A Review of Stroke Research in Malaysia from 2000 – 2014

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ABSTRACT

Over 100 articles related to stroke were found in a search through a database dedicated to indexing all literature with original data involving the Malaysian population between years 2000 and 2014. Stroke is emerging as a major public health problem. The development of the National Stroke Registry in the year 2009 aims to coordinate and improve stroke care, as well as to generate more data on various aspects of stroke in the country. Studies on predictors of survival after strokes have shown potential to improve the overall management of stroke, both during acute event and long term care. Stroke units were shown to be effective locally in stroke outcomes and prevention of stroke-related complications. The limited data looking at direct cost of stroke management suggests that the health economic burden in stroke management may be even higher. Innovative rehabilitation programmes including brain-computer interface technology were studied with encouraging results. Studies in traditional complementary medicine for strokes such as acupuncture, *Urut Melayu* and herbal medicine were still limited.

KEY WORDS:
Stroke, Malaysia, risk factors, presentation, diagnosis, stroke unit, treatment, cost, rehabilitation, survival, outcomes

INTRODUCTION

Stroke is a significant global health problem, contributing to major morbidity and mortality for both developed and developing countries. Worldwide, stroke was ranked as the second commonest cause of death and the third most common cause of disability-adjusted life-years (DALYs) from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) in 2010. [1,2]

Over 100 articles related to stroke were found in a search through a database dedicated to indexing all literature with original data involving the Malaysian population between years 2000 and 2014 using the medical subheadings (MeSH) Stroke, and Ischemic Attack, Transient.[3]

SECTION 1: STROKE EPIDEMIOLOGY IN THE COUNTRY

Before the year 2000, when compared with eight other Asian countries, Malaysia was ranked as a country with incomplete epidemiological data for stroke, consisting mainly of hospital-based information. [4] Over the following decade, reports on stroke epidemiology in the country were derived from vital registry, hospital-based information, and observational studies from local hospitals. It was not until 2009 when the National Stroke Registry was established. This initiative aims to collect basic epidemiological data, as well as to guide the planning and implementation of stroke prevention and intervention programmes.

In Malaysia, stroke was the second leading cause of death according to the Malaysian National Burden of Diseases Study and study on vital registry system in 2000. [5,6] In comparison, using empirical data from vital registry systems in 2000, stroke was reported as the leading cause of death in Indonesia, Myanmar, Vietnam and Thailand. [6] Loo and Gan, however listed stroke as the third leading cause of mortality for males in Malaysia, in 2009, after ischaemic heart disease and pneumonia, while it ranked second for females after ischaemic heart disease.[7]

During the third National Health and Morbidity Survey (NHMS) in 2006, the prevalence of stroke was estimated to be 0.3% among Malaysians. [8] In the fourth NHMS survey in 2011, the prevalence of stroke was reported as 0.7%, with 1.7% among those aged 55-59 years, 2% in 60-64 years, 3% in 65-69 years, 3.5% in 70-74 years and 7.8% in 75 years and beyond. [9] The same survey also illustrated higher prevalence of stroke among those divorced or widowed (2.5%) compared to single (0.1%) and married (0.9%) but no significant difference across gender and ethnicity. [9] The first stroke incidence study in Malaysia was conducted in the South West District of Penang Island between April 2010 and March 2011. [10] The overall age-standardized stroke incidence in the study region was 67 per 100,000 persons. More than half (53.1%) were males and nearly a quarter (23.7%) were recurrent strokes.

A survey on all Malaysian pilgrims going to Mecca in 2003 revealed that 3.9% of elderly pilgrims aged ≥65 years had a previous stroke. [11] In a study involving 40 elderly aged ≥60 years from nursing care centres in Klang Valley, 75% of males and 64.4% of females self-reported that they had history of stroke. [12]

Age and gender

Differences have been noted in the demographic characteristics, stroke subtypes and pathological distribution of vascular lesions between Asian and Caucasian populations. Stroke patients in Malaysia were generally

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Table I: Demographic characteristics of stroke patients reported in various centres in Malaysia

Study	Location	Study period	Study subjects	Mean age (years)	Male gender	Ethnicity			
						Malay	Chinese	Indian	Others
Jaya F *et al*[13]	Kelantan	Jan 97′ – Dec 98′	158*	59.3	58.2%	86.1%	13.9%	-	-
Ong TZ and Azman Ali R[14]	Penang	Dec 98′ – Nov 99′	246	65	56.5%	28.9%	55.7%	14.2%	-
Basri H and Azman Ali R[15]	Kuala Lumpur	Jun 00′ – Jan 01′	218	62.2	48.2%	37.2%	74.8%	8.3%	2%
Tan KS *et al*18	Kuala Lumpur	Jan 07′ – Mac 08′	67**	41.5	58.2%	46.5%	21.1%	32.4%	-
Grover CS and Thiagarajah S[16]	Miri	Jun 08′ – May 09′	215	62.5	60.5%	16.3%	28.4%	-	Iban 37.2% Others 18.1%
Nazifah SN *et al*[17]	Penang and Terrengganu	Aug 09′ – Dec 10′	1018	62.5	54.3%	83.7%	11.1%	4.2%	1%
Neelamegam et al[10]	Penang	Apr 10′ –Mac 11′	228	Age stratified	53%	-	-	-	-
Loo KW and Gan SH[7]	Kelantan	Apr – Aug 11′	57	54.5	-	100%	-	-	-
Tan KS *et al*[19]	Kuala Lumpur	Dec 11′- May 12′	35**	41.1	60%	-	-	-	-

*Study only involved patient with first ever stroke.
**Study involved only young patients with ischaemic stroke aged between 18 and 49 years.

