Research article

Intravenous thrombolysis therapy and dementia risk in acute ischemic stroke patients: A retrospective cohort study in Taiwan

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Abstract

Background: Intravenous thrombolysis (IVT) is the standard treatment for acute ischemic stroke (AIS) to improve functional outcomes. Furthermore, AIS is an important risk factor for dementia. Limited evidence has shown the long-term benefit of IVT on dementia in Western countries.

Objective: We aim to investigate the association between IVT and the risk of dementia in acute ischemic stroke patients in Asian population.

Methods: A retrospective cohort study using medical records from a medical center in Taiwan between 2017 and 2022 was conducted. We included acute ischemic stroke patients aged over 55 years old who had not previously been diagnosed with dementia. The primary outcome was incident dementia ascertained through dementia diagnosis in medical records. The inverse probability of treatment-weighted Cox proportional hazard models were used to estimate the association between IVT and incident dementia.

Results: A total of 1471 patients with AIS were included. 939 (63.8%) were male, and the mean age was 70.7 ± 9.6 years. Among them, 19.1% of patients (n = 281) received IVT. The mean follow-up time was 2.6 ± 1.7 years. Although not statistically significant, the IVT was associated with a decreased risk of dementia (HR: 0.88 [95%CI 0.54–1.41)]).

Conclusions: The IVT was associated with lower risk of dementia, although not statistically significant, in reducing the incidence of dementia in Asian patients with ischemic stroke. Studies with larger sample sizes will be needed in the future.

Keywords

Alzheimer's disease, dementia, ischemic stroke, tissue plasminogen activator, vascular dementia

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Introduction

Stroke is the second leading cause of death and the second most common cause of disability-adjusted life-years worldwide.[1] Among various causes of stroke, ischemic stroke constitutes the majority of strokes in the world. The annual number of stroke is increasing, especially in the older population.[2] Ischemic stroke is associated with cognitive impairment and even dementia, a more severe form of cognitive impairment. A systematic review of 16 studies indicated that both a previous stroke and a new stroke increased the risk of developing all-cause dementia.[3] Among various types of dementia, vascular dementia (VaD) is directly related to ischemic stroke and the second most common form of dementia after Alzheimer's disease (AD). Pathological evidence of VaD is observed in approximately 50% of dementia patients. In most cases, infarcts co-exist with AD pathology[4]; in fact, in addition to VaD, a meta-analysis of six studies found that stroke is also a relatively strong risk factor for AD.[5] These studies,

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taken together, demonstrate a greater impact of symptomatic stroke on dementia risk than underlying vascular risk factors. Given the current lack of disease-modifying treatments and the complexity of multiple pathologies contributing to dementia, aggressive treatment of ischemic stroke might have the potential to reduce the global burden of dementia.

In recent decades, treatment for ischemic stroke has greatly advanced. Several important clinical trials have confirmed the efficacy of intravenous thrombolysis (IVT) with tissue plasminogen activator (tPA) within 3–4.5 h, reducing functional disability and improving short-term outcomes.[6–8] While established evidence showed that IVT decreases disability and improves recovery of neurological function, there have been few studies conducted in Western countries[9,10] to investigate the long-term benefits of aggressive treatment of ischemic stroke, especially the risk of dementia. However, the main cause of stroke varies based on race and ethnicity, with Western populations commonly experiencing emboli from the heart or extracranial large arteries, while Asians tend to have a higher prevalence of small-vessel occlusion or intracranial atherosclerosis.[11] Therefore, the potential benefit of IVT in reducing the risk of dementia in the Asian population remains to be elucidated.

In Taiwan, the reimbursement of IVT with tPA by the National Health Insurance in 2004 was implemented to reduce the incidences of stroke-related morbidities and disabilities. However, the National Insurance Research Database lacks important information, such as stroke severity and potential confounders. As a result, this study aims to conduct a retrospective cohort study using medical records in a medical center in New Taipei City to investigate the relationship between intravenous tPA treatment and the risk of all-cause dementia in patients with ischemic stroke. We expected that intravenous tPA treatments would have a long-term benefit in lowering the risk of all-cause dementia.

