

Protective effect of influenza vaccination on outcomes in geriatric stroke patients: A nationwide matched cohort study



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HIGHLIGHTS

- Stroke patients with influenza vaccination (IV) showed better outcome than non-vaccinated patients.
- IV was associated with reduced post-stroke outcomes in various subgroups.
- Less consumption of medical resources were also noted in stroke patients with IV.

ARTICLE INFO

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ABSTRACT

Background and aims: The effects of influenza vaccination (IV) on stroke outcomes are unclear. The purpose of this study is to evaluate the outcomes after stroke in elderly individuals who have received an IV.

Methods: We used Taiwan's National Health Insurance Research Database 2000–2009 claims data to conduct a nested stroke cohort study including 148,909 hospitalized stroke patients aged 66 years and older. Using a matching procedure by propensity score, we selected 25,248 stroke patients with IV and 25,248 stroke patients without IV for comparison. Logistic regression was used to calculate the odds ratios (ORs) and 95% CIs of post-stroke complications and in-hospital mortality associated with IV.

Results: Stroke patients with IV had significantly lower risks of post-stroke pneumonia (OR = 0.79; 95% CI, 0.74–0.83), septicemia (OR = 0.78; 95% CI, 0.70–0.86), urinary tract infection (OR = 0.87; 95% CI, 0.83–0.92), and 30-day in-hospital mortality (OR = 0.60; 95% CI, 0.54–0.67) compared with non-IV stroke patients. Vaccinated stroke patients also had shorter hospital stays ($p < 0.0001$) and less medical expenditures ($p < 0.0001$) during stroke admission than the control group. Lower rates of post-stroke adverse events in patients with IV were noted in both sexes of all age groups with various types of stroke.

Conclusions: Stroke patients with IV showed fewer complications and lower mortality compared with non-IV patients. These findings suggest the urgent need to promote IV for this susceptible population of stroke patients.

Abbreviations: CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IV, influenza vaccination; OR, odds ratio

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1. Introduction

Influenza is a common respiratory infection that is considered an important burden on health and society all over the world [1–4]. The influence of influenza on the general population is substantial, and the complications caused by influenza occur frequently in the elderly and in those with chronic disease [1]. Among European countries, influenza-related hospitalizations ranged from 95 to 288, and mortality ranged from 57 to 160 per 100,000 elderly patients [2]. In the United States, there were at least 90,000 pneumonia hospitalizations and 44,000 all-cause of deaths associated with influenza annually [3,4].

Although previous studies have reported that vaccinated persons have a lower risk of developing stroke [5–10], these data should be interpreted with caution because of several limitations, such as small sample size, low quality studies, lack of focus on first stroke patients, and high heterogeneity. Not only can influenza prevention provide a protective effect against developing stroke in adult patients but also the beneficial effects of preventing stroke can be observed in children. Although the positive effect of routine influenza vaccination (IV) on reducing stroke risk was reported in previous studies, whether it can reduce the post-stroke adverse events is unknown [11].

The mechanism of why influenza increases the risk of cardiovascular events is unclear. It may accelerate acute thrombotic vascular events or cause cardiovascular abnormalities by inappropriately activating the coagulation cascade [12,13]. IV might decrease the mortality of cardiovascular diseases and all-cause mortality [14,15]. In a cohort study focused on elderly patients with IV [16], the risk of hospitalization for stroke, heart disease and mortality for heart disease was decreased. Both the American Heart Association/American College of Cardiology and the European Society of Cardiology recommend IV annually for individuals with established cardiovascular diseases [17–19].

Yet the beneficial effects of IV on the outcomes of stroke remain unclear. Thus, we conducted a nationwide matched study using Taiwan's National Health Insurance Research Database to investigate the effectiveness of IV on complications and mortality for patients with stroke admission.

