ORIGINAL ARTICLE

Is stroke thrombolysis safe and efficacious in Hong Kong?

CME

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Objective To investigate the safety and efficacy of stroke thrombolysis in a local hospital.

Design Historical cohort study.

Setting A tertiary hospital in Hong Kong.

Patients The outcome of acute ischaemic stroke patients treated with intravenous tissue plasminogen activator between October 2008 and May 2011 was compared to those admitted during the same period who were thrombolysis-eligible, but treated conservatively due to unavailability of the thrombolysis service after-hours.

Interventions Intravenous tissue plasminogen activator.

Main outcome measures Primary outcome was functional independence (modified Rankin Scale score of 2 or below) at 3 months. Safety outcomes were symptomatic intracranial haemorrhage and 3-month mortality. Secondary outcomes were hospital length of stay, direct home discharge, and nursing home discharge.

Results A total of 48 thrombolysis and 63 non-thrombolysis patients were identified. Fifty-two percent of the thrombolysis group achieved functional independence compared to 24% of non-thrombolysis group (P=0.003), without significant increase in mortality (15% vs 13%, P=0.51) or symptomatic intracranial haemorrhage (4% vs 2%, P=0.58). Twenty-nine percent of the thrombolysis group patients were discharged home directly, versus 6% of non-thrombolysis group (P<0.001). Mean length of stay was shorter for the thrombolysis group (25 vs 35 days; P=0.034). A similar percentage from each group was discharged to nursing homes.

Conclusion Implementation of the stroke thrombolysis service in Hong Kong appeared safe and efficacious. Patients who received thrombolysis had better outcomes compared to non-thrombolysis cohort. Further studies are needed to investigate the economics of stroke thrombolysis in Hong Kong, which may help to improve funding for provision of this service.

Key words
Brain ischemia; Hong Kong; Stroke; Tissue plasminogen activator; Thrombolytic therapy

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New knowledge added by this study

- The use of intravenous tissue plasminogen activator for acute ischaemic stroke in Hong Kong is as safe and efficacious as demonstrated in western population–based studies.
- Besides improved clinical outcome, thrombolysis treatment resulted in shorter hospital stays for stroke patients.

Implications for clinical practice or policy

- Implementation of territory-wide, 24-hour stroke thrombolysis service should be a priority for the local health authority.

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Introduction

Intravenous (IV) tissue plasminogen activator (TPA) is an effective treatment for acute ischaemic stroke (AIS) within 3 to 4.5 hours of onset in selected patients, based on two large-scale randomised controlled trials performed in western populations.[1,2] Its efficacy and safety appeared replicable in patients of Chinese[3,4] and other Asian ethnicities in observational series.[5-7] Despite preliminary encouraging results, penetrance of stroke

thrombolysis remains low in the Asian region for socio-economical reasons.[8,9]

With a population of seven million inhabitants in Hong Kong, more than 90% of the approximately 20 000 stroke patients per annum are treated in government-funded public hospitals.[10] Management of AIS has traditionally been conservative. The use of thrombolytic treatment is exceptional rather than the rule. At the beginning, there were reservations in generalising positive findings from western populations to Chinese patients.[11] One particular concern was a potentially higher rate of intracranial haemorrhage (ICH) from TPA due to racial differences.[12] Besides, additional resources within the public health system were lacking for a new service which was as time-sensitive as stroke thrombolysis that requires round-the-clock urgent access not only to stroke neurologists, but also to accident and emergency department (AED) triage, emergency physicians, radiologists, stroke nurses, neuroimaging staff as well as to facilities such as high-dependency stroke beds. In response to increasing public awareness and emerging safety data in Asian patients, in-house thrombolysis programmes have recently been developed to make the best use of available resources, in some of the 19 acute public hospitals.[13]

We aimed to investigate the potential impact if thrombolysis becomes the standard of care for AIS in a predominantly Chinese city like Hong Kong. We studied the safety, efficacy, and implications on health resources for stroke thrombolysis in a local clinical setting by comparing the outcome of TPA-treated patients with those who were not so treated.

