, 1-year, and 5-year mortality.

	3-month		1-year		5-year	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Onset to treatment time (min)						
IVT < 120	.63 (.51–.79)	<.001*	.89 (.72–1.10)	.272	0.91 (0.74–1.23)	.396
≥120 to ≤270	.74 (.60–.92)	.005*	.92 (.74–1.14)	.440	1.02 (.82–1.27)	.851
Non-IVT	1.00		1.00		1.00	
Mechanical thrombectomy	.72 (.52–.99)	.041*	.88 (.66–1.19)	.409	.85 (.64–1.12)	.244
Age (yr)						
18 to 45	1.00		1.00		1.00	
46 to 59	2.29 (.70–7.50)	.172	2.60 (.90–7.55)	.079	.95 (.42–2.17)	.904
46 to 69	5.26 (1.66–16.73)	.005*	6.14 (2.19–17.18)	<.001*	1.25 (.57–2.73)	.575
≥70	16.08 (5.13–50.47)	<.001*	13.16 (4.74–36.55)	<.001*	1.35 (.64–2.87)	.435
Female sex	.88 (.73–1.06)	.171	.88 (.73–1.07)	.200	.90 (.75–1.08)	.242
Health insurance type						
Health insurance	1.00		1.00		1.00	
Medical aid	1.03 (.75–1.40)	.869	1.31 (.98–1.75)	.074	.82 (.61–1.10)	.191
Arrival mode						
EMS	1.00		1.00		1.00	
No EMS	.81 (.67–.97)	.026*	.87 (.73–1.05)	.149	.77 (.64–.92)	.004*
NIHSS score						
0 to 4	1.00		1.00		1.00	
5 to 7	1.39 (1.00–1.93)	.047*	1.27 (0.92–1.75)	.141	1.20 (.89–1.63)	.225
8 to 13	1.74 (1.28–2.37)	<.001*	1.41 (1.03–1.93)	.032*	1.25 (.94–1.67)	.125
14 to 21	2.24 (1.64–3.07)	<.001*	1.77 (1.29–2.43)	<.001*	1.35 (.99–1.83)	.056
22 to 42	3.82 (2.39–6.10)	<.001*	2.67 (1.76–4.05)	<.001*	2.05 (1.35–3.13)	.001*
Door to image time						
≤1 h	1.00		1.00		1.00	
>1 h	1.29 (0.96–1.74)	.092	1.82 (1.27–2.60)	<.001*	1.15 (.82–1.61)	.418
Medical history						
Smoker						
Current smoker	.73 (.57–.94)	.014*	.72 (.55–.95)	.019*	.94 (.73–1.21)	.637
Ex-smoker	.99 (.77–1.29)	.965	.92 (.72–1.18)	.514	.79 (0.61–1.03)	.079
Nonsmoker	1.00		1.00		1.00	
Atrial fibrillation/flutter	1.26 (1.01–1.56)	.041*	1.23 (1.00–1.52)	.056*	1.05 (.85–1.29)	.667
Charlson Comorbidity Index score						
0	1.00		1.00		1.00	
1	1.04 (.80–1.35)	.758	1.13 (.86–1.47)	.378	.94 (.72–1.22)	.620
≥2	1.24 (.51–3.02)	.640	1.70 (1.11–2.63)	.016*	2.59 (1.51–4.42)	<.001*
Medical facility type						
Tertiary general hospital	1.00		1.00		1.00	
General hospital	1.04 (.87–1.24)	.693	1.14 (.96–1.36)	.139	1.06 (.89–1.27)	.494
Poststroke antithrombotic drug						
No medication	1.00		1.00		1.00	
Antiplatelet drug	.49 (.32–.74)	.001*	.45 (.28–.74)	.002*	.48 (.32–.73)	.001*
Anticoagulant drug	.49 (.33–.73)	.001*	.46 (.28–.75)	.002*	.56 (.37–.84)	.005*

CI = confidence interval, EMS = emergency medical service, HR = hazard ratio, IVT = intravenous thrombolysis, NIHSS = National Institutes of Health Stroke Scale.
* $P < .05$ statistically significant.

status. Visiting the tertiary general hospital did not statistically significantly decrease the short- and long-term mortality ($P > .05$). As NIHSS increased, the risk of 3-year mortality increased significantly ($P < .05$). The risk of 3-month (HR, 3.82; 95% CI, 2.39–6.10), 1-year (HR, 2.67; 95% CI, 1.76–4.05), and 5-year (HR, 2.05; 95% CI, 1.35–3.13, $P < .001$) mortality was consistently higher in the very high NIHSS group (22–42) than the low NIHSS group (0–4). Door to image time > 1 hour had higher 3-month (HR, 1.29; 95% CI, 0.96–1.74, $P > .05$), 1-year (HR, 1.82; 95% CI, 1.27–2.60, $P < .001$), and 5-year (HR, 1.15; 95% CI, 0.82–1.61, $P > .05$) mortality.