2. Patients and methods

2.1. Source of data

We used Taiwan's National Health Insurance Research Database to conduct this study. Taiwan's National Health Insurance Program has collected all medical reimbursement claims since 1996 in a Taiwan's National Health Insurance Research Database that is available to researchers with beneficiaries' identification scrambled to protect privacy. The available information of this database includes sex, birth date, diagnoses, examinations, prescriptions, treatments, and medical expenditures of outpatient visits, emergency care, and hospitalization. The reliability of this database has been well accepted by important scientific journals worldwide [20,21]. This study was approved by the institutional review board of Taipei Medical University and E-DA Hospital (TMU-JIRB-201505055; TMU-JIRB-201701050; EDA-JIRB-2017144).

2.2. Study design

To investigate the effects of influenza vaccination on post-stroke outcomes, a nested retrospective cohort study was conducted using the Stroke Cohort Database (one subgroup database included more than 500,000 stroke patients in the Taiwan National Health Insurance Research Database). We examined medical claims and identified 43,294 stroke patients aged 66 or over who had received IV within 12 months before the index stroke admission in 2000–2009. Each older stroke patient with IV was matched with an unvaccinated stroke patient using

a propensity score-matched pair procedure to balance for age, sex, low income, types of stroke, coexisting medical conditions (within the previous 24 months), emergency care (within the previous 12 months) and hospitalization (within the previous 12 months). We compared post-stroke outcomes such as pneumonia, septicemia, underwent intensive care, length of hospital stay, medical expenditure, and mortality for a 30-day period after stroke among patients with or without IV. These post-stroke complications were identified as participants who had a physician's primary or secondary diagnosis in the index admission or 30-day post-admission outpatient care and inpatient care. Patients who had received medical care with a physician's diagnosis of pneumonia and septicemia before stroke admission within 6 months were excluded from this study.

2.3. Measures and definitions

Patients' low-income status was defined by qualifying for waived medical copayment as verified by the National Health Insurance Administration, Taiwan. Based on population density, these units were stratified into tertiles to designate areas of low, moderate and high urbanization. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) was used to define the physicians' diagnoses. Based on our previous studies, prestroke medical conditions determined from medical claims for the 24-month prestroke period included hypertension (ICD-9-CM 401–405), mental disorders (ICD-9-CM 290–319), diabetes (ICD-9-CM 250), chronic obstructive pulmonary disease (ICD-9-CM 491,492, 496), ischemic heart disease (ICD-9-CM 410–414), heart failure (ICD-9-CM 428), hyperlipidemia (ICD-9-CM 272.0, 272.1, 272.2, 272.4), liver cirrhosis (ICD-9-CM 571.2, 571.5, 571.6), and migraine (ICD-9-CM 346). Renal dialysis was defined by administration codes (D8 and D9). Post-stroke pneumonia (ICD-9-CM 480–486), septicemia (ICD-9-CM 038 and 998.5), and urinary tract infection (ICD-9-CM 599.0) after the index stroke admission were also identified by a physician's diagnosis. The subtype of IV was stated clearly in the [Supplementary Data](#).

2.4. Statistical analyses

We used propensity score-matched pair analysis to determine the associations between IV and post-stroke outcomes. A non-parsimonious multivariable logistic regression model was used to estimate a propensity score for stroke patients receiving IV or not. Clinical significance guided the initial choice of covariates in this model to include age, sex, low income, urbanization, type of stroke, hypertension, mental disorders, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, heart failure, hyperlipidemia, liver cirrhosis, renal dialysis, and migraine. We matched stroke patients with IV to non-IV patients using a greedy matching algorithm (without replacement) with a caliper width of 0.2 SD of the log odds of the estimated propensity score. Categorical variables were summarized using frequency (percentage) and were compared between IV and non-IV stroke patients using chi-square tests. Continuous variables were summarized using the mean \pm standard deviation and were compared using *t* tests. Logistic regressions were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of post-stroke outcomes associated with IV. Additional sensitivity analyses stratified by age, sex, number of medical conditions and types of stroke were also performed to examine post-stroke outcomes in patients with and without IV within these strata. In the further strict analysis, we added length of hospital stay and medical expenditure of the index admission as stroke severity in the matching procedure with propensity score.

3. Results

The baseline characteristics of stroke patients with and without IV are shown in [Supplementary Data](#). Under the matching procedure with

Table 1
Characteristics of older stroke patients with and without influenza vaccination after matching.

