EVALUATION OF IMPACT OF GUIDELINE ADHERENCE, ASSOCIATED RISK FACTORS ON MORTALITY AND FUNCTIONAL DISABILITY AND DIRECT COSTS OF IN-HOSPITAL CARE IN PATIENTS WITH FIRST-EVER ACUTE ISCHEMIC STROKE

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by

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ADL	Activity of Daily Living
AF	Atrial Fibrillation
AHA/ASA	American Heart Association/American Stroke Association
BI	Barthel Index
CPG	Clinical Practice Guideline
CT	Computed Tomography
DM	Diabetes mellitus
DVT	Deep Vein Thrombosis
GCS	Glasgow Coma Scale
GWTG-Stroke	Get-With-The-Guidelines-Stroke
HF	Heart failure
ICD-11	International Statistical Classification of Diseases and Related Health Problems 11th Revision
INR	International Normalized Ratio
IQR	Interquartile Range
IV	Intravenous
KPIs	Key Performance Indicators
LACI	Lacunar Infarct
MCA	Middle Cerebral Artery
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NINDS	National Institute of Neurological Disorders and Stroke

NIHSS	National Institutes of Health Stroke Scale
NMDA	N-methyl-D-aspartate
NneuR	Malaysian National Neurology Registry
NOMASS	Northern Manhattan Stroke Study
NSR	Malaysian National Stroke Registry
OCSP	Oxfordshire Community Stroke Project
PACI	Partial Anterior Circulation Infarct
POCI	Posterior Circulation Infarct
rt-PA	Recombinant Tissue-Type Plasminogen Activator
SAMPL	Statistical Analyses and Methods In The Published Literature
SPSS	Statistical Package for Social Sciences
TACI	Total Anterior Circulation Infarct
TIA	Transient Ischemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
tPA	Tissue plasminogen activator
UK	United Kingdom
WHO	World Health Organization

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PENILAIAN IMPAK PEMATUHAN GARIS PANDUAN, FAKTOR RISIKO YANG BERKAITAN DENGAN MORTALITI DAN KETAKUPAYAAN FUNGSI DAN KOS LANGSUNG PENJAGAAN DI HOSPITAL DALAM KALANGAN PESAKIT STROK ISKEMIK AKUT KALI PERT PERTAMA

ABSTRAK

Strok kekal sebagai punca utama kematian dan hilang upaya global. Walau bagaimanapun, terdapat data yang terhad tentang bagaimana pematuhan kepada garis panduan mempengaruhi hasil strok iskemia akut di Malaysia. Kajian ini bertujuan untuk menilai kesan pematuhan garis panduan terhadap hasil strok, membangunkan dan mengesahkan model ramalan berdasarkan garis panduan, dan menilai kos perubatan langsung penjagaan di hospital untuk pesakit dengan strok iskemia akut yang pertama. Kajian itu adalah kajian kohort pemerhatian berbilang pusat yang melibatkan pesakit dewasa dengan strok iskemia akut pertama mereka yang menerima rawatan di pusat klinikal yang mengambil bahagian di Pejabat Pendaftaran Strok Kebangsaan Malaysia (NSR). Ia terdiri daripada tiga fasa: Fasa I (n=899) menilai pematuhan garis panduan menggunakan petunjuk prestasi utama (KPI), Fasa II (n=899) memfokuskan pada pembangunan dan pengesahan model ramalan klinikal berpandukan garis panduan, dan Fasa III (n=122) meneliti kos perubatan langsung rawatan pesakit dalam menggunakan pendekatan kos penyakit dari sudut bawah dari perspektif hospital. Semua kos dikira berdasarkan perspektif hospital (kerajaan). Hasil utama yang dinilai dalam kajian adalah kematian semua sebab, ketidakupayaan fungsi yang diukur dengan skala Rankin yang diubah suai (mRS≥2), dan kos langsung. Data dianalisis menggunakan IBM SPSS Statistics for Windows, versi 26.0. Dalam Fasa I, pematuhan kepada KPI didapati sangat rendah untuk alteplase (5.5%) dan rendah