Current smokers had higher risk of 3-month (HR, .73; 95% CI, .57–.94) and 1-year (HR, .72; 95% CI, .55–.95) mortality. However, smoking status was not associated with 5-year mortality. Atrial fibrillation was associated with decreased risk of 3-month (HR, 1.26; 95% CI, 1.01–1.56) and 1-year (HR, 1.23; 95% CI, 1.00–1.52) mortality. However, atrial fibrillation was not associated with 5-year mortality. High CCI ≥2 was not associated with 3-month or 1-year mortality, but it was associated with decreased risk of 5-year mortality (HR, 2.59; 95% CI, 1.51–4.42). Patients who did take an antithrombotic medicine after stroke had significantly lower risk of 3-month, 1-year, and 5-year mortality. Poststroke antiplatelet medication was associated with 51% (HR, .49; 95% CI, .32–.74), 55% (HR, .45; 95% CI, .28–.74), and 52% (HR, .48; 95% CI, .32–.73) decreases in the risk of 3-month, 1-year, and 5-year mortality, respectively. Poststroke anticoagulant medication was associated with 51% (HR, .49; 95% CI, .33–.73), 54% (HR, .46; 95% CI, .28–.75) and 44% (HR, .56; 95% CI, .37–.84) decreases in the risk of 3-month, 1-year, and 5-year mortality, respectively.

4. Discussion

Our study showed that acute stroke management of thrombolysis with tPA could reduce the risk of 3-month mortality. There is much evidence that thrombolysis could improve survival. Thrombolysis within a limited time window may decrease infarction size and other complications such as cardiopulmonary complications.[14,15] Thrombolysis may reduce the length of hospital stay and risk of pneumonia. Thus, mortality from complications could be reduced in patients with AIS. Thrombolysis could induce hemorrhagic complications. However, another study reported that, although 58 per 1000 cases treated with thrombolysis have intracranial hemorrhage (95% CI, 49–68), risk of 3 to 6 month mortality was not increased in the thrombolysis group.[16] A systematic review found that thrombolysis performed within 6 hours can reduce death or dependency, with a better effect if performed within 3 hours.[16] Our results also showed that thrombolysis performed within 2 hours resulted in lower risk of mortality than thrombolysis performed between 2 and 4.5 hours. The degree of thrombus resolution after thrombolysis increases as the time from symptom onset to thrombolysis decreases.[17] The effect of thrombolysis on recanalization decreases over time, with the treatment effect being decreased after 270 minutes from symptom onset.[18]

Our data showed that the risk of short-term mortality decreased in the thrombectomy group although the data used in this study were from 2013 to 2014 before the endovascular thrombectomy era. Before 2015, the National Health Insurance system of South Korea recommended restriction of stent-retrieval thrombectomy. Thus, only 10.9% of our study population underwent thrombectomy, and this group may have mostly comprised patients who were likely to achieve a good outcome. The positive effect on mortality due to thrombectomy remains under debate. A meta-analysis found that thrombectomy failed to significantly decrease short-term mortality. However, when the time from symptom onset to reperfusion after thrombectomy increased, the mortality tended to increase (6.0% at 240 minutes, 10.5% at 480 minutes).[19]

Our results reflect the status of emergency care for patients with AIS in South Korea. The door-to-image time was within 1 hour for 95% of patients. The median onset-to-door time was 61 mins (IQR: 36–194 minutes). The median door-to-needle time was 46 min (IQR: 35–57 minutes). These results imply that medical accessibility in South Korea is very good.

The National Institute of Neurological Disorders and Stroke trial showed no difference in 12-month mortality between patients treated with and without thrombolysis.[5] The Third International Stroke Trial demonstrated no benefit of thrombolysis in reducing 18-month mortality.[6] The first reported study using a propensity score-matched method in Denmark found that the long-term outcomes in patients with thrombolysis showed lower mortality than those in nontreated patients (n = 4292 patients 1:1 matched, median follow-up period: 1.4 years, range, 0–7.6 years).[7] Another propensity score-matched study in the United Kingdom also reported that thrombolysis reduced long-term mortality risk (n = 738 patients, 1:2 matched, median follow-up time: 5.45 years; range, 0–10 years).[19,20]