	No IV (N = 25,248)		IV (N = 25,248)	
	n	(%)	n	(%)
Sex				
Female	11,332	(44.9)	11,332	(44.9)
Male	13,916	(55.1)	13,916	(55.1)
Age, years				
66–70	7219	(28.6)	7219	(28.6)
71–75	6523	(25.8)	6523	(25.8)
76–80	5363	(21.2)	5363	(21.2)
≥ 81	6143	(24.3)	6143	(24.3)
Low income	367	(1.5)	367	(1.5)
Urbanization				
Low	85	(0.3)	85	(0.3)
Moderate	6175	(24.5)	6175	(24.5)
High	18,988	(75.2)	18,988	(75.2)
Type of stroke				
Occlusion and stenosis	349	(1.4)	349	(1.4)
Intracerebral hemorrhage	3925	(15.6)	3925	(15.6)
Others	17,093	(67.7)	17,093	(67.7)
Subarachnoid hemorrhage	3881	(15.4)	3881	(15.4)
Stay in teaching hospital	23,925	(94.8)	23,925	(94.8)
Medical conditions				
Hypertension	9735	(38.6)	9735	(38.6)
Diabetes	3341	(13.2)	3341	(13.2)
Mental disorder	2097	(8.3)	2097	(8.3)
COPD	1249	(5.0)	1249	(5.0)
Ischemic heart disease	1017	(4.0)	1017	(4.0)
Hyperlipidemia	537	(2.1)	537	(2.1)
Heart failure	276	(1.1)	276	(1.1)
Liver cirrhosis	150	(0.6)	150	(0.6)
Dialysis	23	(0.1)	23	(0.1)
Migraine	23	(0.1)	23	(0.1)
CCI Score				
0	15,766	(62.4)	15,766	(62.4)
1	7108	(28.2)	7108	(28.2)
2	1756	(7.0)	1756	(7.0)
3	428	(1.7)	428	(1.7)
4	96	(0.4)	96	(0.4)
≥ 5	94	(0.4)	94	(0.4)
Anticoagulant	92	(0.4)	92	(0.4)
Anti-platelet agents	10,919	(43.3)	10,919	(43.3)
Lipid-lowering agents	2001	(7.9)	2001	(7.9)
Emergency care in past 2 years				
0	17,432	(69.0)	17,432	(69.0)
1	5548	(22.0)	5548	(22.0)
2	1545	(6.1)	1545	(6.1)
3	349	(1.4)	349	(1.4)
≥ 4	374	(1.5)	374	(1.5)
Inpatient care in past 2 years				
0	21,397	(84.8)	21,397	(84.8)
1	3215	(12.7)	3215	(12.7)
2	486	(1.9)	486	(1.9)
3	71	(0.3)	71	(0.3)
≥ 4	79	(0.3)	79	(0.3)

CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; IV, influenza vaccination.

propensity score (Table 1), there were no differences in age, sex, low income, urbanization, stay in teaching hospital, types of stroke, hypertension, mental disorders, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, heart failure, hyperlipidemia, liver cirrhosis, renal dialysis, migraine, anticoagulants, anti-platelet agents, lipid-lowering agents, emergency care within prior 24-month, or inpatient care within prior 24-month between stroke patients with or without IV.

Compared with controls (Table 2), stroke patients receiving IV previously had lower risks of post-stroke pneumonia (OR = 0.79; 95% CI, 0.74–0.83), septicemia (OR = 0.78; 95% CI, 0.70–0.86), urinary tract infection (OR = 0.87; 95% CI, 0.83–0.92), intensive care (OR = 0.91, 95% CI, 0.88–0.95), and in-hospital mortality (OR = 0.60;

95% CI, 0.54–0.67). Length of hospital stay (11.65 ± 14.68 vs. 13.00 ± 17.32 days, $p < 0.0001$) and medical expenditure (2271 ± 4075 vs. 2500 ± 4347 US dollars, $p < 0.0001$) were also lower in stroke patients receiving IV than in non-IV controls.

