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ORIGINAL ARTICLES

Clinical profile, risk factors and aetiology of young ischaemic stroke patients in Asia: A prospective, multicentre, observational, hospital-based study in eight cities

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Abstract

Background and Objective: There is a lack of international collaborative studies on young adults with ischaemic stroke in Asia. The aim of this study was to investigate risk factors, aetiology and outcome at hospital discharge of these patients across 8 participating countries in Asia. *Methods:* This was a prospective, observational, multicentre, hospital based cohort study. Consecutive young stroke patients with confirmed cerebral infarction between the ages of 18-49 were recruited from December 2011 to May 2012. Data was collected for patient demography, risk factors, investigations, clinical profile and TOAST classification. Outcome measures were death and independence (modified Rankin score≤ 2) at hospital discharge. *Results:* Two hundred and eighteen patients with the mean age was 40.8±6.7 years were recruited. There was a larger proportion of male patients with a ratio of 1.9:1. Traditional risk factors observed were hypertension (n=103; 47.3%), dyslipidaemia (n=93; 42.4%), smoking (n=85; 38.8%), diabetes (n=53; 24.3%), alcohol use (n=33; 15.0%), a previous history of stroke and transient ischaemic attacks (6.4%), family history (n=12; 5.5%), migraine (n=6;2.8%), pregnancy related (n=5; 2.3%) and numerous cardiac risk factors (0.9-5.5%). The majority suffered arterial infarction; n=216 (99.4%) while n=2 (0.6%) had venous strokes. The predominant stroke subtypes were large artery atherosclerosis (LAA); 29.8% and small vessel occlusion (SVO); 20.2%. LAA and SVO accounted for 37.5% of all stroke subtypes in the ≤36 year age-group. Cardioembolism (15.1%) and stroke of determined aetiology (14.7%) contributed to the other categories of identified stroke subtypes. Mortality on hospital discharge was 3.1% while 65.1% of patients were independent on discharge.
Conclusion: This study demonstrated the substantial presence of premature atherosclerosis and conventional risk factors in young ischaemic stroke patients from 8 Asian cities. Venous infarction from cerebral venous thrombosis was rare in this study. Outcome on hospital discharge was poorer compared to Western studies. Detection of vascular risk factors and primary prevention measures should be initiated during late adolescence or early adulthood in urban Asia.

INTRODUCTION

Stroke is the most common cause of adult disability globally. Younger patients with stroke (under the age of 50), account for 5-10% of all strokes worldwide. The majority of studies on young stroke patients have been conducted in homogenous populations within national boundaries. Many of such studies have observed notable variations in the proportions of risk factor profiles and stroke subtypes as well as a broad spectrum of less common causes for ischaemic stroke such as moya-moya syndrome, non-atherosclerotic vascular diseases such as dissection

and vasculitis, systemic lupus erythematosus and substance abuse across different countries and regions.[1-10]

There is a lack of international, multicentred studies on young adults with cerebral infarction in Asia. As such, the Asian Stroke Advisory Panel (ASAP) provided an ideal platform for this effort. Briefly, ASAP was founded in 1996 and consisted of a group of academic neurologists who were interested in the study of stroke in Asia. Research projects that were relevant to the region were formulated by consensus and implemented in the respective countries. Previous projects culminated in publications and provided data for important research issues in Asia.[11-13] This study aimed to clarify the aetiological diagnoses, patterns of disease burden, clinical profille and outcome in young adults with cerebral infarction across several geographical regions in Asia.

METHODS

This was a multicentre, prospective, observational cohort study. The centres were located in major cities in the People's Republic of China, Hong Kong, South Korea, Malaysia, Pakistan, Philippines, Taiwan and Thailand. The relevant investigators enrolled consecutive young ischaemic stroke patients who were admitted into their respective hospitals from December 2011 to May 2012. Clinical parameters were collected through a standardized data collection form for patient demography, classification according to Oxfordshire Community Stroke Project (OCSP) criteria and risk factors. These patients were also investigated for stroke aetiologies and further classified by TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria. Functional outcome on discharge was recorded with modified Rankin scale (mRS). Each centre received approval from their respective institutional review board to conduct the study. Patients included in the study were evaluated and investigated according to the investigators' practice and on local resources.