中風溶栓治療在香港是否安全及有效？

目的 研究一所本地醫院中風溶栓治療的安全性及效用。

設計 歷史隊列研究。

安排 香港一所提供第三層醫療服務的醫院。

患者 比較2008年10月至2011年5月期間因急性缺血性中風入院而接受經靜脈注射組織纖維蛋白溶酶原激酶溶栓治療，和雖適合溶栓治療但因醫院當時未能提供此服務而接受保守治療的病人的治療結果。

介入治療 經靜脈注射組織纖維蛋白溶酶原激酶。

主要結果測量 主要療效指標為於治療後第三個月（即經修定雷氏量表分數為2或以下）病人的生活功能獨立能力。安全指標為具症狀的顱內出血及三個月內的死亡率。次要療效指標為住院期、直接出院返家的比率，及出院後入住護理院的比率。

結果 患者中48名接受溶栓治療及63名未有接受此治療被納入研究範圍。接受溶栓治療與未有接受此治療的患者比較，回復生活功能獨立能力分別為52%及24%（P=0.003），均未有明顯上升的有死亡率（15%比13%；P=0.51）及具症狀的顱內出血（4%比2%；P=0.58）。直接出院返家的比率分別為29%及6%（P<0.001）。接受溶栓治療的患者平均住院期較短（25天比35天，P=0.034）。兩組病人出院後入住護理院的比率相約。

結論 在香港實施中風溶栓治療似乎是安全及有效的。接受溶栓治療的病人有較佳的治療結果。探討本地中風溶栓治療經濟效益的進一步研究將有助增加對此項服務所投入的資源。

Methods

Our centre is a tertiary hospital with catchment population of 600 000. The organisation of our thrombolysis service was described previously.[13] In brief, an expedited stroke triage between AED, radiology department, and neurologists was set up in October 2008 to provide urgent review of AIS patients potentially eligible for thrombolysis. In the initial phase, this service was limited to between 9am and 5pm on weekdays only. Any AIS patients admitted outside these hours were managed according to local practice guidelines without TPA.[11]

All consecutive AIS patients treated with IV TPA between October 2008 and May 2011 (TPA-group) were identified from our stroke registry. Our inclusion criteria for thrombolysis were largely adopted from the National Institute of Neurological Disorders and Stroke (NINDS) trial.[1] The treatment window was extended up to 4.5 hours in 2009, based on the European Cooperative Acute Stroke Study 3 (ECASS-III) results,[2] although we set no upper limit on age or National Institutes of Health Stroke Scale (NIHSS) score. However, we refrained from administering IV TPA to patients with a low computed tomography (CT) Alberta Stroke Programme Early CT Score (ASPECTS) of 0-3, which is predictive of poor outcome and high ICH risk if TPA is given.[14] Patients with ASPECTS of 4-7 were considered for intra-arterial therapy (IAT) if angiographic facility and interventionists were immediately available. In addition, patients with borderline premorbid status on a modified Rankin Scale (mRS) score of ≥3 or a minor deficit of ≤4 on the NIHSS score were excluded. We followed the recommended dose of 0.9 mg/kg but up to a maximum of 50 mg (1 vial) because of concerns about haemorrhagic complications.

For comparison, a group of consecutive thrombolysis-eligible patients admitted after-hours during the same period and therefore not treated with TPA was extracted from the stroke registry (non-TPA group). They were identified by a preliminary screening of all AIS patients with a premorbid mRS score of ≤2, admission NIHSS score of ≥5 and presentation to the AED within 3 hours of onset. A

3-hour cut-off was set to make allowance for an imaginary door-to-treatment delay of up to 1.5 hours. The computerised hospital AED record, clinical notes, and admission brain CT of these screened patients were then assessed independently by two stroke neurologists to identify those who could have received IV TPA using the same criteria set for our treatment group. Consensus was used in case of a disagreement between two assessors.