The stratification analysis showed that receiving IV was associated with reduced post-stroke adverse events (including pneumonia, septicemia, urinary tract infection, and mortality) among men (OR = 0.79; 95% CI, 0.75–0.84), women (OR = 0.79; 95% CI, 0.75–0.84), patients aged 66–70 years (OR = 0.80; 95% CI, 0.73–0.87), patients aged 71–75 years (OR = 0.79; 95% CI, 0.73–0.87), patients aged 76–80 years (OR = 0.76; 95% CI, 0.74–0.86), and patients aged ≥ 81 years (OR = 0.80; 95% CI, 0.74–0.86). Subgroup analysis showed that IV lowered the risk of post-stroke adverse events in patients with subarachnoid hemorrhage (OR = 0.62; 95% CI, 0.46–0.84), intracerebral hemorrhage (OR = 0.77; 95% CI, 0.70–0.84), occlusion and stenosis (OR = 0.79; 95% CI, 0.75–0.83), and other stroke (OR = 0.86; 95% CI, 0.75–0.97). The ORs of receiving IV associated with decreased post-stroke adverse events for stroke patients with 0 and 1 medical condition were 0.76 (95% CI, 0.71–0.81) and 0.80 (95% CI 0.75–0.85), respectively (Fig. 1).

4. Discussion

In this nationwide study, across nine influenza seasons, IV was associated with lower risks of post-stroke pneumonia, septicemia, urinary tract infection, intensive care, and in-hospital mortality when compared with non-IV in stroke patients. The length of the hospital stay and medical expenditure were also lower in stroke patients with IV than in stroke patients who did not receive IV. Further analysis showed the association between IV and reduced post-stroke adverse events was significant in both sexes, all age groups, various stroke subtypes, and in those with fewer comorbidities.

The potential factors associated with stroke and related comorbidities that were identified in previous studies included age, socioeconomic status, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, ischemic heart disease, hyperlipidemia, heart failure, liver cirrhosis, dialysis, and migraine [20,21]. To avoid bias when investigating the relationships between IV and post-stroke outcomes, we used propensity score matching to adjust these potential confounding factors and showed that patients with pre-stroke IV had lower risks of complications and mortality after stroke.

In the past two decades, growing evidence has shown that influenza infection is associated with increased hospitalizations in children younger than 5 years old and in the elderly [3]. Critical illness hospitalizations (acute respiratory failure, severe sepsis and in-hospital death) were also associated with influenza infection [22]. Influenza viruses seem to ally with certain bacterial species by suppressing the immune response of the host to these bacteria and have been shown to disseminate through cardiac, neurological, and muscular tissues [23,24].

Bacterial secondary infection in the lungs and disruption of the epithelial barrier of the respiratory system in people suffering from influenza is a key element that promotes severe disease and mortality. Influenza virus infection affects alveolar macrophage function and induces type I interferon, further endowing bacteria with the ability to colonize the respiratory tract [25,26]. Secondary bacterial infections contribute to pneumonia and the excess influenza-related deaths during seasonal influenza epidemics. By preventing influenza infection and modulating the following immune responses, influenza vaccines have the ability to decrease secondary bacterial infections [27]. Our study also found that stroke patients receiving IV had a lower risk of post-stroke infections, such as pneumonia, septicemia, and urinary tract infection.

In addition to the inflammation *per se*, the influenza-induced systemic inflammatory response might activate the coagulation system and facilitate thromboembolism. Two meta-analysis studies suggested that

Table 2
Outcomes of stroke admission in older patients with and without influenza vaccination.