Table II: Complication prevalence rates according to ward of admission in ten Asian countries, including Malaysia (Total N= 1153) (selected 10 most common complications)

Complications	Stroke Unit (%)	General neurology ward (%)	General medical ward (%)
Recurrent stroke	1.5	2.6	29.0
Depression	1.1	2.2	23.0
Constipation	4.6	0.1	17.0
Urinary retention	3.0	6.0	16.0
Falls	0.2	2.6	9.2
Urinary tract infection	1.8	8.8	7.4
Chest infection	1.5	16.9	7.4
Aspiration	1.8	2.4	4.0
Pressure sore	0.9	3.8	3.1
Deep vein thrombosis	0.2	0.2	1.5

younger. The mean age of stroke onset in Malaysia was between 54.5 and 62.6 years [7,13-17] (Table I). Males accounted for 48.2% to 60.5%. [7,10,13-17] The different proportions in ethnicity across all the studies reflected the geographical variation in ethnic distribution, rather than ethnic-specific prevalence in the country.

A comparison of the Malaysian and Australian stroke registries on young adults aged between 18 and 49 years, showed comparable age of onset as well as gender ratio for ischaemic stroke. [18] The mean age was 41.5±8.8 years for Malaysia and 40.1±8.8 years for Australia with a sex ratio of male to female 1.4: 1 and 1.54: 1, respectively.

Stroke classifications

Up to two-third of reported stroke cases in Malaysia were of ischaemic origin, with the remaining one-third being haemorrhagic (intracerebral and subarachnoid haemorrhages).[10,13-17] In a single centre prospective study, among all stroke patients admitted to Penang Hospital over one-year period, 74.8% were ischaemic and 25.2% haemorrhagic in origin. [14] This result was reproduced in two other larger studies across the country where ischemic stroke was reported in the range of 73.3% to 79.9%. [10,17] Malaysia had a higher proportion of haemorrhagic strokes compared to higher income countries. [10,15] More patients who defaulted antihypertensive treatment had haemorrhagic stroke compared to ischaemic stroke. [16]

Based on the Oxfordshire Community Stroke Project (OCSP) classification, between 2009 and 2010, the Malaysian National Stroke Registry involving two tertiary hospitals in Terengganu and Penang reported that 43.4% of ischaemic stroke patients had partial anterior circulation infarct (PACI), 27.4% had lacunar infarct (LACI), 16% had total anterior circulation infarct (TACI), 7% had posterior circulation infarct (POCI) while 6.2% were unclassified or uncertain. [17] These findings were slightly different from earlier studies. In the late 1990's, 33% of patients with cerebral infarcts in Kelantan were LACI, followed by TACI (28%), PACI (24%) and POCI (15%). [13] In 2000, a study in Kuala Lumpur reported nearly half of their ischaemic stroke patients suffered from lacunar infarct (46.8%), followed by middle cerebral artery (MCA) infarct (14.2%). [15] Up to 38% had cerebral infarcts over right hemisphere, 35.7% left hemisphere, 17.6% both hemispheres and 6.3% cerebellar region. [17]

SECTION 2- STROKE-RELATED RISK FACTORS

Hypertension was the commonest risk factor for stroke (53.2–76.1%) followed by diabetes mellitus (27.4–55.2%) and hyperlipidaemia (4.8–37.3%) across various local studies. [14,16-18,20-22] Other reported risk factors for stroke in Malaysia were smoking (19.4–37.3%), ischaemic heart disease (10.4–35.5%), a history of previous stroke or transient ischaemic attack (TIA) (7.5–25.1%) and chronic kidney disease (10.4%). [13,17,18,21,23]

A one-year review of medical records in Besut, a district hospital in the state of Terengganu, showed that 92% of stroke patients aged ≥50 years, and males (52%) were affected more than females.[21] The prevalence of all risk factors such as hypertension, diabetes, dyslipidemia and heart diseases was higher among males. [21] Nonetheless, as high as 20.9% patients with stroke had no identifiable risk factors. [13]

A review article looking into hypertension and stroke prevalence, control and strategies in Asia found that hypertension and stroke tend to occur at younger age in Asians compared to Westerners, and that the risk of hypertension increases at lower body mass index (BMI) of 23–25kg/m^2. [24] It also concluded that being overweight, sedentary behaviour, alcohol, higher social class, higher salt intake, diabetes and smoking are common risks factors for hypertension and stroke in most Asian countries.

The presence of atherosclerotic disease may also predict increased risk of stroke. Peripheral artery disease (PAD), a manifestation of atherosclerosis was found to be highly prevalent (23%) among high risk patients (established cardiovascular disease, ischaemic stroke or diabetes mellitus for at least 5 years) in Malaysia. [25] But, only 27% of them were symptomatic with classical intermittent claudication. PAD was found in patients with pre-existing cardiovascular disease (33%), ischemic stroke (28%) and diabetes (27%). [25]

Guo Y *et al.*, in their review involving studies conducted in the Far East (Japan, Taiwan, China and South Korea) and Southeast Asia (Singapore), reported that the rate of stroke related to atrial fibrillation (AF) was 13.0–15.4% in the community. [26] The rate varied between 3.1% and 24.2% in studies involving hospitalized patients. This was in accordance with local studies where 6.1-10.6% of stroke patients admitted to tertiary centres had AF. [19,22,23]

Hyperhomocysteinemia is a potentially modifiable risk factor associated with a significant proportion of atherothrombotic ischaemic strokes in the Malaysian population. It is postulated that a high level of homocysteine induces direct endothelial injury causing endothelial dysfunction and accelerates atherogenesis and thrombogenesis, contributing to ischaemic stroke. In a pilot project involving 83 stroke patients, the mean plasma homocysteine level was 13.5µmol/l. [27] About 30% had moderate hyperhomocysteinemia (>15.2µmol/l). Moderate hyperhomocysteinemia was shown to be an independent risk factor for stroke with an odds ratio (OR) of 5.3. Besides, there was a graded association where the stroke risk increased with the higher level of homocysteine. [27] This finding was reinforced in a larger case-control study involving 292 subjects. [28] The homocysteine level was significantly higher in the stroke group (11.35±2.75 µmol/L) compared to the control group (10.38±2.79 µmol/L) (p=0.001). The authors also showed that TT genotype of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphic gene was an important determinant for homocysteine levels in Malaysian ischemic stroke patients. [28] However, no significant difference was noted in the rate of hyperhomocysteinemia, as well as prevalence of C677T polymorphism among stroke patients between the different ethnic groups.