Risk factors were defined in the following manner. Hypertension was defined as previous BP above 140/90 mm Hg or in the presence of previous specific therapy. Dyslipidaemia was defined as total cholesterol level of $\geqslant$ 5.2 mmol/l, triglyceride levels $\geqslant$ 1.8mmol/l and HDL $\leqslant$ 1 mmol/l. Diabetes mellitus was defined as elevated fasting blood glucose above 6.1mmol/l or HbA1c $\geqslant$ 7% or previously on oral hypoglycaemic or insulin injections. Current smokers were defined as patients who smoked $\geqslant$ 10 cigarettes per day for more than 1 year. Significant alcohol consumption was defined as $\geqslant$ 30 g of ethanol per day. Investigations included imaging studies to evaluate the intracranial, extracranial and cardiac status of stroke patients from both centres. Other investigations included chest radiography, ECG, fasting lipid profile, fasting glucose, HbA1c, thrombophilia screen and immunologic studies (anti-nuclear, anti-DNA and anti-ENA antibodies) were also performed where clinically indicated. The decision to perform these ancillary tests were left to the treating clinicians. The stroke events were classified according to the TOAST classification by the respective investigators. The categories were: (1) Large artery atherosclerosis (LAA); (2) Small-vessel occlusion (SVO): Lacunar syndrome and normal CT/MRI or relevant lesion <1.5cm and absent source of emboli; (3) Cardioembolism (CE); with potential large artery atherosclerotic sources of thrombosis or embolism absent; (4) Other determined aetiologies (OD); (5) Undetermined causes (UD): Two or more causes identified, negative evaluation or incomplete evaluation. All completed data forms were sent to the first author (KST) for data entry and analysis. Student's t-test for numerical variables and chi square test were used for categorical variables. All statistical tests were two-tailed and performed with The Statistical Package for Social Science (SPSS Inc., Chicago, USA; version 15.0 for Windows).

RESULTS

Two hundred and thirty four patients were enrolled from 8 centres across Asia. Sixteen patients were excluded due to inadequate imaging and clinical data. Hence, data from 218 patients were analysed. (Table 1) The mean age was 40.8±6.7 years (range 18-49). There was a larger proportion of male patients; n=143 (65.3%) compared to female patients; n=75 (34.4%). Traditional risk factors observed were hypertension (47.2%), dyslipidaemia (42.6%), smoking (38.9%), diabetes (24.3%) and alcohol use (15.1%). Other risk factors noted were a previous history of stroke and transient ischaemic attack(6.4%), family history(5.5%), migraine(2.8%), pregnancy related states (2.3%) and numerous pre-existing cardiac diseases (0.9-5.5%). Patent foramen ovale was noted to exist in n=6 (2.8%) of all the cases evaluated. Less common but recognized risk factors in descending order of frequency were malignancy, substance abuse, systemic lupus erythematosus, radiation angiopathy,

hyperviscosity states, moya-moya disease and oral contraceptive pill. These less common conditions were found in 0.5% to 2.2% of the entire cohort. The complete list of risk factors, demographic profile and country of origin were summarized in Table 1.

The majority of the ischaemic stroke patients were arterial strokes; n=216 (99.4%) while n=2 (0.6%) were venous strokes. The clinical presentations according to the OCSP classification (Table 6) were partial anterior circulation infarction (50.4%), followed by lacunar infarction (23.4%) and posterior circulation infarction (17.9%). With reference to stroke aetiology, the predominant stroke subtypes were LAA (29.8%) and SVO (20.6%), contributing up to half of the entire cohort of patients. CE (15.1%) and stroke of determined aetiology (14.7%) made up the other categories of identified stroke subtypes. The OD category consisted of recognized causes of ischaemic strokes which include migrainous infarction [n=6; (2.8%)], vascular dissection [n=5; (2.3%)], systemic lupus erythematosus [n=3; (1.4%)], substance abuse [n=4; (1.8%)], haematological disorders including acquired coagulopathies [n=6; (2.8%)] and moya-moya disease, n=2 (0.9%). Stroke of UD was 20.6%. About half of this sub-group were contributed by negative evaluation. The proportions derived from TOAST classification were summarized in Table 3.

