ORIGINAL ARTICLE

Intravenous thrombolysis for multi-ethnic Asians with acute ischaemia stroke in Malaysian public primary stroke centres versus acute stroke ready hospitals: Comparison of real-world clinical outcomes

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ABSTRACT

Introduction: Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator is beneficial in acute ischaemic stroke (AIS). We aim to compare the real-world clinical outcomes and service efficiency of IVT in Malaysian primary stroke centres (PSCs) versus acute stroke ready hospitals (ASRHs).

Materials and Methods: We conducted a multi-centre cohort study involving 5 PSCs and 7 ASRHs in Malaysia. Through review of medical records of AIS patients who received IVT from 01 January 2014 to 30 June 2021, real-world data was extracted for analysis. Univariate and multivariate regression models were employed to evaluate the role of PSCs versus ASRHs in post-IVT outcomes and complications. Statistical significance was set at p<0.05.

Results: A total of 313 multi-ethnic Asians, namely 231 from PSCs and 82 from ASRHs, were included. Both groups were comparable in baseline demographic, clinical, and stroke characteristics. The efficiency of IVT delivery (door-to-needle time), functional outcomes (mRS at 3 months post-IVT), and rates of adverse events (intracranial haemorrhages and mortality) following IVT were comparable between the 2 groups. Notably, 46.8% and 48.8% of patients in PSCs and ASRHs group respectively (p=0.752) achieved favourable functional outcome (mRS≤1 at 3 months post-IVT). Regression analyses demonstrated that post-IVT functional outcomes and adverse events were independent of the role of PSCs or ASRHs.

Conclusion: Our study provides real-world evidence which suggests that IVT can be equally safe, effective, and efficiently delivered in ASRHs. This may encourage the establishment of more ASRHs to extend the benefits of IVT to a greater proportion of stroke populations and enhance the regional stroke care.

KEYWORDS:
Acute ischemic stroke, thrombolysis, stroke ready hospitals, functional outcomes, efficiency, safety

INTRODUCTION

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) has been a well-established emergency intervention in acute ischaemic stroke (AIS) since 1995.[1-9] However, such therapy may not be readily available in district/community hospitals, especially in countries with lower neurologist: population ratio. We hypothesise that as (i) the efficacy of IV rt-PA has been extensively proven,[1-7] (ii) coupled with the presence of objective, internationally standardised indications and contraindications of IV rt-PA in AIS,[1-2,9] (iii) in addition to the availability of local evidence-based protocol and (iv) the growing use of telemedicine to guide decision-making, IVT can potentially be administered in these district/community hospitals without neurologist in a timely, safe and effective manner.

Accordingly, evidence has consistently shown the beneficial effects of IVT in AIS even when administered by non-neurologists in non-stroke centres.[10-12] However, similar targeted research involving multi-ethnic Asian populations in this region is scarce. We aim to appraise and compare the real-world efficiency, effectiveness and safety of IVT among multi-ethnic Asians in Malaysian public primary stroke centres (PSCs) versus acute stroke-ready hospitals (ASRHs).

MATERIALS AND METHODS

We conducted a multi-centre cohort study (combination of historical, retrospective and prospective cohort) involving analyses of real-world data. This real-world study involved five public PSCs and seven public ASRHs in Malaysia. Qualifying criteria of PSCs and ASRHs were in accordance

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with the American Stroke Association & The Joint Commission Stroke Certification criteria. The five PSCs were Sarawak General Hospital, Queen Elizabeth Hospital, Sultanah Nur Zahirah Hospital, Seberang Jaya Hospital and Raja Permaisuri Bainun Hospital. Meanwhile, the seven ASRHs were Tawau Hospital, Taiping Hospital, Bintulu Hospital, Miri Hospital, Sarikei Hospital, Sultan Abdul Halim Hospital and Lahad Datu Hospital. Clinical data were collected through a review of medical records and extracted from the local stroke registry.