Arteriovenous malformation (AVM) in the brain may pose a risk to hemorrhagic stroke. A cross-sectional study revealed that brain AVM occurred predominantly in young males (65.5%), and 69% presented with intracranial haemorrhage.[29] There was an association between the AVM architecture and risk of intracranial bleed. Significant factors include small nidal size ≤3cm, deep location of AVM and deep venous drainage.

Subclinical cerebral infarcts (SCI) have been increasingly shown to cause significant impact on clinical outcome. SCI are lesions which share neuropathologic and neuroimaging characteristics with cerebral infarcts but without any recognized clinical symptoms of acute stroke. SCI are associated with risk of future stroke, stroke recurrence, cognitive impairment and functional disability. One-third of ischaemic stroke patients attending an outpatient clinic at a university hospital in Kuala Lumpur had SCI. [30] Hypertension, diabetes and leukoaraiosis were shown to be independent risk predictors of SCI. These factors were postulated to be responsible for the progression of atherosclerotic and lypohyalinotic changes in small arteries in the brain causing dysregulation of cerebral flow and metabolism, leading to small silent cerebral infarcts. [30]

In a comparative study looking at stroke aetiology based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification between 67 Malaysian and 61 Australian young ischaemic stroke patients. Tan KS *et al.* reported that Malaysian patients tend to have large vessel atheroscelerosis (28.3%) and small vessel occlusion (32.8%), while the Australian counterparts had a greater proportions of cardioembolism (21.3%) and vascular dissection (11.5%). [18] Cardioembolic cause accounted for 12.9% of ischaemic strokes in the Malaysian series, while 4.2% could be attributed to cerebral venous thrombosis. [18] On the other hand, the National Stroke Registry reported more than half of cerebral infarcts were of large vessel diseases (58.9%), followed by small vessel disease (28.3%), undetermined causes (10.1%) and cardioembolism (3.4%).[17]

As for the rare causes of strokes, local authors have reported cases which included atrial myxoma where a young gentleman presented with sudden onset of weakness with cerebellar signs,[31] coarctation of aorta,[32] silent meningioma after cardiopulmonary bypass surgery,[33] angioinvasive cerebral aspergillosis in a patient with diabetes,[34] and paradoxical embolism across solitary pulmonary arteriovenous malformation with feeder vessels.[35] A case of

migrainous infarction involving bilateral occipital lobe and migraine-triggered seizure likely precipitated by oral contraceptive pills in a patient with migraine and visual aura has been reported. [36] Apart from migraine, drug abuse such as methamphetamine, [19,37] and systemic lupus erythematous [19] were rarely identified as risk factors in young ischaemic stroke.

SECTION 3- MANAGEMENT FOR ACUTE STROKE AND POST-STROKE SEQUELAE

Clinical manifestations

Stroke is a clinical diagnosis. The majority of patients presented with unilateral body weakness (90.5%), followed by weakness and seizures (21.4%). [38] Other clinical presentations such as headache, vomiting, visual loss and slurring of speech have also been reported. [38]

Clinically it may be difficult to differentiate hemorrhagic from ischemic brain infarcts. Validation work by Kan CH *et al.* showed that Siriraj Stroke Score was not a reliable tool for differentiating intracerebral haemorrhage from infarction following an acute stroke at presentation. [39]

While the majority of stroke patients will present with features of focal neurological deficits, occasionally stroke could present with hyperkinetic disorders. Tai ML *et al.* described a case of a 78-year old man who developed sudden onset of right hemiparesis followed by abnormal involuntary movements involving right upper and lower limbs. [40] His hemiballistic movements were present at rest and worsened with action. Kiu KY *et al.* reported a 57-year old man with bilateral recurrent occipital infarcts presented with cortical blindness and Anton Syndrome (visual anosognosia), where he denied loss of vision although he was unable to see. [41]

Many diseases may have clinical features that could be confused with stroke. They are known as stroke mimics. A case discussion on possible tuberculous meningitis with stroke-like presentation was described by Gnanasan S *et al.* [42]

Stroke may mimic other non-vascular conditions. Hasan S *et al.* described a young lady without any vascular risk factors who presented with features of Miller Fisher syndrome which was later diagnosed to be an acute right medial thalamic infarct. [43] The lady recovered completely in one month with standard stroke treatment.

Sapiah S and Hamidon BB reported a case of an Englishman in Kuala Lumpur, who had suffered from possible Creutzfeldt-Jakob disease diagnosed by electroencephalograph. [44] He had history of recurrent stroke, hypertension and hypercholesterolaemia. He presented with progressive deterioration in cognitive function, a symptom that could be attributed to repeated vascular insult from previous strokes, as well as gait disturbance and cerebellar signs. Therefore, it is important for physician to realize that other neurological conditions may affect stroke patients and vice versa. A thorough history and physical examination are essential in patient's assessment.

Investigations and diagnostic modalities

Brain computed tomography (CT) scan remains as the imaging modality for stroke in most centres in Malaysia. Radhiana H *et al.* described the Alberta Stroke Program Early CT Score (ASPECTS) as a systematic, robust and practical method that could be adopted for detection and reporting of the extent of acute ischemic stroke, in order to overcome challenges in infarct volume estimation in patients eligible for thrombolysis. [45] This scoring system correlates inversely with stroke severity and functional outcomes, but limited to assessment of MCA territory infarct. CT perfusion (CTP), a newer investigative method, was shown to be a useful imaging tool for determining acute cerebral infarction by Man K *et al.* who found that the prevalence of normal unenhanced CT but positive CTP for cerebral ischemia was 22.7%. [38] The same study also reported the mean time of patients presented for scan was 10.5±7.4 hours, with 11.9% of them presented within 4 hours of symptoms onset, 26.2% between 4 and 5.9 hours, and the remaining 73.8% after 6 hours. [38] A systematic review on cerebral CT angiography (CTA) and CTP in detecting acute storke, by Sabarudin A *et al.*, revealed that CTA offers high diagnostic accuracy in detecting the site of occlusion and assessing its severity, whereas CTP provides high specificity in detecting ischaemia, and differentiating infarcts and ischaemic penumbra, which can facilitate decision making in thrombolytic therapy. [46]

In the last decade, the utilization of transcranial doppler (TCD) technologies in the field of stroke has gained interest of neurologists worldwide. Tan KS *et al.* reviewed the potential use of TCD in the diagnosis and prognostification of ischaemic stroke and TIA, and may be routinely applied for asymptomatic patients at high risk of stroke. [47] This non-invasive, reproducible, sensitive and specific technology allows detection of arterial occlusion and recanalization offers real-time monitoring capability.