Baseline characteristics of both groups including gender, age, admission NIHSS score, vascular risk factors, prior antiplatelet and anticoagulant use, stroke subtype, CT ASPECTS (for patients with anterior circulation large artery thrombosis), onset-to-AED ('door'); and for the TPA group, onset- and door-to-treatment time, and TPA dosage were retrieved from stroke registry. Admission CT ASPECTS of non-TPA patients were scored during the patient identification process as noted above. Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

Post-thrombolysis patients were monitored according to the American Academy of Neurology guidelines[15] and all of them were managed by the acute stroke unit (ASU). In contrast, some non-TPA patients were admitted to an acute general medical ward due to full occupancy of ASU, and this was also recorded. Follow-up CT and/or magnetic resonance imaging (MRI) of the brain were performed on day 1 post-thrombolysis, or earlier if the condition deteriorated. Follow-up scans were assessed for presence of ICH by a neuroradiologist who was blinded to patient information. Prospectively recorded mRS scores, adjudicated with a structured interview,[16] were retrieved from the stroke registry, which was scored by neurologist or stroke nurse at the follow-up clinic through telephone interview or on the ward (if not yet discharged at 3 months). Early multidisciplinary rehabilitation was offered to all patients with residual neurological deficits. Hospital length of stay (LOS) and discharge destination were retrieved from computerised hospital record.

Primary outcome was functional independence at 3 months defined as a mRS score of ≤2. Safety outcomes were symptomatic intracranial haemorrhage (SICH) according to ECASS definition (any ICH plus neurological deterioration of NIHSS score of ≥4 within 7 days or leading to death[17]) and 3-month mortality. Secondary outcomes were total LOS including acute and rehabilitation phases, proportion of patients directly discharged home from ASU or acute medical ward, and final discharge destination (including nursing home).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 16.0; SPSS Inc, Chicago [IL], US). Age, NIHSS score, onset-to-door and onset-to-treatment time (in minutes), ASPECTS, and LOS (in days) were used as continuous variables. They were presented as mean and standard deviations (SDs). Gender, vascular risk factors, and discharge destination were used as categorical variables. The mRS was dichotomised to 0-2 (favourable outcome) and 3-6. In the univariate analysis, independent sample *t* tests were used for continuous variables, and the Chi squared or Fisher's exact tests for categorical variables. Logistic regression analysis was performed to calculate the odds ratio (OR) of predictors of favourable functional outcome at 3 months. Pre-specified factors including age, gender, baseline NIHSS score, onset-to-door time, ASU care, and factors associated with favourable outcome in the univariate analysis at a significance level of <0.10 were adjusted in the multivariate regression analysis.

Results

Between October 2008 and May 2011, our stroke registry recorded 2168 AIS patients. A total of 49 received IV TPA, and 48 were included for analysis, as in retrospect one had psychogenic weakness. For reference, another 15 patients underwent IAT within the same period of which eight had no absolute contra-indication to IV TPA except low ASPECTS. Two IV TPA–eligible patients declined thrombolysis.

For comparison, 64 non–TPA-treated AIS patients fulfilling the same criteria of a premorbid mRS score of ≤2, NIHSS score of ≥5, ASPECTS of ≥4, with clearly documented onset or last-seen-well time, and no medical contra-indication to IV TPA were identified from the registry of the same period. In other words, these were patients for whom two stroke neurologists would have offered IV TPA if admitted during the daytime. One tourist patient was lost to follow-up, hence 63 were included for analysis. By combining TPA, non-TPA, and eight patients in the IAT group, the projected thrombolysis rate was 5.5% (119/2168) if the IV thrombolysis service was available around-the-clock.

Table 1 shows the baseline characteristics of both groups, which were comparable except for onset-to-door time, prior anticoagulant, and ASU care. Two (1.8%) of the patients were non-Chinese (Thai and Filipino), one in each group. Regarding the TPA group, the mean (± SD) age was 74 ± 10 years, admission NIHSS score was 15 ± 7, and 44% were male. The mean (± SD) onset-to-door and door-to-treatment time were 63 ± 33 and 81 ± 30 minutes, respectively, with a mean (± SD) overall onset-to-treatment time of 143 ± 43 minutes. Ten (21%) were treated between 3 and 4.5 hours from onset.