In terms of investigations, all patients that were included in this study had neuroimaging either with computed tomography (CT) scan or magnetic resonance (MR). Of the cohort of patients, 73% had CT scan performed while 72% had MR imaging, 47% had both MRI and CT brain. Other non-invasive imaging modalities that were performed in more than 50% of patients were magnetic resonance angiography (60.8%), transcranial Doppler (51.7%) and extracranial carotid Duplex ultrasound (53.4%). The level of brain parenchyma and vascular imaging had been substantial, given the multiple overlapping investigations described above. Transthoracic echocardiogram was performed in 60% of the cohort while an additional 17.8% of the patients had transoesophageal echocardiogram performed. Interestingly, cerebral angiography was not commonly performed either for diagnostic or therapeutic purposes. Of the entire cohort, 6.9% had conventional 4 vessel angiography performed while only one patient (0.45%) had an invasive interventional procedure performed. CT angiography was also not frequently performed despite its inherent advantage. This was performed in 11.8% of patients.

Relevant blood investigations' results which were performed during the index hospital admission were as follows: Serum glucose on admission was performed in 87.6% of patients and abnormal in 29.3%. Interestingly, HbA1c was performed in 52.5% and was abnormal in 18% of the patients. The hypercoagulable panel was performed in less than 26% of patients. From the tests performed, abnormally low levels were detected for Protein C (3.2%), Protein S (6%) and antithrombin III (5.5%). These tests were not repeated as this study ended hospital discharge. Thus, any form of hypercoaguable state was not confirmed by a repeat study. Other ancillary tests such as homocysteine levels were performed in less than 25% of patients with elevated levels detected in only 4% of patients. Anticardiolipin antibody and lupus anticoagulant levels were performed in about 30% of patients and only significantly elevated in 1.4%.

The short term outcome on hospital discharge was dichotomized to good outcome (mRS 0-2) and poor outcome (mRS 3-6). Seven patients (3.2%) were dead before hospital discharge while 31.65% (n=69) had poor outcome at hospital discharge. Of the entire cohort, 65.1% (n=142) was observed to have good outcome. Overall, patients classified as LAA on TOAST were observed to have poor outcome (p=0.02; 95%CI 1.10-3.62) while those with SVO had better outcomes. (p=0.0007; 95%CI 1.78-10.9). Both results were statistically significant. There was a trend towards statistical significance in the OD category. This was not surprising, given that 38% (n=12) of patients in this group had malignancy (n=4), systemic lupus erythematosus (n=3) and pregnancy related strokes (n=5). (Table 4)

When we stratified our data to ages above 36 years and 36 years and below, significantly higher frequencies of traditional risk factors; hypertension, dyslipidemia and diabetes were observed in the older group. In contrast, documented risk factors related to pregnancy and raised anticardiolipin antibodies were observed with statistical significance in the younger group (Table 2). However, the numbers were small in this younger age group and should be interpreted with caution.

More importantly, LAA and SVO stroke subtypes account for 53.7% (94/175) of ischaemic stroke in age group >36 years and 37.2% (16/43) of those ≤36 years. Other significant results in the ⩽36 yr age group were smaller proportions of