Several haemostatic biomarkers have been investigated for acute stroke at presentation. Tissue plasminogen activator (tPA) antigen, a fibrinolytic marker was found to be higher in acute stroke patients (OR=4.6) compared to the controls. [48] The higher level of tPA probably indicated a poor prognosis, as all patients who died within one month of stroke onset had high tPA. Besides, micro-RNAs have emerged as potential biomarkers in diagnosing and prognosticating ischaemic stroke. Interestingly, these stably expressed, dysregulated molecules continued to be detectable up to 18 months after stroke onset. [49] Circulatory microRNA-145 expression which is recognized as a marker and modulator of vascular smooth muscle cell phenotype has been shown to be significantly higher in patients admitted with acute ischemic stroke. [50] It was hypothesized that upregulation of microRNA-145 might be an indicator of good outcome in vascular regeneration to achieve homeostatic equilibrium. However, the role of this biomarker in clinical practice is yet to be elucidated.

Prevention and treatment strategies

Prevention

Rabia K *et al.* briefly discussed the importance of primary prevention for stroke. They emphasized risk factors management such as lifestyle modifications, measures to control hypertension, dyslipidemia, diabetes and AF. [51] For

secondary stroke prevention, they discussed the importance of blood pressure control, treating dyslipidemia and diabetes to target, as well as roles of antiplatelets therapy and carotid endarterectomy. [51] The newly proposed pooled cohort risk scoring to estimate 10-year atherosclerotic cardiovascular disease risk, including fatal and non-fatal stroke, was retrospectively validated in a tertiary primary care setting. [52] It was incorporated as part of the new blood cholesterol management guideline from the American College of Cardiology and American Heart Association.

Roles of stroke unit and stroke education

Improved assessment procedures and early rehabilitation could be the explanation for better outcome observed if stroke patients are admitted to stroke unit compared to general medical or general neurology wards. Complication prevalence rates comparing stroke unit, general medical ward and general neurology wards are illustrated in Table II.[53] Acute stroke units have been set up in some tertiary hospitals in Malaysia to date. [54]

There is an increasing effort to promote community awareness to detect stroke symptoms and to enhance responsiveness to a stroke patient's need. A local acronym, of equivalent to FAST (facial drooping, arm weakness, speech difficulties and time), has been developed by the Kuala Lumpur Regionalized Integrated Stroke Intervention System (KRISIS) team for this purpose. The acronym is "MATA", in Malay, stands for "Muka" (Face), "Angkat Tangan" (Lifting arm), "Tutur" (Speech), "Angkat Telefon" (Dialing telephone). [55] The effectiveness of such promotion at community settings is to be evaluated.

Hassan NH *et al.* conducted a cross sectional study among stroke patients, caregivers and therapists to design a website to deliver stroke information using user-defined two-level hierarchy web navigational structure based on Malaysian perspectives.[56] This approach paves the way for designing an informative, interactive and user-centred website to enhance stroke education in our community.

Cost analysis for stroke care

Stroke carries a substantial socio-economic burden to individuals, family and society. Aznida FAA *et al.* studied the cost of treating an acute ischemic stroke from admission to the out-patient follow-up at a teaching hospital. [57] The average in-hospital length of stay was 9.8 days for major strokes and 3.6 days for minor strokes. There was an average of two outpatient clinic visits per patient in three months period. Outpatient rehabilitation involved 10 and 15 sessions for minor and major stroke respectively over six months. The calculated costs for hospital admission were MYR 9000 and MYR 3353 for a major and minor stroke, respectively. In outpatient setting, the costs were calculated to be MYR 103 for each specialist clinic visit and MYR 43 for one rehabilitation therapy session per patient, regardless of stroke severity. [57]

In another cost analysis study, Nor Azlin *et al.* reported the mean cost of care per patient in a teaching hospital being MYR 3696.40 or 16% of per capita gross domestic product (GDP) of the country. [58] The cost was attributable mainly to human resource amounting to MYR 1343.90 (36.4% of total direct medical cost), followed by medications (MYR 867.30 or 23.5%) and laboratory services (MYR 337.90 or 9.2%). [58] The most severe stroke consumed higher cost than mild stroke, by MYR 1598.10

Ramesh S *et al.* in his reply letter to Nor Azlin *et al.* stressed the importance of involving all stakeholders for healthcare economics analysis for a more accurate cost estimation that would allow better planning of healthcare resources distribution and utilization of limited resources.[54]

Acute stroke management

The management of acute stroke should start before the onset of stroke. Multiple reports derived from a study at Penang Hospital between January 2008 and June 2009, have shown that usage of HMG-CoA reductase inhibitors (or statins), angiotensin-converting enzyme inhibitors and antiplatelets, either alone or in combinations were associated with better functional outcome measured by Barthel Index on discharge, as well as significantly reduced in-patient mortality. [59-62] A sub-analysis on 295 diabetic patients reviewed that 38.3% of them were taking antiplatelet before index admission. [63] The main reason these patients were on antiplatelet was for previous stroke or ischemic heart disease. The data echoed the findings that better functional outcome upon discharge was observed among patients previously taking antiplatelet therapy.

Sahathevan R *et al* reported a case of a 29-year old man presented with acute ischaemic stroke and received thrombolysis at 5.5 hours from the onset of symptoms, beyond the recommended onset-to-treatment time window of 4.5 hours, after careful consideration. [64] He had a small infarct core in the right lenticulostriate territory with a significant penumbra as evidenced from CTP images. He made good neurological recovery at two months.