Twenty-six patients received 0.9 mg/kg of body weight (BW) of TPA based on the patients' or relatives' accounts, or clinician's estimation. One patient received 60 mg (BW, 66 kg), as the treating clinician at the time was unaware of the self-imposed maximum dose. Six patients received less than 0.9 mg/kg, on average 0.73 mg/kg (range, 0.60-0.83 mg/kg). Among them, 0.6 mg/kg was prescribed on purpose for a 94-year-old patient. Infusion of TPA was stopped prematurely in one patient at 0.6 mg/kg-equivalent due to neurological deterioration. Records of BW were not available for 16 patients who received a maximum dose of 50 mg. While the exact amount per kilogram was unknown, they were likely to have received at least 0.6 mg/kg as elderly stroke patients weighing more 80 kg were rarely encountered from past experience in our centre.

Regarding the primary outcome, 52% (25/48) of the TPA group achieved functional independence at 3 months, versus 24% (15/63) of the non-TPA group (P=0.003) [Fig 1]. The proportion of TPA-treated patients with excellent neurological recovery (mRS score ≤1, or no significant disability) was also higher (46% vs 10%, P<0.001). Univariate analysis of baseline variables showed that TPA (OR=3.5; 95% confidence interval [CI], 1.5-7.8; P=0.003), ASPECTS (OR=2.3; 95% CI, 1.5-3.51; P<0.001), age (OR=0.93; 95% CI, 0.90-0.97; P=0.001), and NIHSS score (OR=0.85; 95% CI, 0.79-0.92; P<0.001) were predictive of functional independence at 3 months with statistical significance. In the multivariate logistic regression analysis adjusted for age, gender, onset-to-door time, baseline NIHSS score, ASPECTS, and ASU care, the effect of TPA remained independently significant (OR=15.2; 95% CI, 2.6-87.3; P=0.02).

Two secondary outcomes were also in favour of the TPA group (Table 2). Thus, 29% (14/48) of TPA-treated patients were discharged home directly from ASU, compared to 6% (4/63) for the non-TPA group (P<0.001). Moreover, 63% of the TPA and 87% of the non-TPA group were referred to the rehabilitation ward (P=0.001). The respective values for mean (± SD) total LOS including acute and rehabilitation phases were 25 ± 24 versus 35 ± 21 days (P=0.034). There was no significant difference in the respective proportions discharged to nursing home in the two groups (25% vs 30%; P=0.29).

To assess the ICH rate, follow-up CTs or MRIs were available for 46 of 48 TPA patients. Arrangement for follow-up scan was overlooked in one patient whose NIHSS score decreased from 21 to 7 on day 1. Another patient with terminal internal carotid artery occlusion succumbed within 12 hours of onset, and no follow-up scan was performed for the moribund patient as the families opted for comfort care. We assumed the second patient to have SICH based on rapid neurological deterioration. In all, ICH was detected on follow-up scans of nine patients; in eight

TABLE 1. Baseline characteristics of the patients*

Baseline characteristic	TPA (n=48)	Non-TPA (n=63)	P value
Age (years)			
Mean ± SD	74 ± 10	72 ± 10	0.23
Median (range)	74 (51-94)	74 (46-88)	0.39
Male	21 (44%)	33 (52%)	0.44
Diabetes mellitus	12 (25%)	24 (38%)	0.16
Hypertension	39 (81%)	52 (83%)	1.00
Hyperlipidaemia	33 (69%)	46 (73%)	0.68
Ischaemic heart disease	6 (13%)	5 (8%)	0.52
Atrial fibrillation	27 (56%)	32 (51%)	0.70
Prior ischaemic stroke	11 (23%)	12 (19%)	0.64
On aspirin	13 (27%)	26 (41%)	0.16
On warfarin	4 (8%)	0	0.03
Ischaemic stroke subtype			
Atherothrombosis	5 (10%)	13 (21%)	0.20
Cardioembolism	27 (56%)	32 (51%)	0.70
Lacune	6 (13%)	9 (14%)	1.00
Undetermined and others	10 (21%)	9 (14%)	0.45
NIHSS score			
Mean ± SD	15 ± 7	15 ± 8	0.63
Median (range)	16 (5-32)	13 (5-36)	0.43
Median ASPECTS (range)†	9 (4-10)	8 (4-10)	0.13
ASPECTS ≤7†	12 (34%)	15 (39%)	0.81
Onset-to-AED time (minutes)			
Mean ± SD	63 ± 33	80 ± 39	0.01
ASU care	48 (100%)	52 (83%)	0.002