The data collection period was from December 2019 to December 2021. All patients who received IVT from 1 January 2016 to 31 December 2021 in these 12 study centres were potential subjects. These patients were being followed up for functional outcomes in Modified Rankin Scale (mRS) and mortality status. Assessments findings were documented contemporaneously in their medical records and stroke registries. This study was a combination of historical, retrospective and prospective cohort study as we included patients who (i) received IVT and had at least 3 months of follow-up post-IVT at the beginning of data collection period (historical cohort); (ii) received IVT and were still under ongoing follow-up at the beginning of data collection period (retrospective cohort); (iii) received IVT within the data collection period, followed by the standard follow-up for at least 3 months (prospective cohort).

The first author (S.J.P.), who is also the principal and coordinating investigator of the study, had full access to the data. The authors vouch for the accuracy and completeness of data, in addition to strict adherence to study protocol and statistical analysis.

Study Populations/Patients

Our inclusion criteria were patients (i) with clinical diagnosis of AIS according to WHO criteria[13], (ii) age of ≥18 years at the time of receiving IVT, (iii) received IVT within 4.5 hours from AIS onset, at a dose of 0.9 mg/kg and maximum 90 mg, (iv) ≥3 months of follow-up after IVT. Patients who died within 3 months post-IVT were included in the analyses on mortality outcome. Exclusion criteria were patients (i) aged <18 years at the time of receiving IVT, (ii) received IVT in an extended window, i.e., >4.5 hours after AIS onset, (iii) received other reperfusion therapies (e.g. intra-arterial thrombolysis, mechanical/endovascular thrombectomy) within 90 days post-IVT, (iv) no data on door-to-needle time (DNT), intracranial haemorrhages following IVT, mRS at 3 months post-IVT and mortality up to 3 months post-IVT. Anonymized real-world data were collected through a review of medical records and local stroke registry. Informed consent was obtained from all study subjects, approving the use of their anonymised data in analyses and publication of findings.

Clinical Assessments and Outcome Measures

Subtypes of AIS among study patients were grouped according to the TOAST classification.[14] These five subtypes were (i) large artery atherosclerosis, (ii) small vessel occlusion, (iii) cardioembolism, (iv) other determined aetiologies and (v) undetermined aetiologies. Stroke severity upon presentation, measured by National Institutes of Health Stroke Scale (NIHSS), was assessed by neurologists in PSCs and trained physicians in ASRHs, respectively. The Alberta Stroke Program Early CT Score (ASPECTS) were evaluated and reported by radiologists.[15,16]

The onset-to-needle time (ONT) was defined as the duration from the onset of AIS symptoms to the time of IVT administration. The DNT was defined as the duration from the time of patient's arrival at emergency department to the time of first bolus dose of thrombolytic. mRS was employed to measure the degree of disability. Intracranial haemorrhages (ICH) following IVT, namely (i) any ICH, (ii) symptomatic ICH (sICH) as per ECASS III definition[2] and (iii) fatal ICH were recorded. Mortality following IVT, namely (i) inpatient mortality, i.e., mortality within the same/index hospital admission and (ii) all-cause mortality within 3 months (90 days) post-IVT, were recorded.

AIS characteristics and severity upon presentation were evaluated by using TOAST subtypes, NIHSS and ASPECTS score. The efficiency of IVT delivery was evaluated through DNT and proportion of patients with DNT <60 minutes. The effectiveness of IVT was assessed through mRS at 3 months (90 ± 5 days), number of patients with favourable functional outcomes (mRS ≤1 at 3 months) and unfavourable functional outcomes (mRS ≥ 2 at 3 months). Meanwhile, safety of IVT was assessed by rates of any ICH, sICH, fatal ICH, inpatient mortality and 90 days all-cause mortality.

Statistical Analysis

Statistical Package of Social Sciences (SPSS) for Windows version 28.0 (IBM Corporation, Armonk, NY, USA) was employed. Baseline demographic and clinical characteristics were presented as absolute numbers and percentage for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile ranges for continuous variables with skewed distribution or ordinal data. Shapiro–Wilk test was used to assess the normality of data distribution.