Rasool *et al.* in their review stressed that the effect and safety of early lowering of blood pressure after intracranial haemorrhage has not been reliably examined. [65]

There was a pilot study on 18 subjects with hemorrhagic stroke involving the induction of intravascular hypothermia within 48 hours after presentation. [66] The hypothermia was induced with an intravascular catheter placed over inferior vena cava at 34°C and maintained for 24 hours followed by gradual re-warming. Stroke severity measured by modified Rankin Scale (mRS) at 6 months and 1 year follow-up showed a significant improvement for patients receiving the study intervention.

In recent studies, comparison of recanalization success and clinical outcomes in acute ischemic stroke using intra-arterial therapy and intravenous tissue plasminogen activator have been inconsistent. Ramaiah SS *et al.* described the potential role of arterial collateralization assessment as a selection tool to identify suitable acute stroke candidates whom will likely to benefit from intra-arterial therapy. [67] This assessment focuses on leptomeningeal anastomoses, which composes of secondary network of cerebral collateral circulation besides the Circle of Willis.

The Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study tested the investigational product MLC601 in patients with acute, moderately severe ischemic stroke presented within 72 hours from stroke onset. [68] MLC601 (NeuroAID) combines extracts of 9 herbal and 5 animal components in capsule form. At the end of 3 months, MLC601 was not statistically better than placebo in improving stroke severity and functional outcomes. But post hoc analysis showed that it was associated with reduced early vascular fatal and non-fatal composite outcomes such as recurrent stroke, acute coronary syndrome and vascular death at 3 months after index stroke. [69]

In addition, prevention of acute post-stroke complications such as venous thrombosis, pressure ulcer, aspiration pneumonia and gastrointestinal bleed is important. In a six-month observational trial, the in-hospital stroke complication rate was 20.9%. [23] Stroke-associated infections such as pneumonia (12.3-15.8%), septicaemia (11.0%), urinary tract infection (3.7-4.3%) were the leading complications, followed by upper gastrointestinal bleeding (3.7-5.2%), recurrent stroke (3.1%), depression (2.5%), bed sores (1.2%) and deep vein thrombosis (0.6%). [23,70-72] It was also demonstrated that MCA infarcts, diabetes, severe disability, poor Glasgow Coma Scale (GCS) independently predicted these post-stroke complications, which led to increased in-patient mortality. In another larger study involving 1,153 patients from 10 Asian countries which included Malaysia, complications occurring within 14 days of stroke included chest infections (9.4%), constipation (7.9%), urinary retention (5.0%), recurrent stroke (4.9%), urinary tract infections (4.9%), depression (4.0%), pressure sores (2.6%), aspiration (2.5%), falls (2.4%), upper gastrointestinal bleeding (1.6%), epileptic seizure (1.3%), arthritis (0.7%), deep vein thrombosis (0.5%), cardiac arrhythmias (0.3%), congestive heart failure (0.2%) and pulmonary embolism (0.1%). [53]

Tan KS *et al.* performed a literature research on the available evidence of venous thromboembolism (VTE) among ischemic stroke patients in Asia and found a wide range of reported prevalence of VTE after stroke. [73] The prevalence of 1% was reported in clinical studies and 4.8% to 45% in imaging studies. These prevalence rates were lower compared to Western studies. However, the available literature involved only small sample size. [73]

Stem cell therapy in the treatment of stroke is still at the experimental stage. Gopurappilly R *et al.* reviewed the latest success and future prospects of stem cell therapy. [74] Current works suggest that the earlier belief of stem cell mechanism of action via cell replacement may be incorrect. There are evidence that cell therapy works mainly by providing trophic support to the damaged neurons to foster neurogenesis and angiogenesis. The authors further emphasized the importance of continued preclinical work to understand better the mechanisms of action of stem cells.

Long term stroke management

Aznida FAA *et al.* conducted a survey among family medicine specialists using a semi structured self-administered questionnaires to evaluate practices in managing post-discharge stroke patients at primary care setting. [75,76] As high as 72.4% of the interviewed physicians did not have a standard care plan although about 96% would agree on the importance of having one to improve the quality of post-stroke care. [76] Apart from a standardized guideline, they also emphasized the needs of access to rehabilitative services, coordinated multidisciplinary care with tertiary centre and good family and caregiver support in strengthening stroke management in primary care. [76]

Asian population has a slightly lower incidence and prevalence of AF than the Western population, but have a similar relative risk of stroke and mortality. [77] A lenient approach for long term control aiming for a ventricular rate of less than 110 bpm may be adequate. However, stricter rate control may be needed if patients continue to complain of symptoms. One review reported an AF prevalence of 2.8% among hospitalized patients in Malaysia and overall use of warfarin for AF was only 20%. [26]

Warfarin resulted in an increased rate of hemorrhagic stroke in Asians compared to non-Asians in a controlled trial. Newer anticoagulation agent such as dabigatran etexilate posed a lower risk of major bleeding and hemorrhagic strokes compared to warfarin, and was consistent across Asian and non-Asian subgroups. [78] A retrospective observational study involving 510 patients attending the Malaysian National Heart Institute reported that usage of dabigatran in AF patients for stroke prevention had low rates of side effects (3.9% with dyspepsia) and bleeding (3.3% with minor bleeding and 0.4% with major bleeding). [79] Their median age was 68 years, median CHA2DS2-VASc was 2 and median HAS-BLED score was 2. None had ischaemic stroke, but one (0.2%) had haemorrhagic stroke, up to an average of 10-month follow-up.

Management of stroke should also target non-motor complications. Stroke survivors may suffer from dysphagia, which can lead to malnutrition and aspiration pneumonia. Those with moderate to severe dysphagia may require enteral tube feeding. A small prospective randomized trial involving 22 subjects comparing the effectiveness of percutaneous endoscopic gastrostomy (PEG) and nasogastric (NG) tube feeding found that PEG feeding had a modest but clinically significant improvement in serum albumin after 4 weeks of intervention, with a lower treatment failure. [80] Zaherah MSF *et al.* conducted a prospective study to examine the nutritional adequacy of patients on long term NG tube and to determine barriers to PEG feeding in these patients. [81] They found that 64.3% on long term NG tube feeding had complications such as tube dislodgement (50.5%), aspiration of feed content (8.6%) and trauma from tube insertion (4.3%). Only half of the clinicians interviewed would routinely recommend PEG feeding, while 47.1% of the caregivers named 'lack of information' as the main reason of not opting for PEG feeding.