* TPA denotes tissue plasminogen activator, SD standard deviation, NIHSS National Institutes of Health Stroke Scale, ASPECTS Alberta Stroke Programme Early CT Score, AED accident and emergency department, and ASU acute stroke unit

† ASPECTS applicable in 35 TPA-treated and 38 non–TPA-treated patients

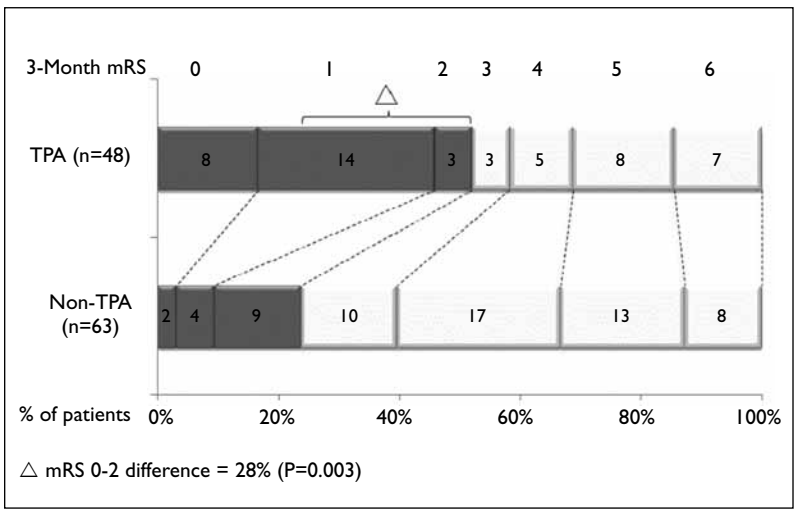


FIG 1. Comparison of 3-month modified Rankin Scale (mRS) scores in the thrombolysis and non-thrombolysis groups

Bar chart numericals denote number of patients, and TPA tissue plasminogen activator

they were regarded as asymptomatic haemorrhagic transformation (HT). One patient with a right middle cerebral artery territory infarct developed symptomatic parenchymal haemorrhage (PH) of the left cerebellum plus HT of the infarct site. Together with the aforementioned patient with presumed SICH, the SICH rate was 4% for the TPA group. The ASPECTS were 6 for both patients with SICH. As there was no mandatory requirement to perform a follow-up scan for non-TPA patients, it was not available in nine; none of whom had neurological deterioration during their admission. These nine patients were assumed to have no SICH. For those with follow-up scans, one had a SICH (2%) with PH at the infarct site, nine had asymptomatic HT, and two had asymptomatic PH. The rates of SICH were not statistically different in the two groups (P=0.58).

The respective 3-month mortality rate was similar in the TPA and non-TPA groups (15% vs 13%; P=0.51). Four TPA patients died in ASU between days 1 and 8, of whom one died from assumed SICH and three from massive infarction. Two died of urinary tract infections while in the rehabilitation ward and one died of chest infection after discharge to the nursing home. In the non-TPA group, four patients died in acute wards—one from SICH and three from a massive infarction. Another four died during rehabilitation, two from chest infections, one from subsequently diagnosed lung cancer, and one from massive internal bleed from a ruptured splenic artery aneurysm.