Methods

Population and database

This is a single-center, retrospective cohort study. We included acute ischemic stroke patients from a research database at a medical center in New Taipei City, Taiwan. Patient demographic data, admission notes, discharge notes, emergency medical records, and prescription dispensing records are collected.

We included incident acute ischemic stroke patients aged 55 years and older to capture a population with higher risk of developing dementia. Furthermore, we included patients arriving at a hospital within 24 h in order to encompass a wider spectrum of patients who should have been eligible for IVT as a comparison group. For patients with recurrent stroke episodes during whole study period, only the first episode is included. However, for patients with recurrent stroke occurred within a month, both the first and the second episode would be excluded to avoid complicated stroke etiology (such as cancer-related stroke). Therefore, detailed inclusion criteria include patients over 55 years old who were diagnosed with acute ischemic stroke between 2017 and 2020. Exclusion criteria include (1) duration between stroke onset and arrival at the hospital longer than 24 h; (2) with recurrent stroke within a month; (3) Following episodes in the same patient; (4) dementia diagnosis/medications before stroke onset; (5) dementia diagnosis / clinical dementia rating (CDR) $\geqq 0.5$ during the admission or within 1 month after discharge; (6) missing the National Institutes of Health Stroke Scale (NIHSS) at admission (7) without neuroimaging; (8) receiving endovascular thrombectomy (EVT) during the admission.

Exposure

We classified those receiving IVT during emergency visits or upon admission as the treatment group. All patients in the treatment group also received the standard of care, such as antiplatelet or hydration. The control group is defined as those who receive standard of care only.

Outcome measurements

The outcome is incident dementia, defined as diagnoses of all types of dementia documented in the medical record (ICD-10: F00, F01, F03, G30). Additionally, we linked our study database with records from the dementia care center to identify individuals with a CDR score ≥ 0.5. In our hospital, stroke patients who are followed up in outpatient clinics and show signs of cognitive impairment are referred for comprehensive neuropsychological assessments, including the Cognitive Abilities Screening Instrument (CASI), Mini-Mental State Examination (MMSE), and CDR. If the CDR score is ≥ 0.5, which has been classified as indicative of very mild dementia in previous epidemiological studies in Taiwan,[12,13] these patients are further referred to the dementia care center.

For patients identified with a CDR score ≥ 0.5 at the dementia care center, a neurologist (YHW) and a psychiatrist specializing in dementia (YFC) reviewed the neuropsychological test results and patient histories to confirm the diagnosis of dementia.

Besides, we defined a one-month lag period to ensure temporality, i.e. we considered the incident dementia diagnosis that occurred one month after the admission as a history of dementia. Therefore, cohort entry date would be the date of arrival, and the index date would be 30 days after the cohort entry date.

Covariates

Covariates include demographic data (age, sex[male/female], calendar year[2017/2018/2019/2020], work status[yes/no]

and education level[Illiteracy/Elementary/Junior high/Senior high and above), health behavior (drinking habits[Current/Stop/Never] and smoking status [Current/Stop/Never]), comorbidities (hypertension[yes/no], diabetes[yes/no], hyperlipidemia[yes/no], atrial fibrillation[yes/no], coronary artery disease[yes/no], congestive heart failure[yes/no] and other cardiovascular diseases[yes/no]), medication use (anticoagulant use[yes/no] and antiplatelet use[yes/no] in past 3 months), and stroke-related factors (stroke history[yes/no], stroke severity[NIHSS], hemisphere side of infarction[left/right/multiple] and stroke subtype[Large/Small/Cardio/Other/Undetermined]). Other cardiovascular diseases are defined as having one of the following diseases: peripheral vascular disease, valvular heart disease, deep vein thrombosis, and carotid stenosis. Medication use is obtained from dispensing records at the medical center. Stroke severity is measured by the NIHSS. Stroke subtype is determined by TOAST classification documented in patients' discharge notes, which is judged by neurologists in charge. For the missing TOAST classification, the neurologist (YHW) on our team assessed the stroke subtype based on additional information available in the discharge notes. All the other covariates are measured by patient's self-report or diagnoses by physicians.