Stroke rehabilitation

In the past, it was believed that neurological improvement after stroke plateaued off after 6 months, hence cessation of rehabilitative services follows. A Cochrane review by Aziz NA *et al.* on the potential benefit of rehabilitation services for

patients after more than one year with stroke showed inconclusive evidence on the positive influence of the services to both patients' and carers' outcomes.[82] Moreover, Aziz NA and Raymond AA in their review article stressed on the needs for longer-term stroke patients in the community.[83] Evidence showing improvement in stroke patient even after 1 year of stroke requires the healthcare managers to consider re-structuring stroke rehabilitation beyond the first year of stroke and this service should encompass all aspects of patients' life.[83] Both rehabilitation professionals and stroke survivors expressed the needs for long term rehabilitation and recognized the barriers to such provision are multi-factorial.[84] Establishment of community-based rehabilitation centres and family-assisted home therapy were the potential strategies identified in the focused group discussion.

New innovative motivational community rehabilitation programmes were studied in RCTs. Subjects were allocated to two groups: the experimental group received 30 minutes of virtual reality balance games in addition to 90 minutes of standard physiotherapy while the control group received a total of 120 minutes of standard physiotherapy.[85] After 12 sessions of therapy, the outcome showed a significant improvement in Timed Up and Go test and the 30-second Sit to Stand test for the experimental group. There was however no difference in functional outcome measured using Barthel Index suggesting that this innovative method of physiotherapy could be an alternative to standard physiotherapy for stroke rehabilitation in community.[85] Another RCT assessed the effectiveness of digital videodisk containing therapy at home combined with twice monthly outpatient follow-up as compared to the conventional weekly outpatient therapy.[86] At 3 months, there was no difference in functional improvement, complication rates and Caregiver Strain Index among the two methods. This study suggested that video-based therapy at home for post-stroke rehabilitation is safe and did not increase caregiver stress, which can be an alternative for home care rehabilitation.[86]

Aziz *et al.* looked into the outcome of community rehabilitation provided by primary care clinic in a prospective observational study.[87] The median interval between stroke event and point of first contact with the clinic for 91 patients was 4 months. It was shown that rehabilitation provided by primary care clinic had favorable outcome for blood pressure control (significant reduction in systolic blood pressure) and functional level (improved Barthel Index). There was also a trend of improvement but insignificant in depression scale measured by Patient Health Questionnaire (PHQ9).[87]

Botulinum toxin is effective in reducing post-stroke spasticity. A RCT on 27 subjects showed that intramuscular injection of botulinum toxin A was safe and effective in the treatment of chronic post-stroke focal spasticity of the wrist and fingers, without serious treatment-related adverse effects.[88]

Up to 70% of stroke patients reported the use of traditional complementary medicine as part of their rehabilitative care, such as acupuncture, massage and herbal medicine.[89] Recently, 17 post-stroke patients and 2 *urut Melayu* hospital practitioners were interviewed for their experience and views on urut Melayu for stroke. This is a whole-body massage involving not only the body parts affected by stroke. Overall, *urut Melayu* gave the patients an unique and positive experience and were well-received.[90] A case report has described a 32-year old woman, following postpartum haemorrhagic stroke which rendered her bed-bound, had progressively improved speech and fine motor skills after 14 sessions of *urut Melayu*.[91]

On the other hand, Home Care Nursing Program designed by a university hospital did not show difference in terms of functional improvement outcome in post-stroke rehabilitation when compared to the routine therapy.[89] While this raises concerns on the efficacy of such programme, the small sample size and lack of clarity on the programme information might have affected interpretation on the study outcomes.

Yakub F and colleagues provided an interesting review on the current development of rehabilitative robotics as a promising tool for stroke rehabilitation.[92] Besides, Abdullah MZ *et al.* described the potential use of brain-computer interface (BCI) technology in stroke rehabilitation.[93] The BCI is a computer-aided apparatus which decodes brain electrical activities and translates them to signals for activating external devices. It provides communication interface which can match with a stroke patient's residual motor disabilities to facilitate robotic-assisted rehabilitation. Recent experiment on stroke survivors suggested that BCI promotes cortical plasticity which allows the brain to re-organize around damaged cortical areas, hence recovering the functions of these areas.[93]

Stroke outcomes for survivors and care-givers

Mortality and morbidity

In Malaysia, mortality due to stroke constituted 8.9% and 12.1% of total certified death for males and females, respectively.[94] The estimates of age-standardized stroke mortality were 103 per 100,000 males and 97 per 100,000 females.[6]

Stroke mortality varied widely between different studies, ranging from 3.3% to 37%.[7,13,15-18] In the late 1990s, a prospective observational study in a tertiary centre in Kelantan revealed a 30-day mortality among first-ever stroke patients of 34%, with two-third occurred as in-patients,[13] while in Penang Hospital it was 20.3%.[14] Patients with haemorrhagic stroke had a higher mortality rate (27.3-36.8%) than those with ischaemic stroke (10.1-11.7%).[15,16] Death occurred at a mean of 8 days after admission for ischaemic stroke and 3.8 days for haemorrhagic stroke.

Morbidity associated with stroke poses substantial burden to patients, their caregivers, healthcare systems and providers. The main contribution to morbidity is functional disability. In a prospective observational study, at discharge, only 13% of post-stroke patients were able to ambulate with aids and 87% needed assistance for ambulation of varying degree.[95] At 3 months, 82% showed improvement in overall function, 60% were ambulating independently with the remaining

40% still required assistance.