Our study is the first to report long-term mortality of AIS patients in South Korea using a propensity-score matching method with data from a well-designed national stroke registry. Overall, 2634 patients (1:1 matched) were enrolled in the current study. All patients were enrolled in the Acute Stroke Registry and were tracked with administrative data and health insurance data for a median follow-up period of 3.45 years (range, 0–5.4 years). Such data are very reliable to determine long-term outcomes with an observational study. The patients treated using thrombolysis failed to achieve lower mortality than the nonthrombolysis group during long-term follow-up (1 year and 5 years), similar to results of previous studies about long-term mortality among patients treated using thrombolysis.[6] Although several studies attempt obtaining better long-term outcomes after thrombolysis in AIS; however, the hypothesis that thrombolysis lowers the mortality risk, long-term, is still under debate. The long-term outcome of AIS before 2015 were not affected by the initial treatment. The rapidly developed paradigm shift in AIS treatment may have affected the long-term prognosis of AIS patients after 2015. Poststroke antithrombotic drugs significantly reduced short- and long-term mortality in the current study. Poststroke antiplatelet and anticoagulant medication is important to prevent recurrent stroke and other cardiovascular diseases. Because atherosclerotic plaque can develop and progress with platelets, antiplatelet therapy with aspirin, clopidogrel, and combined therapy have been shown to be effective and safe to prevent recurrent stroke or adverse events in patients with cardiovascular disease. On the basis of many trials, antiplatelet therapy and anticoagulant medication have become critical first-line treatment in ischemic stroke or transient ischemic attack.[21] In addition, some studies have found that, compared with current antiplatelet therapy, discontinuation of antiplatelet therapy could increase recurrent stroke and mortality.[22]

Our data showed the high frequency of anticoagulant use in Korea. Even though our data had no source of stroke definition according to the Trial of Org 10172 in Acute Stroke Treatment criteria, it is well-known that a high proportion of the Asian population has a tendency towards intracranial stenosis.[23] Moreover, an undetermined cause of ischemic strokes still represents about 20% to 30% of AIS cases. Our study refers to patients with atrial fibrillation on admission; thereafter, newly diagnosed AF during the follow-up period has more potential. Another study also showed that the rate of prescription for anticoagulants at discharge was commonly higher than the proportion of AF at admission.[24]

Our study also found that 3.5% of patients who had not been administered antithrombotic medication, or only received short-term administration of medication (within 1 month) had consistently poorer outcomes during long-term follow-up. This implies that patients with AIS should be managed by antithrombotic drugs to improve their long-term outcomes.

Our study has limitations. Our data were from 2013 to 2014 during the prethrombectomy era. The low proportion of thrombectomy during this period seemed to influence our finding of high mortality after stroke. The number of patients who underwent thrombectomy in Korea increased at an annual rate of 25.8% from 2008 to 2016.[25,26] This large nationwide registry had no data that met the Trial of Org 10172 in Acute Stroke Treatment criteria or included CT or MRA imaging, and the occlusion site could not be evaluated. The occurrence of diabetes mellitus, myocardial infarction, moderate or severe renal disease and hypertension did not differ significantly between IV-tPA and NO IV-tPA use. We used the CCI, which included the history of diabetes mellitus, myocardial infarction, moderate or severe renal disease, and hypertension to analyze the severity of stroke. This accuracy of this method for representing the comorbidities of patients, has been verified previously.[26] Therefore, CCI was

evaluated and represented the severity of stroke. Our data are from a well-designed national registry created by the National Health Institute and administrative data from Korea that provides good medical accessibility and a National Health Insurance System for all people. Therefore, we expect that the long-term outcomes of the thrombectomy era may be different in future studies. Furthermore, this study had no data about the cause of death. Many epidemiologic studies such as those based on cancer registry or any specific disease include the cause of death; however, studies about the long-term outcome after AIS generally report the mortality rate without the cause of death. This is because those with stroke generally have high mortality and high morbidity risk with 50% of survivors being chronically disabled. Therefore, most studies on mortality following stroke report the rates of survivors and functional outcomes. Our study also reported the mortality rate after the first-ever stroke.[20] Disability in stroke survivors is important, so many studies represented the difference of modified Rankin scale (mRS) at 3 months or during follow-up between treatment and control group. Our registry had data about the functional outcome on discharge. The proportion of good outcome (mRS 0–2) on IVT group was significantly higher than non-IVT group (64% vs 51%, $P < .001$, Table 1). This difference of functional outcome could affect the lower mortality after thrombolysis.

5. Conclusion

Compared to nonthrombolysis, thrombolysis reduced short-term mortality by 47%. Thrombolysis and thrombectomy are associated with improved short-term survival, although they did not significantly reduce long-term mortality. Poststroke antithrombotic medication could significantly reduce both short- and long-term mortality of patients with AIS. Faster active management in the acute phase and poststroke antithrombotic medication are important for good short- and long-term outcomes in patients with ischemic stroke.

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