Statistical analysis

In descriptive statistics, ANOVA and chi-square tests are used for continuous and categorical variables. The Cox proportional hazard model is used to analyze the treatment effect. The date of the first recorded diagnosis of dementia was the event date. Patients who survived without developing dementia or were lost to follow-up were censored at the latest available outpatient/inpatient record or administratively on December 31, 2022. We adjust for the confounders by using the inverse probability weighting (IPTW) with the propensity score estimated by the logistic regression model. Covariates include age, gender, calendar year, work status, education level, drinking habits, smoking status, hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary artery disease, congestive heart failure, other cardiovascular diseases, anticoagulant use in past 3 months, antiplatelet use in past 3 months, stroke history and stroke severity. Since there were missing data, obesity was not adjusted in main analysis but would be later included in the sensitivity analysis. Stabilized weights were obtained by multiplying the marginal probability of the treatment group. Subgroup analyses include age stratification (<70/≧70), sex (male/female), and stroke locations (left/right side). Sensitivity analyses included expanding the lag period to three or six months, imputing missing data (such as obesity) using multiple imputation with a joint model, limiting the time window to 4.5 h, and including patients who had a recurrent stroke within a month of the first episode. New IPTW would be calculated for each analysis.

All analyses were conducted using R (version 4.1.0). This study has been approved by the Institutional Review Board (IRB) at Far Eastern Memorial Hospital (112065-F) and National Yang Ming Chiao Tung University (YM111156E).

Results

During 2017–2020, 5636 patients were admitted with stroke. Age at admission < 55 years old (N = 1094), unknown stroke onset duration (N = 20), stroke onset duration exceeds 24 h (N = 1580), no data of NIHSS at admission (N = 91), diagnosis other than acute ischemic stroke (N = 684), with previous dementia diagnoses before admission (N = 179), loss of follow up (N = 15), follow up time less than 1 month (N = 238), recurrent stroke within 1 month (N = 32), following stroke episodes of the same patients (N = 49), and under EVT at the same episode (N = 183) are excluded. Therefore, we included 1471 patients in the final analysis. Among these, 281 patients were treated with IVT (Figure 1).

There are 939 males (63.8%) in the study population, with an average age of 70.7 ± 9.6. The characteristics of the IVT and the standard-of-care groups are shown in Table 1. Before weighting, there are more patients with current work, current habits of alcohol consumption, a higher proportion of having coronary artery disease, and higher NIHSS in the IVT group. Additionally, there is a greater proportion of having diabetes and stroke history in the standard-of-care group. After weighting, all the observable characteristics are balanced (Table 1).

There were 140 events during the study period, with a mean follow-up time of 2.64 years ± 1.71. The estimated incidence rate is 31.47 per 1000 person-year (95%CI 19.72–47.65) in the IVT group and 37.64 per 1000 person-year (95%CI 31.16–45.08) in the standard-of-care group (Table 2). Overall, we found a slightly protective effect in the IVT group (weighted HR: 0.88, 95%CI 0.54–1.41). However, the association is not statistically significant (Table 2). The Kaplan-Meier plot and the log-log survival curve to evaluate the proportional hazard assumption were provided in Supplemental Figures 1 and 2.

In subgroup analyses, the association between IVT and lower risk of dementia might be more pronounced in the younger elderly (weighted HR: 0.56, 95%CI 0.22–1.40), in the male (weighted HR: 0.70, 95%CI 0.34–1.44) and in the patients with right sides stroke (weighted HR: 0.72, 95%CI 0.33–1.56) (Figure 2). In sensitivity analyses, similar results were shown (Supplemental Figure 6).

Discussion

This is the first study in the Asian population to investigate the association between IVT and the risk of dementia and did not show a protective effect of IVT on lowering incident dementia among patients with ischemic stroke.