Manaf H *et al.* explained the post-stroke sensorimotor and balance dysfunctions and how they affect the mobility of stroke survivors when performing daily functions which require substantial walking coordination. [96] However, they concluded the lack of studies in understanding dual-task ability (motor and cognitive) on stroke patients, and proceeded to conduct two studies on this domain. They found that gait performance among stroke patients was compromised during dual-task conditions and recommended to incorporate attentional loading into routine gait assessment and rehabilitation. [97] Besides, they demonstrated that functional balance might be an influential domain in successful dual-task Timed Up and Go test. [98]

Other post-stroke disabilities include dysphagia, [80,99] emotion recognition deficit, [100] dementia [101,102] and sleep-disordered breathing (SDB). [103] In a single centre observational study, as high as 41% of stroke patients experienced dysphagia at initial presentation and was reduced to 21.6% at one-month after index stroke.[99] Age ≥75 years (OR=5.20), diabetes (OR=2.91) and MCA infarct (OR-2.48) independently predicted the occurrence of dysphagia after an acute stroke. [99] In a more recent study, the prevalence of dysphagia was reported lower at 15.8%. [104]

Yuvaraj R *et al.* discussed the problems of diminished ability to recognize emotions in post-stroke patients. [100] The extent of emotion recognition deficit appears to be correlated with interpersonal difficulties such as complaints of frustration, desire to attach with another person, feelings of social discomfort and use of controlling behaviours. [100] Such deficits were more frequently observed in individuals with right brain damage compared to those with left brain damage.

Stroke causes dementia and vascular risk factors appear to be independent risk factors for dementia. Hence, cognitive assessment must be included in post-stroke care. The Malay version of Montreal Cognitive Assessment (MoCA) had been validated for use in local stroke population. [105] Al-Qazzaz NK et al. reviewed the available neuropsychological assessments and proposed a post-stroke memory assessment (PSMA) as a tool for evaluating impairment of different memory functionalities (working, short and long term memories) and their severity. [106,107] It may also detect the earliest stages of dementia before significant mental decline in post-stroke patients. [106] Sahathevan R *et al.* reinforced that risk factors such as hypertension, diabetes and dyslipidemia are independently associated with the increased risk of Alzheimer's dementia and vascular cognitive impairment.[102] However, the mechanism of cardiovascular risk factors affecting Alzheimer's dementia remains largely unknown. Stroke patients aged ≥65 years were prone to have cognitive impairment. [108] This study also illustrated that cognitive impairment among stroke patients had significant relationship with general health status, depression, activities of daily living, overall social and family support.

Prevalence of SDB was reported at 78.5% with a cut-off of apnoea-hypopnoea index ≥10 in a study involving 28 acute ischemic stroke patients. [103] Diabetes and smoking history were the significant predictors for post-stroke SDB.

Mood disorders such as depression, [109-111] mania [112] and bipolar disorders, [113] often received limited attention in stroke care process. Other rarer complications include emotional incontinence [114,115] and complex regional pain syndrome [116] have been described.

The prevalence of depression was as high as 36% between 4 to 8 weeks after stroke, using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria. [110] Depression was associated with left hemisphere brain lesion, physical disability measured by mRS >2 and previous history of depression. [110] Glamcevski *et al.* had reported even higher prevalence of depression (66%) at 3 to 6 months after stroke, whereby 51% having mild depression and the remaining 15% with moderate to severe depression. [109] In the same study, depression was higher in both Malay and Chinese ethnic groups than the Indians. Other significant factors included age, discontinuation of pre-stroke lifestyles and poor performance in the activities of daily living. [109] The prevalence of depression was also comparable to stroke patients with vascular dementia at 31.6%. [111] Patients in this subgroup who were older, suffered large artery stroke or right-sided large artery stroke, lower Mini Mental State Examination score and lower Barthel Index were more likely to suffer from depression.

On the other hand, patients with stroke affecting the right cerebral hemisphere or limbic structures may present with the other extreme of mood disorders. A 72 year-old lady presented with abnormal increased goal-directed behaviour associated with visual and auditory hallucinations had a right MCA territory infarct. [112] Tan EC *et al.* reported a case of multifocal cerebral infarcts with right thalamic bleed and illustrated that post-stroke mania and psychosis could potentially due to either the stroke process itself, underlying bipolar disorder or a side-effect of medication. [117] In this report, amitriptyline could have contributed to the development of neuropsychiatric manifestations. Post-stroke mania, however, is a very rare phenomenon. Two other reports described post-stroke emotional incontinence, where patients have heightened tendency to cry or laugh, out of the proportion of their underlying mood as a sequelae of brain damage. [114,115] An interesting case report described a previously healthy 15-year old teenage girl presented with sudden onset of right-sided weakness and subsequently developed alternating depressive and maniac symptoms, who was later diagnosed of having bipolar mood disorder secondary to mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS). [113] Her brain MRI showed multifocal enhancing lesions in bilateral basal ganglia, internal capsules and brainstem.

Quality of life

In a study by Nor Azlin et al., mean score for all eight health domains in the Short-Form Health Survey (SF-36) among stroke patients was lower compared to the general population, except bodily pain. [118] Female subjects reported higher score in all domains compared to men, especially in general health and social functioning domains. [118] The health-related quality of life was not affected by post-stroke duration in this study. Similar findings were reported by

Samsiah *et al.* using a different measuring tool for quality of life, namely Stroke Specific Quality of Life (SS-QOL). [119] This cross-sectional study conducted on 107 post-stroke patients revealed that their mean SS-QOL was 141.8±40.32. The two domains affected were work and productivity, as well as thinking. However, few items from SS-QOL were inappropriate in developing country and not culturally sensitive.

Caregivers of stroke survivors
Fatimang L *et al.* investigated the stroke care burden among 96 women caring for elderly stroke survivors and factors influencing it. Using Zarit Burden Interview short version to measure care burden, more than one-third of them perceived of having high burden as caregivers. [120] Factors associated with high care burden included caring for stroke patients who were bed bound and duration of daily care duty of ≥8 hours.