Upon comparing the variables between two groups (PSCs versus ASRHs), the independent sample t test and Mann–Whitney U test were used for the analyses of continuous variables, while Pearson's chi-square and Fisher's exact test were used for the analyses of categorical variables. A two-sided P value of <0.05 was considered statistically significant. Univariable and multivariable logistic regression analyses were conducted to investigate the association between various outcomes of interest and independent variables. All variables with p value of <0.1 in the univariable analyses were included in the final multivariable analyses. The results were presented in the form of crude odds ratios (OR) and adjusted OR with the respective 95% confidence interval (CI). P value of <0.05 signifies statistical significance.

Standard Protocol Approvals and Study Registrations

This study was registered with the Malaysian National Medical Research Register (study ID: NMRR-19-3731-52272). Study protocol was approved and supported by the National Institutes of Health Malaysia. Ethical approval was obtained from the Malaysian Medical Research and Ethics Committee. Approval for publication was granted by the Director-General of Health Malaysia.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was conducted in strict compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Strictly no minor nor vulnerable subjects were enrolled in the study. Only anonymised, non-identifying data were extracted/collected.

RESULTS

A total of 313 multi-ethnic Asian patients, namely 231 (73.8%) from PSCs and 82 (26.2%) from ASRHs were included. The baseline demographic (age, gender, ethnicity) and clinical characteristics (comorbidities/vascular risk factors) of these two groups of patients were comparable, with the exception of the proportions of active smokers. Rates of prior antiplatelet and/or anticoagulant use within 7 days prior to stroke onset were similar in both PSCs and ASRHs groups (29.0% vs 29.3%) as well. Types of antiplatelets and anticoagulants used were listed in Table I.

Stroke Characteristics and Severity at Presentation

These two groups of patients demonstrated similar proportions in each TOAST subtype. Both groups recorded comparable NIHSS upon presentation, namely a median NIHSS of 11 (IQR: 8–17) in PSCs and a median NIHSS of 12 (IQR: 9–16) in ASRHs (p = 0.833). Both groups also have comparable ASPECTS, with a median ASPECTS of 9 (IQR: 8–10) in both PSCs and ASRHs (p = 0.879) groups (Table I).

Efficiency of Delivery of IVT

Both groups recorded similar ONT. Notably, the DNT was comparable between the two groups as well, namely a median of 85 (IQR: 56–118) minutes in PSCs and a median of 93 (IQR: 60–125) minutes in ASRHs, p = 0.470. In addition, the proportion of patients with DNT <60 minutes was similar, namely 30.7% in PSCs and 30.5% in ASRHs, p = 0.967 (Table II).

Clinical Outcomes Following IVT

mRS at 3 months was identical between the two groups, with a median of 2 (IQR: 1–4) in PSCs and 2 (IQR: 1–3) in ASRHs, p = 0.707. Percentage of patients with favourable functional outcomes, i.e., mRS ≤ 1 at 3 months post-IVT, was comparative as well, namely 46.8% in PSCs and 48.8% in ASRHs, p = 0.752 (Table II and Figure 1 mRS bar chart).

Haemorrhages and Mortality following IVT

Both PSCs and ASRHs groups demonstrated similar rates of (i) any ICH, 17.7% vs 18.3%, p = 0.912; (ii) symptomatic ICH, 10.4% vs 7.3%, p = 0.417; (iii) fatal ICH, 3.9% vs 4.9%, p = 0.749, (iv) inpatient mortality, 13.9% vs 11.0%, p = 0.507 and (v) all-cause mortality within 90 days post-IVT, 15.2% vs 14.6%, p = 0.910. Causes of death were listed in Table II. The most common causes of death in both groups were fatal ICH, pneumonia and acute coronary syndrome (Table II).

Subgroups Analyses

Among the 313 study patients, 148 patients (47.3%) had favourable functional outcomes (mRS ≤1) whereas 165 patients (52.7%) had unfavourable functional outcomes (mRS ≥2) at 3 months post-IVT. Patients with favourable functional outcomes demonstrated significantly (i) younger age, (ii) lower NIHSS at presentation, (iii) higher ASPECTS at presentation, (iv) shorter DNT, (v) greater proportion with DNT <60 minutes and (vi) lower rates of ICH. These two groups of patients are comparable in terms of gender, ethnicity, comorbidities/vascular risk factors, and TOAST subtype (Table III).