Outcomes of stroke admission	No IV (N = 25,248)		IV (N = 25,248)		Risk of outcomes	
	Events	%	Event	%	OR	(95% CI) ^a
30-day in-hospital mortality	925	3.7	565	2.2	0.60	(0.54–0.67)
Pneumonia	2579	10.2	2070	8.2	0.79	(0.74–0.83)
Septicemia	937	3.7	732	2.9	0.78	(0.70–0.86)
Urinary tract infection	3405	13.5	3026	12.0	0.87	(0.83–0.92)
Intensive care admission	6726	26.6	6289	24.9	0.91	(0.88–0.95)
Adverse event	6230	24.7	5201	20.6	0.79	(0.76–0.83)
Length of stay, days ^b	13.00 ± 17.32		11.65 ± 14.68		<i>p</i> < 0.0001	
Medical expenditure, US dollars ^b	2500 ± 4347		2271 ± 4075		<i>p</i> < 0.0001	

CI, confidence interval; IV, influenza vaccination; OR, odds ratio.

^a Crude odds ratios calculated in the logistic regressions; adverse event included with 30-day in-hospital mortality, pneumonia, septicemia, urinary tract infection.

^b Mean ± SD; coefficient beta of IV associated with length of stay and medical expenditure are −1.35 (*p* < 0.0001) and −228.18 (*p* < 0.0001), respectively.