Predictors of stroke-associated disability and survival
A prospective study on 218 patients has identified several independent predictors of in-hospital mortality for acute ischemic stroke patients, such as MCA infarct (OR=1.21), AF (OR=9.77), diabetes (OR=4.88), Barthel Index <5/20 (OR=4.2) and GCS <9 (OR=3.9), regardless of age and gender. [15] Another study demonstrated GCS deterioriation (OR=46.04), poor GCS on admission (OR=12.35) and haemorrhagic stroke (OR=3.45) being the independent predictors of one-month mortality for stroke patients. [14] Besides, dysphagia at initial presentation has been shown to be an independent predictor for stroke-associated mortality during hospitalization [16] and at one-month. [99] Diabetes with high blood glucose level on admission (OR=4.88) was also a significant predictor of mortality. [20] Stroke patients with AF had longer hospital stay, higher mortality rate and greater functional disability upon discharge, compared to patients without AF. [22]

High blood pressure after intracranial hemorrhage may have detrimental outcome, possibly contributing to complications such as re-bleeding and hematoma expansion. [65] Patient who developed stroke-associated pneumonia (OR=14.90) had significant shorter mean survival compared to patients who did not. [72]

In a prospective observational study involving 79 subjects, fewer stroke patients with BMI ≥25kg/m^2 had severe disability (mRS=5) at 1 month compared to their counterparts with BMI <25kg/m^2. [121] However, multivariate analysis did not support BMI being an independent predictor for stroke severity in this study, besides the patient's age.

Leukoaraiosis or white matter abnormality was present in 48% among a small cohort of 60 acute stroke patients admitted to a tertiary university hospital. [122] Such abnormality correlated significantly with aging and hypertension. Its presence did not affect functional disability (Barthel Index was <60) and mortality at three months post-stroke, but could predict early cognitive dysfunction.

The role of biomarkers in predicting stroke outcome remained equivocal. Plasma for tissue factor (thromboplastin) did not correlate with physical functionality at one month post stroke and recurrent stroke event. [123] However, age and MCA infarcts were significant independent predictors for severe disability with Barthel Index ≤9 at one month. On the other hand, elevated C-reactive protein (CRP) within 72 hours after an acute ischaemic stroke was significantly associated with poorer physical functional outcome at one month and predicted a larger infarct size. [124] It was hypothesized that CRP elevation may reflect the extent of ischaemic area while post-ischaemic inflammation may contribute to continuing ischaemic brain injury.

SECTION 4: FUTURE RESEARCH DIRECTION FOR STROKE IN MALAYSIA

Stroke is a leading cause of adult disability and dependency, resulting in substantial demands in individual, family and healthcare resources in the country. There are many challenges in stroke research closely related to socioeconomic, political and regulatory factors. Nonetheless, there are growing potential areas for epidemiological, clinical, genetic, psychosocial and economic research in stroke, given the quantity and diversity of patients in Malaysia. [125]

There were only two large epidemiological studies comparing of the disease burden with neighouring ASEAN countries. [4,6] The majority of the prospective studies looking at stroke outcomes mainly focused on mortality and morbidity, with their associated predictors, and were of single centre experience. Further research comparing the vital registries of the population (mortality) and those reported from NSR, as well as head-to-head comparisons with other developing and developed countries will depict a clearer picture of stroke burden in Malaysia and to understand the gaps in stroke services in the country. Epidemiological research on ethnographic propensity for stroke, factors contributing to recurrent strokes, issues pertinent to cardioembolic stroke are in need. The National Stroke Registry could be improved with mandatory updates from all regional hospitals, and increasing financial and logistical supports from the government. [126]

With regards to risk factors for stroke, there were few single centre studies looking at risk factors associated with acute ischemic stroke. Few case reports have described rare causes of stroke. Data on common risk factors management and stroke incidence are lacking. Studies on post-stroke risk factors control and outcomes will help to identify areas for improvement in stroke care. Besides, the increasing young stroke and haemorrhagic stroke with their associated risk factors are yet to be further explored.

There have been growing interests in identifying potential biomarkers (fibrinolytic markers, microRNA profiling, tissue factor, CRP, homocysteine with specific genotype), which might prognosticate the disease. However, these studies with small sample size might have led to inconclusive results. There was a small prospective observational assessing the role of CT perfusion scan, in identifying hyperacute stroke, to guide thrombolysis therapy. Review articles on ASPECTS score and assessment of arterial collateralization will be of interest for clinicians in pursuit of advancement in this field. [45,67] Further research require larger sample size and to assess the feasibility and applicability of these diagnostics and prognostics tools at the local settings.

There has been encouraging involvement of Malaysian researchers, and Malaysian patients in RCTs for acute and post-stroke interventions at both local and international settings. Although local RCTs were of small sample size, the results were encouraging. For instances, intravascular hypothermia might have beneficial effect in acute haemorrhagic stroke, PEG-tube feeding improved nutritional status with reduced complications compared to NG tube feeding, and botox injection was beneficial for post-stroke wrist and finger spasm. Some observational studies demonstrated the beneficial roles of statins, ACEi, antiplatelet or combination in improving stroke mortality. While the review articles on robotically assisted brain controlled interface and stem cell therapy for neuro-regeneration are interesting, field studies are yet to be conducted. Given the magnitude of the disease burden and emerging treatment modalities, many more hypotheses can be tested through RCTs. In the coming years, more local data on outcomes of thrombolytic therapy will be reported, as the study is currently undergoing.

With the growing prevalence of stroke over time, the burden of post-stroke complications, particularly depression and dementia, poses threats to the already overwhelmed healthcare system, not to mention the strains on the psychosocial aspects of patients and their caregivers. In fact, these long term complications are not routinely addressed in clinical practice during long term follow-up. Continuous surveillance and effective screen-to-treat strategies should be designed and incorporated into the integrated stroke care pathways.

Rehabilitation is a vital component in stroke care. Innovative home-based therapies as an alternative to standard physiotherapy have been studied. However, their feasibility and applicability to the larger affected population remain unknown. There is a need to assess the readiness of community services to handle growing stroke patients, to map the healthcare facility such as rehabilitation centre, to the needs of the population. While primary care services are "well" designed for managing majority of non-communicable diseases, it is rather a fragmented one for stroke, due to the lack of coordination and organized care pathway for patients. Besides, the potential roles of traditional complementary medicine as an adjunct rehabilitative are to be further explored.

There have been attempts to study the healthcare cost for managing stroke patients. Undoubtedly, there is a great need to evaluate the cost of stroke not only to the healthcare sector which involves acute admission, complications and management, recurrent admissions and long term follow-up, but also to the society at large. The latter should include DALYs, all the indirect costs incur to patients and care-givers.

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