untuk terapi penurun lipid (30.8%), profilaksis trombosis urat dalam (DVT) (38.5%), dan antikoagulasi untuk fibrilasi atrium (AF).) (45.6%). Pematuhan yang lebih baik terhadap KPI diperhatikan untuk rawatan antitrombotik dalam tempoh 48 jam selepas kemasukan (75.9%), pemeriksaan disfagia (74.7%), rawatan antitrombotik semasa keluar (74.4%), pendidikan strok (72.3%), dan pemulihan strok (57.2%). Pematuhan kepada KPI, termasuk rawatan antitrombotik awal, pemeriksaan disfagia, rawatan antitrombotik semasa keluar, terapi penurun lipid, pendidikan strok, dan pemulihan, dikaitkan dengan kematian yang lebih rendah dan hasil ketidakupayaan berfungsi yang lebih baik ($p<0.001$). Dalam Fasa II, model akhir mengenal pasti umur, skor NIHSS, dan diabetes sebagai peramal kematian selepas strok. Peramal lain termasuk pematuhan kepada rawatan antiplatelet dalam masa 48 jam, pemeriksaan disfagia, rawatan antiplatelet semasa keluar, terapi penurun lipid, pendidikan strok, dan pemulihan. Model-model ini menunjukkan diskriminasi yang sangat baik (kawasan di bawah lengkung ciri operasi penerima, AUROC) dan penentukuran (ujian Hosmer-Lemeshow). Peramal ketidakupayaan berfungsi adalah umur, jantina wanita, dan diabetes. Peramal lain termasuk infark peredaran posterior (POCI), pematuhan kepada rawatan antiplatelet dalam masa 48 jam, terapi penurun lipid, pendidikan strok, dan pemulihan. Model untuk ketidakupayaan berfungsi menunjukkan diskriminasi dan penentukuran yang baik. Dalam Fasa III, purata keseluruhan (±SD) kos perubatan langsung bagi rawatan strok pesakit dalam bagi setiap pesakit ialah RM1,970.7±1,385.8. Kos kemasukan (RM754.6±632.2) dan perbelanjaan radiologi (RM794.0±284.4) menyumbang paling banyak kepada kos keseluruhan. Purata kos penjagaan adalah lebih tinggi dengan ketara dalam kalangan pesakit yang mempunyai status fungsi yang tidak menggalakkan berbanding mereka yang mempunyai hasil yang menggalakkan ($p=0.002$). Kesimpulannya, kajian ini menyerlahkan keperluan

untuk penambahbaikan yang ketara dalam pematuhan KPI garis panduan pada pesakit dengan strok iskemia akut pertama mereka, kerana ia dikaitkan dengan hasil strok yang lebih baik. Kajian itu juga membangunkan dan mengesahkan model ramalan klinikal berpandukan garis panduan untuk hasil strok dengan prestasi yang memuaskan dan berpotensi untuk kegunaan klinikal. Model ini boleh membantu dalam meramalkan hasil selepas strok dan memberikan sokongan yang berharga untuk pengurusan pesakit dan membuat keputusan klinikal. Tambahan pula, kajian itu menekankan bahawa kos langsung rawatan strok pesakit dalam adalah besar dan dipengaruhi oleh ciri-ciri pesakit, keterukan strok, jenis intervensi, dan tempoh tinggal di hospital. Merawat pesakit mengikut garis panduan boleh mengurangkan kos, meningkatkan hasil pesakit dan meningkatkan kepuasan.

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ABSTRACT

Stroke remains a significant global cause of death and disability. However, there is limited data on how adherence to guidelines affects outcomes of acute ischemic stroke in Malaysia. This study aimed to assess the impact of guideline adherence on stroke outcomes, develop and validate prediction models based on the guidelines, and evaluate the direct medical costs of in-hospital care for patients with their first-ever acute ischemic stroke. The study was a multi-centered observational cohort study involving adult patients with their first-ever acute ischemic stroke who received care at participating clinical centers of the Malaysian National Stroke Registry (NSR). It consisted of three phases: Phase I (n=899) assessed guideline adherence using key performance indicators (KPIs), Phase II (n=899) focused on developing and validating guideline-guided clinical prediction models, and Phase III (n=122) examined the direct medical costs of inpatient care using a bottom-up cost-of-illness approach from the hospital's perspective. All costs were calculated based on the hospital's (government's) perspective. The primary outcomes assessed in the study were all-cause mortality, functional disability measured by the modified Rankin scale (mRS≥2), and direct costs. Data were analyzed using IBM SPSS Statistics for Windows, version 26.0. In Phase I, adherence to KPIs was found to be very low for alteplase (5.5%) and low for lipid-lowering therapy (30.8%), deep vein thrombosis (DVT) prophylaxis (38.5%), and anticoagulation for atrial fibrillation (AF) (45.6%).