Univariable and Multivariable Logistic Regression Analyses

Among the overall cohort of 313 patients, factors that were significantly associated with favourable functional outcomes (Table IV) include (i) younger age, (ii) lower NIHSS at presentation, shorter DNT and (iv) absence of sICH. Notably, functional outcomes were independent of the role of PSCs or ASRHs, gender, ethnicity and comorbidities/vascular risk factors.

Factors significantly associated with any type of post-IVT ICH among the overall cohort of 313 patients (refer Supplementary Table I) included (i) older age and (ii) higher NIHSS at presentation. Meanwhile, factors significantly associated with sICH (refer Supplementary Table II) included (i) lower ASPECTS at presentation and (ii) longer DNT. The role of PSCs versus ASRHs, age, gender, ethnicity, comorbidities/vascular risk factors, NIHSS at presentation and antiplatelet or anticoagulant use were not significantly associated with ICH.

In addition, factors significantly associated with 90-day all-cause mortality among the overall cohort of 313 patients (refer Supplementary Table III) included (i) longer DNT and (ii) presence of sICH, regardless of the role of PSCs vs ASRHs, age, gender, ethnicity, comorbidities/vascular risk factors, NIHSS and ASPECTS at presentation.

In the PSC cohort, (i) factors significantly associated with favourable functional outcomes (refer Supplementary Table IV) included lower NIHSS at presentation, shorter DNT and absence of sICH; (ii) factors significantly associated with any type of post-IVT ICH (refer Supplementary Table V) included lower ASPECTS at presentation and longer DNT; (iv) factors significantly associated with post-IVT sICH (refer Supplementary Table VI) included female gender, lower ASPECTS at presentation, and longer DNT and (v) factor significantly associated with overall 90-day all-cause mortality (refer Supplementary Table VII) included older age and longer DNT.

In the ASRH cohort, (i) factors significantly associated with favourable functional outcomes (refer Supplementary Table VIII) included younger age and lower NIHSS at presentation and (ii) factors significantly correlated with overall 90-day all-cause mortality (refer Supplementary Table IX) was lower ASPECTS at presentation.

DNT ≤60 Minutes Versus DNT >60 Minutes

Almost equal proportion of patients, namely 30.7% in PSCs and 30.5% in ASRHs, recorded DNT ≤60 minutes. Among the overall cohort of 313 study patients, 96 (30.7%) recorded DNT ≤60 minutes while 217 (69.3%) recorded DNT >60 minutes. Subsequently, 59 (61.5%) of the 96 patients with DNT ≤60

Table I: Baseline Demographic, Clinical and Stroke Characteristics

Patient's characteristics	PSCs (n = 231)	ASRHs (n = 82)	P value
Age (mean ± S.D.)	57.4 ± 13.1	56.4 ± 12.6	0.540[I]
Gender (male:female)	150:81	54:28	0.881[II]
	64.9%:35.1%	65.9%:34.1%	
Ethnicity (Malay:Chinese:Indian:Others)	129:31:14:57	41:14:8:19	0.537[III]
	55.8%:13.4%:6.1%:24.7%	50.0%:17.1%:9.8%:23.2%	
Diabetes mellitus	80/231 (34.6%)	28/82 (34.1%)	0.937[II]
Hypertension	152/231 (65.8%)	58/82 (70.7%)	0.414[II]
Dyslipidemia	63/231 (27.3%)	29/82 (35.4%)	0.167[II]
Coronary artery disease	46/231 (19.9%)	15/82 (18.3%)	0.750[II]
Atrial fibrillation/flutter	39/231 (16.9%)	13/82 (15.9%)	0.830[II]
Valvular heart diseases	5/231 (2.2%)	1/82 (1.2%)	1.000[III]
History of previous CVA/TIA	33/231 (14.3%)	12/82 (14.6%)	0.938[II]
Smoking (active smokers)	87/231 (37.7%)	43/82 (52.4%)	0.020[II]
Prior antiplatelet/anticoagulant use	67/231 (29.0%)	24/82 (29.3%)	0.964[II]
I. Aspirin	52/67	18/24	
II. Clopidogrel	3/67	1/24	
III. Warfarin	7/67	4/24	
IV. NOACs	2/67	1/24	
V. Aspirin + clopidogrel	2/67	0/24	
VI. Aspirin + warfarin	1/67	0/24	
Stroke characteristics			
Subtype (TOAST classification)			
I. Large artery atherosclerosis	102/231 (44.2%)	35/82 (42.7%)	
II. Small vessel occlusion	68/231 (29.4%)	24/82 (29.3%)	N/A
III. Cardioembolism	40/231 (17.3%)	17/82 (20.7%)	
IV. Other determined aetiologies	2/231 (0.9%)	0/82 (0%)	
V. Undetermined aetiology	19/231 (8.2%)	6/82 (7.3%)	
Median NIHSS at presentation	11 (8-17)	12 (9-16)	0.833[IV]
Median ASPECTS at presentation	9 (8-10)	9 (8-10)	0.879[IV]