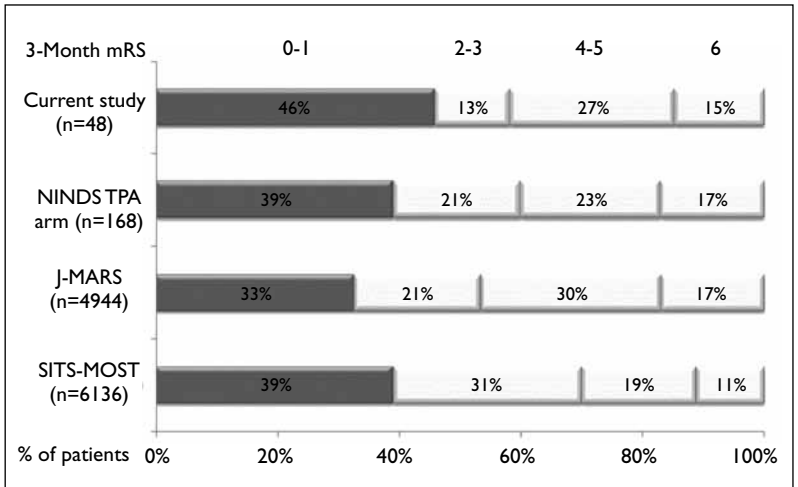
TABLE 2. Secondary outcomes of the patients*

Secondary outcome	Mean ± SD or No. (%)		P value
	TPA (n=48)	Non-TPA (n=63)	
Total length of stay (days)†	25 ± 24	35 ± 21	0.034
Acute ward (days)	7 ± 3	8 ± 5	0.12
Rehabilitation ward (days)‡	30 ± 24	31 ± 19	0.82
Directly discharged home from ASU/ acute ward†	14 (29%)	4 (6%)	<0.001
Transferred to rehabilitation ward	30 (63%)	55 (87%)	0.001
Final discharge destination			
Final discharge destination of nursing home†	12 (25%)	19 (30%)	0.29
Final discharge destination of home	30 (63%)	35 (56%)	0.44
Home with mRS ≥3	6 (13%)	20 (32%)	0.001

* SD denotes standard deviation, TPA tissue plasminogen activator, ASU acute stroke unit, and mRS modified Rankin Scale score

† Pre-specified secondary outcomes

‡ TPA group (n=30) and non-TPA group (n=55)



(Age and baseline NIHSS score of above studies)

	Age (years)	Baseline NIHSS (median)
Current study	74 (mean and median)	15.5
NINDS TPA[1]	69 (mean)	14
J-MARS[5]	71 (median)	15
SITS-MOST[12]	68 (median)	12

FIG 2. Comparison of 3-month modified Rankin Scale (mRS) scores in the current thrombolysis patients and previous reports

Bar chart numericals denote percentage of patients, TPA tissue plasminogen activator, and NIHSS National Institutes of Health Stroke Scale

Discussion

Although clinical trial results originating from western populations cannot be generalised to other ethnicities without scrutiny, it would be impractical to repeat trials for stroke thrombolysis based on racial difference alone. Uncertainty and conservatism, however, have contributed to delays in approval from regulatory bodies for its use in some non-Caucasian regions.[3,18] A higher haemorrhagic complication rate was feared for Chinese and Japanese, and the optimum TPA dosage for orientals remains controversial.[19] Cost and infrastructural deficiency for time-critical conditions like AIS, in addition to scepticism about its efficacy by clinicians,[20] have resulted in a low thrombolysis rate.

Our study focused on some of these concerns regarding stroke thrombolysis for Chinese patients in the local clinical setting. At 3 months, 52% and 46% of TPA-treated patients achieved mRS scores of ≤2 and ≤1, respectively. Although inclusion criteria differ, our results were comparable to the NINDS trial part-two TPA-arm (mRS score ≤1=39%[1]), Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST; mRS score ≤2=55%, ≤1=39%[21]), and multi-centre registries of Taiwan (mRS score ≤2=53%, ≤1=39%[3]), and Japan (mRS score ≤1=33-39%[5]) [Fig 2]. Of note, our patients were older, had higher median NIHSS scores, and we did not include mild strokes with NIHSS scores of ≤4. On the other hand, our treatment decision was based on both time and tissue windows. We exercised discretion in administering TPA to patients with low ASPECTS even if they presented within the time window. Although

this might create patient selection bias in our study, it is reasonable in daily clinical practice to balance risk and benefit in individual patients.