Table 1: Baseline demographic data of the study patients

	All n(%)	China n(%)	Hong Kong n(%)	Korea n(%)	Taiwan n(%)	Philippines n(%)	Thailand n(%)	Malaysia n(%)	Pakistan n(%)
Total patients	218 (100)	21 (9.6)	47 (21.6)	26 (11.9)	30 (13.8)	18 (8.3)	14 (6.4)	35 (16.1)	27 (12.4)
Non modifiable risk factors									
Age	40.8±6.7	39.9	42.9	40.6	41.8	41.6	41.1	41.1	35.6
Gender									
Male	143 (65.6)	18 (85.7)	25 (53.2)	22 (84.6)	24 (80)	10 (55.6)	9 (64.3)	21 (60)	14 (51.9)
Female	75 (34.4)	3 (14.3)	22 (46.80)	4 (15.4)	6 (20)	8 (44.4)	5 (35.7)	14 (40)	13 (48.1)
Family history of stroke	12 (5.5)	5 (23.8)	0 (0)	0 (0)	0 (0)	3 (16.7)	0 (0)	4 (11.4)	0 (0)
Previous stroke or TIA	14 (6.4)	0 (0)	12 (25.5)	0 (0)	0 (0)	1 (5.5)	0 (0)	1 (2.9)	0 (0)
Modifiable risk factors									
Hypertension	103 (47.2)	15 (71.4)	22 (46.8)	9 (34.6)	9 (30)	12 (66.7)	4 (28.6)	22 (62.9)	10 (37)
Dyslipidemia	93 (42.6)	11 (52.4)	29 (61.7)	6 (23.1)	14 (46.7)	10 (55.6)	5 (35.7)	16 (45.7)	2 (7.4)
Diabetes	52 (23.8)	6 (28.6)	7 (14.9)	2 (7.7)	9 (30)	7 (38.9)	0 (0)	16 (45.7)	5 (18.5)
Smoking	85 (38.9)	14 (66.7)	17 (36.2)	8 (30.8)	15 (50)	10 (55.6)	2 (14.3)	14 (40)	5 (18.5)
Alcohol	33 (15.1)	10 (47.6)	5 (10.6)	3 (11.5)	2 (6.7)	9 (50)	0 (0)	3 (8.6)	1 (3.7)
Risk Factors for Cardioembolism									
Atrial fibrillation	12 (5.5)	1 (4.8)	3 (6.4)	2 (7.7)	0 (0)	2 (11.1)	1 (7.1)	3 (8.6)	0 (0)
Rheumatic valvular heart disease	11 (5.5)	0 (0)	5 (10.6)	0 (0)	3 (10)	2 (11.1)	1 (7.1)	0 (0)	1 (3.7)
Ischaemic heart disease	10 (4.5)	3 (14.3)	3 (6.4)	0 (0)	0 (0)	1 (5.6)	0 (0)	2 (5.7)	1 (3.7)
Patent foramen ovale	6 (3.6)	0 (0)	4 (8.5)	0 (0)	0 (0)	1 (5.6)	1 (7.1)	0 (0)	2 (7.4)
Prosthetic heart value	2 (0.9)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.9)	0 (0)

Table 1: Baseline demographic data of the study patients

	All n(%)	China n(%)	Hong Kong n(%)	Korea n(%)	Taiwan n(%)	Philippines n(%)	Thailand n(%)	Malaysia n(%)	Pakistan n(%)
Total patients	218 (100)	21 (9.6)	47 (21.6)	26 (11.9)	30 (13.8)	18 (8.3)	14 (6.4)	35 (16.1)	27 (12.4)
Other Risk Factors									
Migraine	6 (2.8)	1 (4.8)	3 (6.4)	0 (0)	0 (0)	1 (5.6)	0 (0)	1 (2.9)	2 (7.4)
Pregnancy related	5 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (18.5)
Dissection	5 (2.3)	0 (0)	0 (0)	0 (0)	4 (13.3)	0 (0)	1 (7.1)	0 (0)	0 (0)
Malignancy	4 (1.8)	0 (0)	2 (4.3)	0 (0)	1 (3.3)	1 (5.6)	0 (0)	0 (0)	0 (0)
Drug abuse	4 (1.8)	0 (0)	0 (0)	0 (0)	1 (3.3)	1 (5.6)	1 (7.1)	1 (2.9)	0 (0)
Haematological									
a) Raised ACL antibodies/+ve LA	3 (1.4)	0 (0)	0 (0)	0 (0)	1 (3.3)	0 (0)	0 (0)	1 (2.9)	1 (3.7)
b) Hyperviscosity	2 (0.9)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.9)	0 (0)
SLE	3 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)	0 (0)	1 (2.9)	1 (3.7)
Moya Moya disease	2 (0.9)	0 (0)	2 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oral contraceptive pill(OCP	1 (0.5)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Post radiation angiopathy	1 (0.5)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Risk factors > 100% due overlapping risk factors in some patient
ACL, anticardiolipin antibodies; LA, Lupus anticoagulant