I. Independent sample t test
II. Pearson's chi square
III. Fisher's exact test
IV. Mann–Whitney U test

Others = natives/indigenous populations of Southeast Asia.
ASRH, acute stroke-ready hospital; CVA, TIA,

minutes recorded favourable functional outcomes while only 89 (41.0%) of the 217 patients with DNT >60 minutes recorded favourable functional outcomes at 3 months, p = 0.001. At 3 months, patients with DNT ≤60 minutes recorded median mRS of 1 (IQR: 0–2) while patients with DNT >60 minutes recorded median mRS of 2 (IQR: 1–4), $p < 0.001$.

DISCUSSION

Comparison of the efficiency, effectiveness and safety of IVT administration in public primary versus acute stroke-ready hospitals were reflected in this real-world study through performance metrics in DNT, functional outcomes by mRS, mortality and rates of intracerebral haemorrhages. Our patients in both public PSC and ASRH cohorts demonstrated similar demographics and baseline clinical characteristics, stroke subtypes as defined by TOAST classifications and stroke severity upon presentation in terms of NIHSS and ASPECTS. Comparable efficiency (DNT), effectiveness (functional outcomes) and safety (ICH and mortality rates) profiles of IVT were recorded in both groups. This may imply that IVT service can be equally safe, effective and efficiently delivered in ASRHs.

As of date, there were only 138 registered neurologists in Malaysia (both public and private sectors), which translates to 1 neurologist to almost 250,000 populations. Thus, there are critical shortage of neurologists to support the IVT service nationwide, especially in East Malaysia. Majority of the rural and remote hospitals are not equipped with in-house neurologists. Hence, there was an increasing need to establish ASRH to extend the benefits of IVT to a greater proportion of stroke patients. In Malaysia, physicians (specialists in Internal Medicine) have taken the initiative to initiate IVT service in some of these centres, guided by telemedicine consultation with neurologists. These physicians are tasked to draft acute stroke protocols and workflows while ensuring strict adherence to the protocol in daily practice.

Challenges and limitations in Malaysian ASRHs include (i) lack of certified expertise namely in-house neurologists; (ii) lack of stroke centres and regional stroke networks in close proximity; (iii) logistic constraints which limit inter-hospital transfer; (iv) lack of established telestroke network or teleradiography system; (v) limited healthcare facilities and (vi) lack of advanced neuroimaging.

The results of our study may proactively advocate the establishment of more ASRHs despite the current challenges and limitations. A few collaborative efforts and initiatives are needed, which includes (i) establishing structured training and certification programme to equip physicians in offering

Table II: Efficiency of IVT delivery,Post-IVT clinical outcomes, Incidence of haemorrhages and mortality