In previous observational studies, there were no significant associations between intravenous thrombolysis and

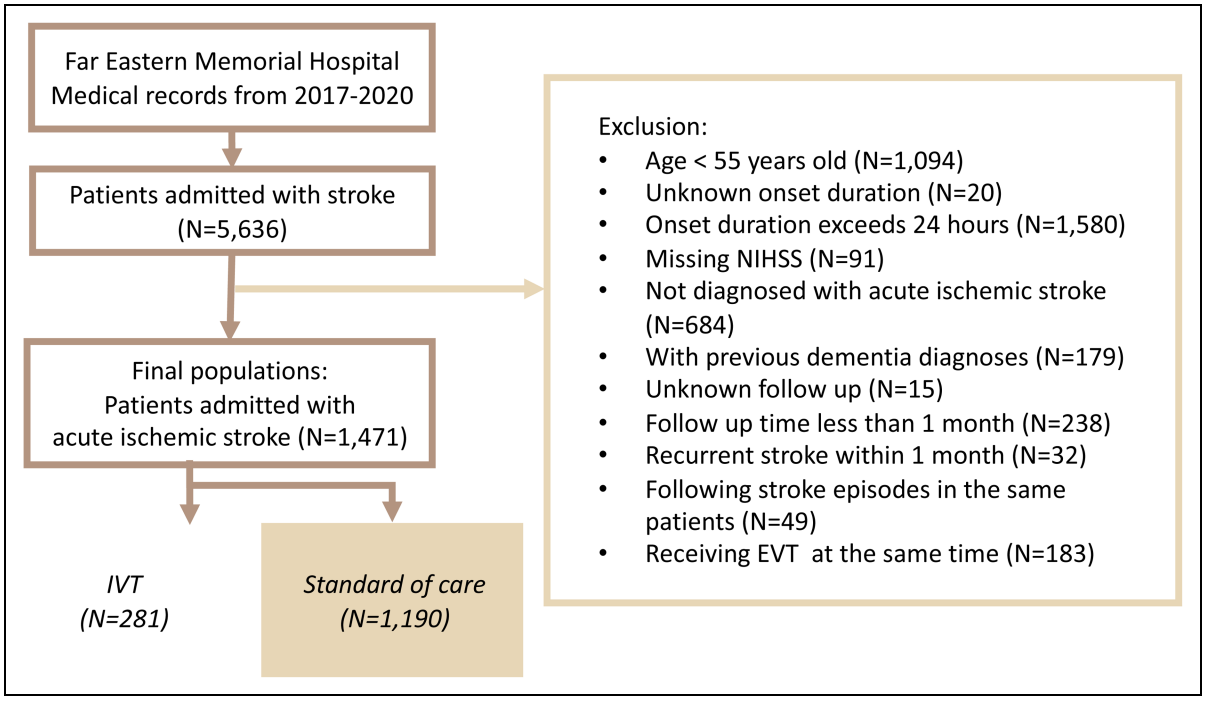

Figure 1. Flow chart. IVT, intravenous thrombolysis; EVT, endovascular thrombectomy; NIHSS, National Institute of Health Stroke Scale.

cognitive decline.[14–17] One of the possible reasons could be that the follow-up period (3–6 months) was too short to detect differences in post-stroke cognitive outcomes. A study conducted by Joshua et al.[9] through a cohort from a stroke registry showed a protective effect of IVT on dementia evaluated at 1 and 5 years after treatment (weighted HR: 0.76 (95%CI 0.58–0.97) at 1 year; weighted HR: 0.79 (95% CI 0.66–0.91) at 5 year). Another study by Vestergaard et al.[10] further confirmed the protective effect with longer follow-up year through Denmark nationwide register-based cohort (all-cause dementia HR 0.63 (0.40–0.99) at 2 year; HR 0.65 (0.46–0.91) at 5 year; HR 0.83 (0.64–1.07) at 10 year). Because the proportion of ischemic stroke subtype classification differs between races and ethnicity,[11] our study would be the first to present Asian results. Among our study population, the most prevalent subtype is small-vessel occlusion (43.0%), followed by large-vessel occlusion (25.1%) and cardioembolism (17.9%). It potentially explains the inconsistent results, while acute ischemic strokes in the Western world countries are mainly caused by large-vessel occlusion or cardioembolism.