The proportion of TPA-treated patients achieving functional independence at 3 months was more than double that of the non-TPA group. The difference was even more marked if mRS scores of ≤1 were used for comparison (46% vs 10%). For a retrospective cohort study prone to selection and assessment bias, the net benefit was likely to be exaggerated. In our study, both groups were naturally well-matched for baseline characteristics. We also used mRS as an outcome measure, which was less likely to be influenced by assessor bias compared to the Barthel index and NIHSS score, and our radiological assessment for ICH was blinded to patient information. Nevertheless, a number of limitations remained due to our study design: (1) Blinded assessment of mRS score was not achieved in our routine clinical practice, and assessor bias was only minimised by structured interview. (2) Eight patients otherwise eligible for IV TPA with ASPECTS 4-7 were treated with IAT. They were expected to fare poorer if IV TPA was given, and would have had a negative impact on overall outcome by potentially lowering the rate of 3-month mRS scores of ≤2 from 52% to 45%. (3) Patients with severe deficits on presentation but spontaneously recanalised and recovered to NIHSS score of ≤4 within the first few hours were not captured into the non-TPA group, although we estimated the number of these patients to be small.[22] (4) Non-TPA patients were admitted after-hours, during weekend or public holiday. Their initial care was not provided by stroke physicians, and their neurological assessment might be less intense than those with TPA treatment. (5) Clinicians were less aggressive in the choice of supportive therapy (eg antibiotics) for non-TPA patients who sustained massive infarcts, as opposed to more intensive treatment and rehabilitation for TPA patients who were perceived to have a higher potential for recovery. This last confounder reflects that the real-life difference thrombolysis has made on clinicians' overall attitudes towards treatment of AIS in favour of patients. Hence, we believe, whilst the comparison is flawed, its clinical relevance remains valid.

The 3-month mortality rate of 15% for our TPA group was higher than 11% in SITS-MOST which recruited younger patients, Caucasians patients with less severe strokes,[21] and 10% of younger, predominantly Chinese patients in a Singaporean study.[4] Our rate was closer to that of Japanese registry (13%) with similar baseline characteristics.[5] The SICH rate of 4% was in line with previous Caucasian, Japanese, and Chinese studies.[3,5,21] Our results should add weight to the argument that stroke thrombolysis is just as safe in Chinese patients, although the optimal TPA dosage could not be evaluated from our study due to incomplete BW data.

A full analysis of stroke thrombolysis economics was beyond the scope of this study, but several observations were made. Patients treated with TPA were more likely to be directly discharged home from acute wards and had shorter overall LOS. Although similar proportions were discharged to nursing homes, the functional status of non-TPA patients who ultimately returned home was poorer. Nearly two-thirds (20/35) remained carer-dependent (mRS score, 3-5), as opposed to one-fifth of TPA-treated patients (6/30) [Table 2]. We believe the mismatch in functional outcome and discharge destination might partially be accounted for by the availability of foreign domestic maids in Hong Kong, which made homecare of disabled persons more manageable. As the direct increase in cost associated with stroke thrombolysis is offset by long-term savings in nursing home care and social costs,[23] how local customs influences the cost-effectiveness of stroke thrombolysis in this region requires further investigation.

In conclusion, our study pragmatically compared the outcomes of AIS patients treated with thrombolysis in our local setting, to those who were not. While the benefit of thrombolysis appeared compelling, multiple confounders of this non-randomised study should be recognised. Nevertheless, a fledging stroke thrombolysis service in Hong Kong for predominantly Chinese patients seemed safe and efficacious. From a clinical perspective, thrombolysis is the standard of care for eligible stroke patients. In a real world where health resource is limited, improving thrombolysis coverage remains one of the top challenges for stroke physicians.

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