Table 2: Cerebral infarction in young adults with risk factors stratified by age

	All (N = 218)	Age		P	Odds ratio (95%CI)	Significant
		>36 years (N = 175)	⩽36 years (N = 43)			
Non modifiable risk factor						
Gender						
Male	143 (65.6)	113 (64.6)	30 (69.8)	0.52	1.27 (0.62-2.60)	NS
Female	75 (34.4)	62 (35.4)	13 (30.2)			
Previous stroke or TIA	14 (6.4)	12 (6.9)	2 (4.7)	0.6	1.51 (0.32-7.01)	NS
Family history of stroke in siblings	12 (5.5)	9 (5.1)	3 (7)	0.64	1.38 (0.36-5.34)	NS
Modifiable risk factors						
Hypertension	103 (47.3)	94 (53.7)	9 (20.9)	**0.0001**	**4.38 (1.98-9.68)**	**S**
Dyslipidaemia	93 (42.7)	85 (48.6)	8 (18.6)	**0.0003**	**4.13 (1.81-9.41)**	**S**
Diabetes	52 (24.3)	47 (26.9)	5 (11.6)	**0.03**	**2.87 (1.07-7.73)**	**S**
Smoking	85 (38.9)	68 (38.9)	17 (39.5)	0.93	1.03 (0.52-2.04)	NS
Alcohol	33 (15.1)	28 (16)	5 (11.6)	0.47	1.45 (0.52-4.00)	NS
Risk factors for cardioembolism						
Atrial fibrillation	12 (5.5)	11 (6.3)	1 (2.3)	0.31	2.82 (0.35-22.44)	NS
Rheumatic or valvular heart disease	11 (5.0)	9 (5.1)	2 (4.7)	0.9	1.11 (0.23-5.34)	NS
Ischaemic heart disease	10 (4.5)	9 (5.1)	1 (2.3)	0.43	2.28 (0.28-18.48)	NS
PFO/ASD/MVP	8 (3.7)	5 (2.9)	3 (7)	0.2	0.39 (0.09-1.71)	NS
Prosthetic Heart Valve	2 (0.9)	2 (1.1)	0 (0)	0.48	0	NS
Other risk factors						
Migraine	6 (2.8)	4 (2.3)	2 (4.7)	0.4	0.48 (0.08-2.71)	NS
Pregnancy related	5 (2.3)	1 (0.6)	4 (9.3)	**0.0006**	**0.06 (0.01-0.52)***	**S**
Malignancy	4 (1.8)	4 (2.3)	0 (0)	0.32	0	NS
Miscarriage	4 (1.8)	2 (1.1)	2 (4.7)	0.12	0.24 (0.03-1.73)	NS
Substance abuse	4 (1.8)	3 (1.7)	1 (2.3)	0.79	0.73 (0.07-7.22)	NS
SLE	3 (1.4)	2 (1.1)	1 (2.3)	0.55	0.49 (0.04-5.48)	NS
Raised anticardiolipin antibodies / +ve LA**	3 (1.4)	1 (0.6)	2 (4.7)	**0.04**	**0.12 (0.01-1.33)***	**S**
Moya Moya disease	2 (0.9)	2 (1.1)	0 (0)	0.48	0	NS
Oral contraceptive	1 (0.5)	1 (0.6)	0 (0)	0.62	0	NS
Radiation angiopathy	1 (0.5)	1 (0.6)	0 (0)	0.62	0	NS
Hyperviscosity -Thrombocytosis - Polycythemia	1 (0.5)	0 (0)	1 (2.3)	0.04	NA	NS