Stroke may directly lead to vascular-type dementia since lesions on large vessels that can result in the infarction of specific brain area related to cognition, or lesions on small cerebral vessels that lead to micro-bleeding. The lesions cause vascular cognitive impairment and may eventually progress to vascular dementia.[18] There is evidence about the presence of cerebral small vessel disease and a higher risk of AD. The possible mechanism is either through cerebral hypoperfusion accelerating the accumulation of cerebral amyloid-β or through the reduced clearance of cerebral amyloid-β caused by blood-brain barrier disruption.[19] Moreover, research suggests that the presence of AD pathology in patients with cerebral infarction leads to a higher risk of dementia compared with those without cerebral infarction.[20] Therefore, treatments, such as IVT which restore the perfusion of cerebral vessels and may prevent ischemic damage or dysfunction in the brain, are expected to reduce the risk of post-stroke dementia.

We had some interesting observations in our subgroup analysis. For example, we observed a higher risk of dementia in left-side stroke than in right-side stroke, though without significance. This finding might be explained by the severity of the stroke at baseline. Prior studies consistently indicated a higher NIHSS in patients having left-sided infarction. However, these studies found no significant difference in functional outcomes.[21,22] Another study delved deeper into which specific domain (defined by the Alberta Stroke Program Early CT Score, ASPECTS) strongly predicts the poor outcome.[23] It revealed that the M4 region in the left hemisphere and M6 region in the right hemisphere are significant predictors. Therefore, considering both hemisphere sides and regions, the location of infarction might influence the prognosis of stroke. While existing evidence primarily focuses on functional outcomes, the findings of our study could serve as an exploration of the association

Table 1. Baseline characteristics.

	Crude				Weighted			
	IVT (N = 281)	Standard of care (N = 1190)	p[a]	SMD	IVT (N = 275)	Standard of care (N = 1191)	p[a]	SMD
Age, mean (SD)	69.83 (9.66)	70.96 (9.63)	0.076	0.118*	70.88 (9.65)	70.76 (9.77)	0.861	0.012
>=70, n (%)	122 (43.4)	568 (47.7)	0.216	0.087	134 (48.7)	557 (46.8)	0.581	0.039
Male, n (%)	175 (62.3)	764 (64.2)	0.593	0.040	172 (62.7)	759 (63.8)	0.737	0.023
Work, n (%)	90 (32.0)	266 (22.4)	0.001*	0.219*	67 (24.2)	288 (24.2)	0.996	0.001
Education, n (%)			0.422	0.113*			0.956	0.039
Illiteracy	34 (12.1)	131 (11.0)			30 (10.8)	133 (11.2)		
Elementary	68 (24.2)	287 (24.1)			71 (26.0)	289 (24.3)		
Junior	61 (21.7)	313 (26.3)			69 (25.1)	303 (25.4)		
Senior and above	118 (42.0)	459 (38.6)			105 (38.1)	465 (39.1)		
Behavior factors								
Alcohol, n (%)			0.016*	0.183*			0.933	0.026
Current	34 (12.1)	88 (7.4)			23 (8.5)	99 (8.4)		
Stop	22 (7.8)	130 (10.9)			31 (11.2)	124 (10.4)		
Never	225 (80.1)	972 (81.7)			221 (80.4)	967 (81.2)		
Smoking, n (%)			0.935	0.024			0.998	0.005
Current	82 (29.2)	336 (28.2)			79 (28.7)	340 (28.5)		
Stop	38 (13.5)	168 (14.1)			38 (13.9)	166 (13.9)		
Never	161 (57.3)	686 (57.6)			158 (57.4)	686 (57.5)		
Diseases, n (%)								
Hypertension	219 (77.9)	942 (79.2)	0.711	0.030	219 (79.5)	940 (79.0)	0.861	0.012
Diabetes mellitus	102 (36.3)	494 (41.5)	0.125	0.107*	110 (40.0)	483 (40.6)	0.859	0.013
Hyperlipidemia	165 (58.7)	717 (60.3)	0.686	0.031	160 (58.1)	713 (59.9)	0.608	0.036
Atrial fibrillation	65 (23.1)	247 (20.8)	0.427	0.057	56 (20.5)	252 (21.1)	0.816	0.016
Congestive heart failure	16 (5.7)	67 (5.6)	1.000	0.003	16 (5.9)	68 (5.7)	0.898	0.009
Coronary artery disease	47 (16.7)	142 (11.9)	0.039*	0.137*	34 (12.5)	153 (12.8)	0.875	0.010
Other CVD[b]	15 (5.3)	72 (6.1)	0.753	0.031	16 (5.9)	70 (5.9)	0.992	0.001
Medications, n (%)								
Anticoagulants	9 (3.2)	55 (4.6)	0.376	0.073	11 (4.1)	52 (4.3)	0.900	0.010
Antiplatelets	48 (17.1)	210 (17.6)	0.891	0.015	48 (17.6)	209 (17.5)	0.973	0.002
Stroke factors								
NIHSS, mean (SD)	6.73 (6.29)	5.74 (6.12)	0.015*	0.160*	6.27 (5.54)	5.97 (6.78)	0.479	0.049
Stroke history, n (%)	55 (19.6)	293 (24.6)	0.087	0.122*	64 (23.2)	282 (23.7)	0.874	0.012
TOAST[c], n (%)			<0.001***	0.321*			0.003**	0.280*
Large Vessel Occlusion	92 (32.7)	277 (23.3)			89 (32.5)	281 (23.6)		
Small Vessel Occlusion	91 (32.5)	541 (45.5)			95 (34.5)	533 (44.8)		
Cardioembolism	53 (18.9)	210 (17.6)			47 (17.1)	214 (18.0)		
Others	1 (0.4)	18 (1.5)			1 (0.4)	18 (1.5)		
Undetermined	44 (15.7)	144 (12.1)			43 (15.5)	144 (12.1)		
Follow-up time, y, mean (SD)	2.52 (1.62)	2.67 (1.73)	0.210	0.085	2.59 (1.80)	2.64 (1.72)	0.661	0.031