Efficiency of IVT delivery	PSCs (n = 231)	ASRHs (n = 82)	P value
Median onset-to-needle time (minutes)	190 (155–225)	185 (139–226)	0.276[IV]
Median door-to-needle time (minutes)	85 (56–118)	93 (60–125)	0.470[IV]
Door-to-needle time <60 minutes	71/231 (30.7%)	25/82 (30.5%)	0.967[II]
Post-IVT clinical outcomes			
Median 3 months mRS	2 (1–4)	2 (1–3)	0.707[IV]
Favourable functional outcomes (3 months mRS ≤1)	108/231 (46.8%)	40/82 (48.8%)	0.752[II]
Poor functional outcomes (3 months mRS ≥5)	40/231 (17.3%)	14/82 (17.1%)	0.960[II]
Haemorrhages and mortality			
Any intra-cranial haemorrhages (ICH) (including haemorrhagic transformation)	41/231 (17.7%)	15/82 (18.3%)	0.912[II]
Symptomatic ICH (ECASS III definition)	24/231 (10.4%)	6/82 (7.3%)	0.417[II]
Fatal ICH	9/231 (3.9%)	4/82 (4.9%)	0.749[III]
Inpatient mortality	32/231 (13.9%)	9/82 (11.0%)	0.507[II]
I. Fatal ICH	9/32	4/9	
II. Pneumonia	9/32	3/9	
III. ACS and cardiac failure	7/32	1/9	
IV. Severe stroke/massive infarct	4/32	1/9	
V. Other stroke-related complications	3/32	0/9	
90 days all-cause mortality	35/231 (15.2%)	12/82 (14.6%)	0.910[II]
I. Fatal ICH	9/35	4/12	
II. Pneumonia	10/35	4/12	
III. ACS and cardiac failure	9/35	3/12	
IV. Severe stroke/massive infarct	4/35	1/12	
V. Other stroke-related complications	3/35	0/12	

V. Independent sample t test
VI. Pearson's chi square
VII. Fisher's exact test
VIII. Mann–Whitney U test
ASRH, acute stroke-ready hospital; IVT, intravenous thrombolysis; mRS, Modified Rankin Scale; PSC, primary stroke centres.

IVT, (ii) establishing and enhancing telestroke networks and teleradiography system, hence allowing more neurologists and radiologists to remotely support IVT service, (iii) improving inter-hospital patient transfer system and (iv) increasing availability of CT machine in rural/remote areas. The national clinical practice guidelines on stroke management is an essential tool to supplement these efforts as well.

Essentially, there are multiple unmet needs in the provision of IVT in resource-limited settings, namely number of trained professionals, supporting staffs, facilities and information technology (IT) services. However, there are certain measures which can be carried out in the short run, for example, by increasing the number of training platforms/resources online, stroke simulation training or hands-on workshop organised by tertiary stroke centres to address the knowledge gap. Meanwhile, with regards to longer term planning, an increase in budget allocation to procure basic equipments, such as scan machine, beds, blood pressure/cardiac monitoring devices should be prioritised.

Findings of our regression analyses highlight the importance of shortening DNT as it is a modifiable factor significantly associated with favourable functional outcomes. Longer DNT is significantly associated with poorer functional outcomes, sICH and overall 90-day all-cause mortality. Results presented in "Subgroups Analyses" and "DNT ≤60 Minutes Versus DNT >60 Minutes" further supplement such findings. Almost 70% of study patients recorded DNT >60 minutes in both PSCs and ASRHs. Comprehensive data on door-to-CT time and CT-to-needle time was not consistently available across all centres. Hence it is not feasible to determine whether our long DNT was caused by either or both components. However, the causes of our long DNT in general may include (i) delay in decision making and offering consent by patients and/or family (ii) delay in organising neuroimaging due to limited infrastructure and (iii) stroke code workflow unfamiliarity among healthcare personnel.

We hereby propose measures which can be undertaken to shorten DNT: (i) increase public awareness regarding the availability and benefits of IVT in acute stroke through widespread campaign and education nationwide. (ii) equip high-volume public centres with more CT machines to accommodate the increasing patient's loads locally. (iii) minimise delay between steps during stroke code activation by introducing better-structured training and refresher course for stroke care personnel nationwide, (iv) conduct regular quality improvement projects and clinical audits to improve performance and consequentially quality of care and (v) establish telestroke networks involving dedicated neurologists and neuroradiologists in respective states nationwide. This may assist physicians in swift decision-making on IVT with greater confidence, especially in ASRHs.