Significant ⩽36 age group

TIA, transient ischaemic attack; PFO, patent foramen ovale; ASD, atrial septal defect; MVP, mitral valve prolapse; S, significant; NS, not significant; SLE, systemic lupus erythematosus; LA, lupus anticoagulant

Table 3: Stroke Aetiology on TOAST classification

All (n=218)	n (%)
Large vessel atherosclerosis (LAA)	65 (29.8)
Cardioembolism (CE)	33 (15.1)
Small vessel occlusion (SVO)	45 (20.6)
Other determined aetiology (OD)	32 (14.7)
Non – atherosclerotic inflammatory vasculopathies	
Dissection	5 (2.3)
Post radiation angiopathy	1 (0.5)
Moya Moya disease	2 (0.9)
Vasospastic disorders	
Migranous infarction	6 (2.8)
Pregnancy related	5 (2.3)
Substance abuse	4 (1.8)
Systemic lupus erythematosus	3 (1.4)
Haematological disorders & acquired coagulopathies	
Malignancy	4 (1.8)
Hyperviscosity states	
Polycythaemia	1 (0.5)
Thromobocytosis	1 (0.5)
Undetermined aetiology (UD)	45 (20.6.)
Two or more possible causes	5 (2.3)
Negative evaluation	22 (10.1)
Incomplete evaluation	18 (8.3)

Raised anticardiolipin antibody antibodies/+ve lupus anticoagulant excluded from TOAST classification as repeat tests were not performed
Oral contraceptive pill excluded from TOAST classification

Table 4: TOAST classification and functional outcome

Toast criteria		Good Outcome(0-2) n = 142 (%)	Poor Outcome(3-6) n = 76 (%)	p	OR 95% CI
Large artery atherosclerosis	(65)	35 (24.6)	30 (40.0)*	0.02	0.50 (0.276-0.92)
Cardioembolism	(33)	21 (14.8)	12 (16.0)	0.84	0.93 (0.43-2.00)
Small vessel occlusion	**(44)**	**39 (27.5)**	**6 (8.0)**	**0.0007**	**4.42 (1.78-10.99)**
Other determined aetiologies	(32)	16 (11.2)	16 (21.1)	0.052	0.48 (0.22-1.02)
Undetermined aetiologies	(45)	32 (23.2)	13 (21.3)	0.35	1.41 (0.69-2.88)

*Denotes statistical significance for poor outcome in large artery atherosclerosis category

patients classified as SVO and larger proportions of patients classified as other determined aetiology (OD) categories.(Table 5)

DISCUSSION

To our knowledge, this is the first prospective multicentre observational study on young adults with cerebral infarction in Asia. The collective data provides a contemporary, cross sectional description of the clinical profile, risk factors, aetiological diagnoses and short term outcomes for a diverse group of young Asian patients.

Our study found a male to female ratio of 1.9 to 1 and this male predominance was consistent with many previous studies of cerebral infarction in young adults in Asia and elsewhere.[1-10] Male predominance was observed to be highest in Asia with a lower male/female ratio has been noted in European[1,14-17,22] and North American studies.[18-20] The main findings from this study were the substantial presence of traditional risk factors in our cohort of patients. Hypertension was documented in 47.2% of the entire cohort of patients and was the most common risk factor. The risk factors in descending order were dyslipidemia, smoking, diabetes and alcohol excess. These risk factors were observed in 42.6%, 38.9%, 24.3% and 15.1% of the entire cohort of patients respectively. Many previous studies have detected this pattern of risk factors.[2-6,8-10]

Hypertension was a frequent risk factor with 32% to 65% of the young ischaemic stroke patients implicated. This risk factor was also noted more commonly in Asian studies[2-6,8-10], among young black patients in the United States(55%)[18] and in recent European studies. (39.1%)[1,22] Cigarette smoking is a known risk factor for ischaemic stroke, increasing its relative risk three-fold.[23] The prevalence of smoking in our study was 38.8% which was less than several Western studies (prevalence of 44-47%[1,22]) but higher than previous Asian studies.[2,4-9]