*p value < 0.05 or SMD > 0.1; ** p value < 0.01; ***p value < 0.001; SMD, standardized mean difference;
[a] p value from ANOVA for continuous variables and from chi-square test for categorical data.
[b] Other CVD (cardiovascular diseases) including peripheral vascular disease (PVD), valvular heart disease (VHD), deep vein thrombosis (DVT), carotid stenosis.
[c] There were originally 36% missing in TOAST classification.

between stroke location and cognitive outcomes. Another possible explanation is the high incidence of post-stroke aphasia in left-sided infarction, which could be misinterpreted as dementia due to difficulties in communication during testings.[24] It is important to interpret these subgroup analyses with caution, as they are underpowered and have wide confidence intervals. Further research with larger sample sizes is needed to validate these findings and provide more definitive conclusions.

Our study has several strengths. First, this is the first hospital-based study to explore the long-term effect on cognition of intravenous thrombolysis in the Asian

population. Second, we included those who arrived at the hospital in one day after stroke onset, making treatment groups and control groups more comparable. Third, we described the NIHSS score at arrival to show the different baseline stroke severity, and we adjusted it through the inverse probability of treatment weighting to create a balanced population. Our study is not without limitations. First, although the inverse probability of treatment weighting was used to create a balanced population, confounding by indication cannot be entirely eliminated. Intravenous thrombolysis is indicated for patients able to arrive at the hospital within 4.5 h after stroke onset. Many factors, such as geographic location, transportation availability, and patient awareness, can lead to delays beyond the optimal therapeutic window. As a result, we included patients who arrived within 24 h to capture a broader, more representative sample of the stroke population, reflecting actual clinical scenarios and also to lessen confounding by indication. For example, among two patients arriving within the 4.5-h window, the one who did not receive t-PA likely had contraindications for t-PA treatment, such as a prior history of intracranial hemorrhage, a brain tumor, etc. Including a wider arrival time frame helps mitigate this bias and provides a more comprehensive understanding of stroke management in diverse clinical settings. Second, we might underestimate the incidence of dementia if patients seek care for dementia at other hospitals. Usually, acute stroke patients are followed up at the neurology outpatient clinic in the same hospital after discharge. However, it is still possible that patients go to other hospitals for dementia care. Third, the study is underpowered and has limited generalizability due to the small sample size from a single center. Larger studies are needed to confirm and validate our findings. Fourth, we did not have access to mortality data, and therefore, the competing risk of death was not accounted for in our analysis. As an alternative approach, we censored patients at their latest recorded visit. Finally, some unobservable confounders are not included in the database, such as exercise, depression, living alone, and certain social factors.