Table III: Distribution of Modified Rankin Scale (mRS)

Modified Rankin Scale (mRS)	Overall (n = 313) mRS ≤1	mRS ≥2	*p* values
N (%)	148/313 (47.3%)	165/313 (52.7%)	-
Mean age ± SD (years)	53.6 ± 12.3	60.3 ± 12.8	<0.001
Gender (Male:Female)	90:58 61%:39%	114:51 69%:31%	0.125
Ethnicity (Malay:Chinese:Indian:Others)	73:24:8:43 49%:16%:6%:29%	97:21:14:33 59%:13%:8%:20%	0.131
DM	50/148 (34%)	58/165 (35%)	0.799
Hypertension	96/148 (65%)	114/165 (69%)	0.427
Dyslipidaemia	45/148 (30%)	47/165 (28%)	0.710
CAD	26/148 (18%)	35/165 (21%)	0.416
AF	23/148 (16%)	29/165 (18%)	0.629
Valvular CD	5/148 (3%)	1/165 (1%)	0.074
Hx of TIA/CVA	26/148 (18%)	19/165 (12%)	0.128
Active smoking	64/148 (43%)	66/165 (40%)	0.561
Prior antiplatelet/anticoagulant use	47/148 (32%)	44/165 (27%)	0.322
TOAST subtypes			
I. Large artery atherosclerosis	47/148 (31.8%)	90/165 (54.5%)	
II. Small vessel occlusion	62/148 (41.9%)	30/165 (18.2%)	
III. Cardioembolism	24/148 (16.2%)	33/165 (20.0%)	
IV. Other determined aetiology	1/148 (0.7%)	1/165 (0.6%)	
V. Undetermined aetiology	14/148 (9.4%)	11/165 (6.7%)	
Median NIHSS (at presentation)	10 (7–13)	13 (10–20)	<0.001
Median ASPECTS (at presentation)	9 (8–10)	9 (8–9.5)	<0.001
Median onset-to-needle time (minutes)	190 (160–225)	190 (150–230)	0.986
Median door-to-needle time (minutes)	75 (50–104.5)	98 (65–132)	<0.001
DNT <60 minutes	59/148 (39.9%)	37/165 (22.4%)	0.001
Any ICH	10/148 (6.8%)	46/165 (27.9%)	<0.001
sICH	3/148 (2.0%)	27/165 (16.4%)	<0.001
Fatal ICH	0/148 (0%)	13/165 (7.9%)	<0.001
Inpatient mortality	0/148 (0%)	41/165 (24.8%)	<0.001
90 days all-cause mortality	0/148 (0%)	47/165 (28.5%)	<0.001

ICH, intra-cranial haemorrhage.

The strengths of this study include (i) inclusion of 12 public centres nationwide, namely both East Malaysia and Peninsular Malaysia; (ii) inclusion of multi-ethnic Asian patients and (iii) inclusion of all consecutive patients who received IVT in all PSCs and ASRHs in Malaysia. Furthermore, prospective local stroke registries at study centres offer reliable real-world data. Despite not performing propensity score matching, there were no statistically significant differences in demographic, clinical and stroke characteristics upon comparing patients in both PSC and ASRH cohorts. In addition, univariable and multivariable logistic regression analyses with appropriate adjustments were performed to assess the role of ethnicity and types of centres (i.e. PSCs vs ASRHs) in clinical outcomes while identifying factors associated with various outcomes of interest.

Limitations of this study include (i) the observational nature of study; however, this real-world study still offers valuable insights on the benefits of IVT in both PSCs and ASRHs, (ii) lack of comprehensive data on extra-cranial haemorrhages in some study centres; however, there was no significant morbidity or mortality resulted from extra-cranial haemorrhages among all study patients and (iii) lack of detailed data on door-to-CT and CT-to-needle time, however, definite DNT was clearly documented and (iv) lack of detailed standardised blood pressure recording in some patients as the timings of blood pressure measurements were varied (any point from upon arrival to Emergency Department to immediately prior to Alteplase bolus); however, it has been a nationwide standard practice (as per national clinical practice guidelines) that blood pressure must be <185/110 mmHg prior to IVT initiation.