The prevalence of diabetes varied widely between studies in the Asian literature, ranging from 7.3% to 52.2%.[2-10] Our study recorded a prevalence rate of 24.8%, a percentage consistent with the rising impact of diabetes in the Asian region.[21] Of our patients, 42.4% had dyslipidemia and this figure was higher than most published studies with the exception of studies from Finland[1], Taiwan [5] and Italy.[22] Our data highlight the rising complications of chronic lifestyle diseases in major Asian cities. Possible contributory factors were rapid urbanization, lack of early diagnosis due to insufficient or uncoordinated primary care as well as poor treatment compliance leading to premature atherosclerosis and ischaemic strokes in these young patients.

The major stroke sub-types in our study by TOAST criteria were LAA and SVO at 29.8% and 20.6% respectively. Our findings were similar to several studies in Asia but different from studies in Europe and North America. Asian studies found that the proportions of large vessel

Table 5: TOAST Classification stratified by age

TOAST classification	All (N = 218)	Age		P	Odds ratio (95%CI)	Significance
		>36 years (N = 175)	≤36 years (N = 43)			
Large artery atherosclerosis	65 (29.8)	52 (29.7)	13 (30.2)	0.95	0.98 (0.47-2.02)	NS
Small vessel occlusion	45 (20.2)	42 (24.0)	3 (7.0)	**0.02**	**4.21 (1.24-14.31)**	**S**
Cardioembolism	33 (15.1)	28 (16.0)	5 (11.6)	0.47	1.45 (0.52-4)	NS
Other determined aetiology	32 (14.7)	21 (12)	11 (25.6)	**0.02**	**2.52 (1.11-5.74)***	**S**
Undetermined aetiology						
Two or more possible causes identified	5 (2.3)	3 (1.7)	2 (4.7)	0.25	0.36 (0.06-2.21)	NS
Negative evaluation	20 (9.2)	14 (8.0)	6 (14.1)	0.23	0.54 (0.19-1.49)	NS
Incomplete evaluation	20 (9.2)	17 (9.7)	3 (7.0)	0.58	1.43 (0.4-5.14)	NS

* Significance noted in ≤36 year-old group for other determined aetiology category

atherosclerosis ranged between 7.5% to 28.3%[2-9] but our study exceeded all previous single hospital-based studies. Previous studies from Asia also described 17.4% to 42.5%[2-9] of patients in the SVO category and the figures in our study was consistent with the lower part of this published range. European and North American studies generally observed lower percentages of SVO and LAA, noted between 3%-17.4% and 2-16% respectively.[1,14,15,19-20] The stated figures excluded a study which revealed small vessel occlusion in 21% of young black men in the United States.[18] The same studies[1,14,15,19-20] also observed larger percentages of patients in the determined stroke and CE categories.

It is well recognized that SVO and LAA are more common in Asians compared to other populations.[24-26] However, when we stratified our data by age groups, SVO was significantly more common in the older age group (>36 years) compared to the younger group (⩽36 years), while the proportion of LAA was more evenly distributed across both ages groups.(Table 5) One possible explanation was that SVO presenting as small subcortical infarction (SSI) may have been overdiagnosed with the TOAST classification. Recent data demonstrated that the orifices of perforating arteries can be obstructed in mild large artery stenosis (under 50%), giving rise to SSI.[27] In addition, small undetectable plaques on conventional MRA but observable via high resolution MR studies can contribute to further erroneous SVO diagnoses.[28]

Interestingly, there were high proportions of SVO and LAA in both the ⩽36 age group (16/43 ~ 37%) and in the >36 age group (94/175 ~ 53.7%) when compared to European and North American studies.[1,14,15,19-20] In both age groups, relatively higher proportions of conventional risk factors (diabetes, hypertension, dyslipidaemia, smoking and alcohol excess) were also noted. In the ⩽36 year old age group, the presence of these risk factors was observed in 11.6%-39.5% of patients. Statistically significant differences were also observed in hypertension, dyslipidaemia and diabetes in the >36 year age group.