Table 2. Observed dementia incidence rate by treatments.

	IVT (N = 281)	Standard of care (N = 1190)
End of study		
Hazard ratio[a], crude	0.81 (0.52–1.29)	*ref*
Hazard ratio[a], weighted	0.88 (0.54–1.41)	*ref*
Incidence rate[b], per 1000 person-years	31.47 (19.72–47.65)	37.72 (31.22–45.18)
Dementia, n	22	118
Total person-years	699.1	3127.6

[a] Cox proportional hazard model is used to analyze the risks of dementia between IVT and standard of care.
[b] 95%CI is estimated by assuming Poisson distribution.

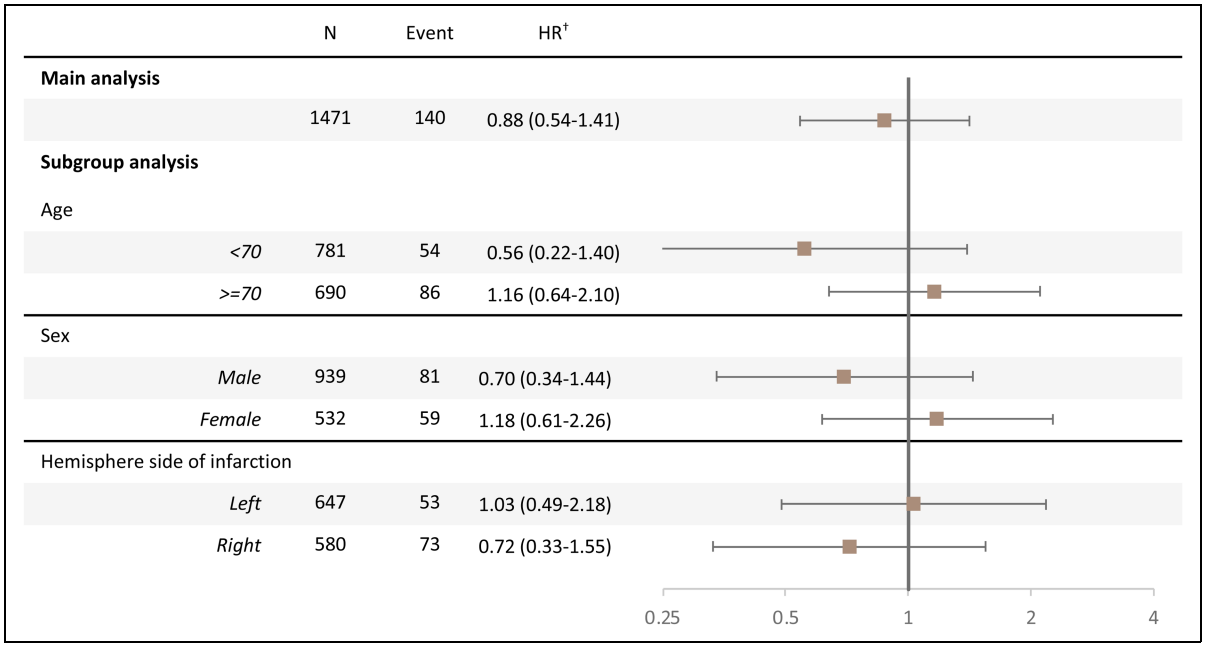

Figure 2. Dementia risks between IVT and standard of care after IPTW. IVT, Intravenous thrombolysis; IPTW, Inverse probability of treatment weighting.
† Hazard ratio after weighting. Cox proportional hazard model is used to analysis the risks of dementia of IVT with standard of care as reference.

Conclusion

In our study, intravenous thrombolysis demonstrated a trend of a protective effect, although not statistically significant, on the risk of dementia in the Asian population. Studies with larger sample sizes will be warranted in the future.

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Statements and declarations

Author contributions

Yi-Fang Chuang (Conceptualization; Formal analysis; Funding acquisition; Investigation; Writing – original draft); Yan-Siang Huang (Conceptualization; Data curation; Funding acquisition; Project administration; Writing – original draft); Te-Jung Kung (Data curation; Formal analysis; Investigation; Writing – original draft).