Given the inherent bias in an observational study, statistical adjustment techniques, i.e. logistic regression, have been employed to produce unbiased estimates of effects. Moreover, the findings from this study were replicated in other studies internationally.[10-12] Additional evidence to bolster the potential causal association with longer DNT would be an understanding of the Malaysia's healthcare landscape by the authors and inputs/reviews from the local stroke experts.

Evidence on the provision of IVT by non-neurologists is not expansive so far, especially in resource-limited regions (low-middle income countries) where the neurologist:population ratio is low and substantial proportions of acute stroke patients receive emergency care by non-neurologists. This project, with strengths and limitations as stated, is still among the largest real-world study providing real-world evidence which may suggest comparable IVT safety, effectiveness and service efficiency when administered by non-neurologists in ASRHs as compared to administration by neurologists in PSCs, in a resource-limited setting.

Table IV: Factors associated with favourable outcomes

Odd ratios	Crude OR (95% CI)	*p* value	Adj OR (95% CI)	*p* value
Centre				
ASRH	1.09 (0.66–1.80)	0.752		
PSC	Ref	–		
Age	0.96 (0.94–0.98)	<0.001	0.97 (0.95–0.99)	0.012
Gender				
Female	1.44 (0.90–2.30)	0.125		
Male	Ref	–		
Ethnicity				
Malays	0.58 (0.34–0.997)	0.049	0.52 (0.27–1.02)	0.055
Chinese	0.88 (0.42–1.84)	0.729	0.95 (0.38–2.36)	0.916
Indians	0.44 (0.17–1.17)	0.099	0.43 (0.14–1.33)	0.143
Others	Ref	–	Ref	
Diabetes mellitus				
Yes	0.94 (0.59–1.50)	0.799		
No	Ref	–		
Hypertension				
Yes	0.83 (0.52–1.32)	0.427		
No	Ref	–		
Dyslipidaemia				
Yes	1.10 (0.67–1.79)	0.710		
No	Ref	–		
CAD				
Yes	0.79 (0.45–1.39)	0.417		
No	Ref	–		
Atrial				
Yes	0.86 (0.47–1.57)	0.629		
No	Ref	–		
VHD				
Yes	5.73 (0.66–49.7)	0.113		
No	Ref	–		
CVA /TIA				
Yes	1.64 (0.87–3.10)	0.130		
No	Ref	–		
Anti-platelet/anti-coagulant				
Yes	1.28 (0.79–2.09)	0.323		
No	Ref	–		
Smoking status :				
Current/Ex Smoker	1.14 (0.73–1.79)	0.561		
Non	Ref	–		
NIHSS at presentation	0.85 (0.81–0.90)	<0.001	0.85 (0.81–0.91)	<0.001
ASPECTS	1.67 (1.33–2.11)	<0.001	1.28 (0.997–1.65)	0.053
Onset-to-needle time	1.00 (0.99–1.004)	0.998		
Door-to-needle time	0.988 (0.983–0.994)	<0.001	0.988 (0.981–0.995))	0.001
Symptomatic ICH				
Yes	0.11 (0.03–0.36)	<0.001	0.13 (0.04–0.48)	0.002
No	Ref	–	Ref	–

1. Younger age
2. Lower NIHSS at presentation
3. Shorter DNT
4. No sICH

ASRH, acute stroke-ready hospital; AF, atrial fibrillation; CAD, coronary artery disease; CVA, cerebrovascular disease; TIA, transient ischaemic attack; sICH, symptomatic intracranial haemorrhage; VHD, valvular heart disease; PSC, primary stroke centres.

CONCLUSION

This real-world study may provide translational real-world evidence which suggests that IVT in AIS can be equally safe, effective and efficiently delivered in both PSCs and ASRHs. This may further encourage the establishment of IVT service in some centres without in-house neurologists, hence extending the benefits of IVT to a greater proportion of stroke populations. Accordingly, through collaborative efforts and initiatives, the development of more ASRHs equipped with trained stroke teams should be proactively advocated to enhance regional and international acute stroke care.

DECLARATION OF INTEREST

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