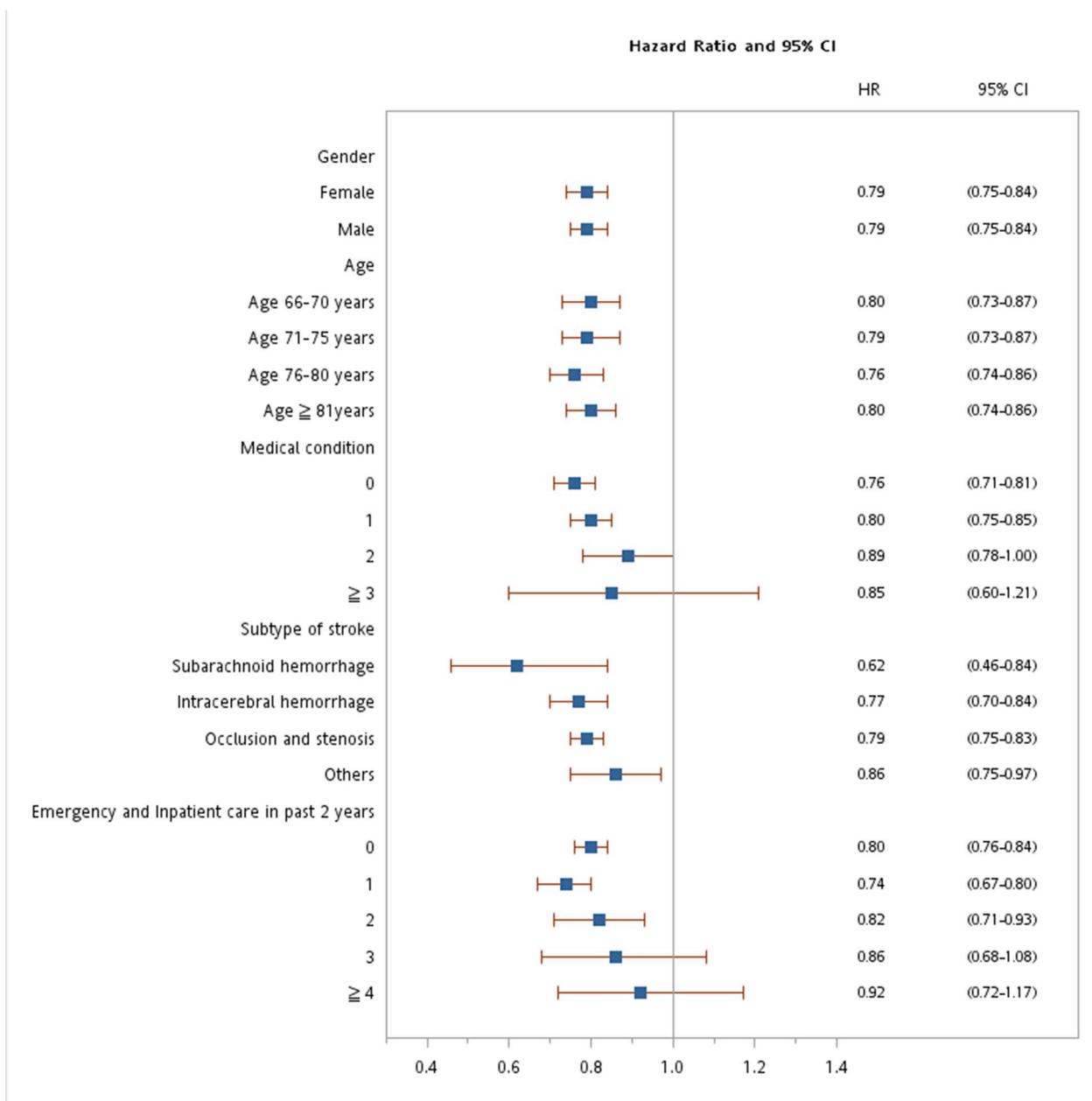


Fig. 1. The stratification analysis for influenza vaccination associated with post-stroke adverse events.

IV reduced the mortality in patients with cardiovascular diseases [14,15]. Major cardiovascular events were also reduced, especially among patients with recent acute coronary syndrome but not among those with stable coronary artery disease. The risk of major cardiovascular events might be reduced by IV [11,16,28], and our inference is that the subsequent risk of post-stroke adverse events and mortality were both reduced in this study.

Patients' knowledge, attitude, and practice of health might be one of possible explanations for the relationship between IV and reduced post-stroke adverse outcomes. Patients receiving vaccination annually exhibit better health consciousness and ambulatory independence. Attitudes toward health maintenance, such as primary prevention like vaccination, were closely associated with higher health consciousness and socioeconomic factors. Healthier people at a lower risk for stroke might be more likely to be vaccinated [29]. After matching with low-income status and urbanization level of residency, such differences might still exist and are not uncommon [30].

In the sensitivity analysis of this study, the protective effects of IV on post-stroke adverse events were observed in both sexes, every adult age group, every subtype of stroke, and patients with 0, 1, 2, and 3 comorbidities. Similar results were also noted in the previous investigations [31,32]. Among diabetic patients, IV was associated with decreased risks of influenza and pneumonia-related hospitalization [31]. The reduced pneumonia/influenza and other morbidities, ICU stay, hospitalization and death were also present in patients with end-stage renal disease who received IV, particularly in the elderly [32]. However, we failed to investigate the beneficial effects of IV in stroke patients who had more than 4 comorbidities, considered people with severe medical conditions. One possible explanation is that severe medical conditions may dilute the protective effects of stroke outcomes, and thus, we could easily investigate the beneficial effects of IV among this special population.

Although this study had several strengths, including a large sample of stroke patients, coverage of nine influenza season-years, and well-matched study design, some limitations should not be ignored. First, we had limited information on sociodemographic characteristics, lifestyle factors (such as smoking habits, alcohol consumption, family history and physical activity level), and laboratory data. Second, the power of protection gained from the IV might be different in each year due to the different serotypes of influenza vaccine. Although it is impossible to standardize the types of vaccine for the study, the same vaccine for each year was applied, and we examined the post-stroke outcomes for a 30-day period to limit this potential bias. Third, a causal relationship could not be established due to the limitation of retrospective cohort study. If the patient did not seek medical care during the period, the medical comorbidities might be underestimated. However, the possible underestimation might be equally distributed between both groups, thus minimizing this bias.

In conclusion, we found that stroke patients receiving IV had a lower risk of post-stroke complications and mortality when compared with non-IV patients. However, these findings need future randomized trials to evaluate the effectiveness of IV on post-stroke outcomes. We suggest the IV might be beneficial for this susceptible population of stroke patients.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

FL, HYC, CCL, and TLC conceived the study; FL, TLC, and CCL completed the study design, data acquisition, and statistical analysis; FL, TLC, CCS, CSL, CCY, YJL, CJH, HYC, and CCL contributed to the study design and interpretation of data; FL and CCL drafted the

manuscript; FL, TLC, CCS, CSL, CCY, YJL, CJH, HYC, and CCL reviewed and contributed to the revision of the manuscript for important intellectual content; CCL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2019.01.008>.

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