It has been widely recognised that traditional risk factors and SVO/LAA stroke subtypes increase with age. In Asia, the impact of these conventional risk factors from late adolescence (as seen in our study) and from a higher baseline prevalence have resulted in larger proportions of SVO and LAA subtypes. These findings underscore the importance of early risk factor detection and primary prevention, given the premature onset of cerebrovascular complications.

Our study also revealed a low frequency of cerebral infarction from cerebral venous thrombosis. A previous study by Wasay *et al*.[29] observed that 21% of ischaemic strokes in women were caused by cerebral venous thrombosis, highlighting geographical differences within Asia in the frequency and risk factors for cerebral venous thrombosis. Of our patients 90% were recruited from South East Asia and East Asia while studies by Wasay *et al*.[29-30] recruited about 70% of the patients from India, Pakistan and Sri Lanka. (South Asia)

With reference to routine investigations, the high level of admission blood glucose was likely to be related to the higher prevalence of diabetes (24.2%) in our cohort of patients.[21] Interestingly, 18% of patients tested with HbA1c showed abnormal levels indicating sub-optimal glycaemic control. The reference values for glucose and HbA1c were derived from the principal investigator's laboratory. However, the final abnormal values were reliant upon the respective co-investigators' laboratory as there was no funding for central facilities.

Coagulation abnormalities that were detected in our patients were transient and secondary to acute phase reactions. These changes were well described in the literature.[31] Coagulation tests were also infrequently performed among the participating countries during the index admission. This practice may be the result of a combination of low perceived yield and the cost of these tests in ischaemic stroke patients, given that hereditary coagulation deficiencies are extremely rare.[31-33]

In our study, vascular dissection was an infrequent cause of young ischaemic stroke and accounted for 2.3% of our study subjects. This proportion was much lower than a study from Taiwan in which vascular dissection accounted for 7.6% of patients.[5] Overall, these figures were lower than studies from outside Asia which reported vascular dissection in up to 20% of their study patients.[1,16] There were several possible explanations for these differences. Firstly, arterial dissection could be underdiagnosed due to incomplete diagnostic work up such as fat suppressed MR sequences and the selective use of conventional angiography. Secondly, although its pathophysiology is poorly understood, patients with arterial dissection may have underlying constitutional factors such as connective tissue disorders and genetic predisposition[34] interacting with environmental factors (trauma or infection) or other epistatic effects.[34,35]

Our data also showed that young stroke patients with LAA had significantly poorer outcomes at hospital discharge compared to patients with SVO. (Table 4) This observation was consistent with previous studies in Asia which described worse outcomes in patients with large intracranial or extracranial atherosclerosis.[36-38] The overall mortality rate at hospital discharge was 3.2%. This rate was better than a previous Asian multi-centre study which recruited consecutive stroke patients of all ages. A complication rate of 42.9% and a mortality rate of 6.1% was observed in this previous study while the proportion of patients admitted into an organized stroke unit was documented as under 50%.[12] The lack of stroke units in the region may explain the lower percentage of patients with good outcome at hospital discharge (65.1%) while similar studies from Europe and North America documented favourable outcomes in more than 85% of surviving patients.[14,20]

There were several limitations to this study. Firstly, the number of patients were relatively small due to the short recruitment period. There were also no resources for central imaging and laboratory facilities for data storage and analysis. Nevertheless, the major strengths of this study were its prospective study design and the enrollment of consecutive patients across several representative geographical regions in Asia. Patients were also not likely to be missed as young patients with cerebral infarction were likely to require hospital admission or referred for neurological evaluation.

In conclusion, this study demonstrated the feasibility and importance of international collaboration within Asia. Detection of risk factors and primary prevention are important in mitigating future increases of cerebral infarction in young Asian adults. The findings related to vascular dissection, cerebral venous thrombosis and the trend for poorer outcome in the OD category are areas for future research.

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DISCLOSURE

Conflict of interest: None

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