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supplemental material

Supplemental material for this article is available online.

References

1. Gorelick PB. The global burden of stroke: persistent and disabling. *Lancet Neurol* 2019; 18: 417–418.
2. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021; 20: 795–820.
3. Savva GM and Stephan BCM. Epidemiological studies of the effect of stroke on incident dementia. *Stroke* 2010; 41: e41–e46.
4. Fernando MS and Ince PG. Vascular pathologies and cognition in a population-based cohort of elderly people. *J Neurol Sci* 2004; 226: 13–17.
5. Zhou J, Yu J-T, Wang H-F, et al. Association between stroke and Alzheimer's disease: systematic review and meta-analysis. *J Alzheimers Dis* 2014; 43: 479–489.
6. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. *Stroke* 2015; 46: 3020–3035.
7. 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: 1581–1588.
8. Jacquin A, Virat-Brassaud ME, Rouaud O, et al. Vascular aphasia outcome after intravenous recombinant tissue plasminogen activator thrombolysis for ischemic stroke. *Eur Neurol* 2014; 71: 288–295.
9. Cerasuolo JO, Mandzia J, Cipriano LE, et al. Intravenous thrombolysis after first-ever ischemic stroke and reduced incident dementia rate. *Stroke* 2022; 53: 1170–1177.
10. Vestergaard SB, Dahm CC, Gottrup H, et al. Intravenous thrombolysis for acute ischemic stroke is associated with lower risk of post-stroke dementia: a nationwide cohort study. *Eur Stroke J* 2023; 8: 947–955.
11. Kim BJ and Kim JS. Ischemic stroke subtype classification: an Asian viewpoint. *J Stroke* 2014; 16: 8–17.
12. Tsai P-H, Liu J-L, Lin K-N, et al. Development and validation of a dementia screening tool for primary care in Taiwan: brain health test. *PLoS One* 2018; 13: e0196214.
13. Sun Y, Lee H-J, Yang S-C, et al. A nationwide survey of mild cognitive impairment and dementia, including very mild dementia, in Taiwan. *PLoS One* 2014; 9: e100303.
14. Nys GMS, Zandvoort MJE, Algra A, et al. Cognitive and functional outcome after intravenous recombinant tissue plasminogen activator treatment in patients with a first symptomatic brain infarct. *J Neurol* 2005; 253: 237–241.
15. Rosenbaum Halevi D, Bursaw AW, Karamchandani RR, et al. Cognitive deficits in acute mild ischemic stroke and TIA and effects of rt-PA. *Ann Clin Transl Neurol* 2019; 6: 466–474.
16. Hajjar K, Fulton RL, Diener H-C, et al. Does the cognitive measure Cog-4 show improvement among patients treated with thrombolysis after acute stroke? *Int J Stroke* 2013; 8: 652–656.
17. Strambo D, Bartolini B, Beaud V, et al. Thrombectomy and thrombolysis of isolated posterior cerebral artery occlusion. *Stroke* 2020; 51: 254–261.
18. Sun J-H, Tan L and Yu J-T. Post-stroke cognitive impairment- epidemiology, mechanisms and management. *Ann Transl Med* 2014; 2: 80.
19. Kim HW, Hong J and Jeon JC. Cerebral small vessel disease and Alzheimer's disease: a review. *Front Neurol* 2020; 11: 927.
20. Schneider JA, Wilson RS, Bienias JL, et al. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. *Neurology* 2004; 62: 1148–1155.

21. Rosso C, Blanc R, Ly J, et al. Impact of infarct location on functional outcome following endovascular therapy for stroke. *J Neurol Neurosurg Psychiatry* 2019; 90: 313–319.
22. Cheng B, Forkert ND, Zavaglia M, et al. Influence of stroke infarct location on functional outcome measured by the Modified Rankin Scale. *Stroke* 2014; 45: 1695–1702.
23. Rangaraju S, Streib C, Aghaebrahim A, et al. Relationship between lesion topology and clinical outcome in anterior circulation large vessel occlusions. *Stroke* 2015; 46: 1787–1792.
24. Berthier ML. Poststroke aphasia - epidemiology, pathophysiology and treatment. *Drugs Aging* 2005; 22: 163–182.