Improved adherence to KPIs was observed for antithrombotic treatment within 48 hours of admission (75.9%), dysphagia screening (74.7%), antithrombotic treatment upon discharge (74.4%), stroke education (72.3%), and stroke rehabilitation (57.2%). Adherence to KPIs, including early antithrombotic treatment, dysphagia screening, antithrombotic treatment upon discharge, lipid-lowering therapy, stroke education, and rehabilitation, was associated with lower mortality and improved functional disability outcomes ($p<0.001$). In Phase II, the final models identified age, NIHSS score, and diabetes as predictors of mortality after stroke. Other predictors included adherence to antiplatelet treatment within 48 hours, dysphagia screening, antiplatelet treatment upon discharge, lipid-lowering therapy, stroke education, and rehabilitation. These models demonstrated excellent discrimination (area under the receiver operating characteristic curve, AUROC) and calibration (Hosmer-Lemeshow test). The predictors of functional disability were age, female gender, and diabetes. Other predictors included posterior circulation infarct (POCI), adherence to antiplatelet treatment within 48 hours, lipid-lowering therapy, stroke education, and rehabilitation. The models for functional disability showed good discrimination and calibration. In Phase III, the overall average (±SD) direct medical cost of inpatient stroke care per patient was RM1,970.7±1,385.8. The admission costs (RM754.6±632.2) and radiology expenses (RM794.0±284.4) contributed the most to the overall cost. The average cost of care was significantly higher among patients with unfavorable functional status compared to those with favorable outcomes (p=0.002). In conclusion, this study highlights the need for significant improvement in adherence to guideline KPIs in patients with their first-ever acute ischemic stroke, as it is associated with improved stroke outcomes. The study also developed and validated guideline-guided clinical prediction models for stroke outcomes with satisfactory performance and

potential for clinical utility. These models can assist in predicting outcomes after stroke and provide valuable support for patient management and clinical decision-making. Furthermore, the study emphasizes that the direct costs of inpatient stroke care are substantial and influenced by patient characteristics, stroke severity, type of intervention, and length of hospital stay. Treating patients according to guidelines may reduce costs, improve patient outcomes, and enhance satisfaction.

CHAPTER 1

INTRODUCTION

1.1 Background

Stroke is the second-leading cause of mortality and disability worldwide, after ischemic heart disease (Valery L. Feigin et al., 2021). The burden of stroke has risen significantly, with an incidence of 16 million and over six million deaths in 2019 (Valery L. Feigin et al., 2021). Developing countries account for the bulk of stroke-related deaths (75.2%) and disability-adjusted life years (DALYs) (81.0%) (Rajsic et al., 2019). Asia, home to more than half of the world's population and several developing countries, is a region where the burden of stroke is a significant problem (Venketasubramanian et al., 2017a).

Malaysia, a Southeast Asian nation with a developing economy, has identified stroke as an important public health issue. It is the third most frequent cause of death and the second highest cause of morbidity in Malaysia (Chia et al., 2020). It is estimated that stroke incidence will rise exponentially in the next two decades due to the aging population, and about 20,000 deaths due to stroke were recorded in 2020 (about 12.9% of total deaths) (Tan & Venketasubramanian, 2022). However, compared to many Southeast Asian nations, Malaysia has reduced stroke mortality and DALYs based on age and gender indicators (Venketasubramanian et al., 2017a).

1.1.1 Stroke history

Stroke is a cerebrovascular disorder caused by reduced blood supply to the brain (Engelhardt, 2017). The term "stroke" originated from the ancient Greek word "apoplexy," meaning "struck down with violence" (Schutta & Howe, 2006). In 460–

370 BC, Hippocrates was the first to describe the sudden paralysis associated with ischemia, using the term "apoplexy" (Karenberg, 2015; Thaakur, 2019). Johann Jacob Wepfer (1620-1695) later identified cerebral hemorrhage as the cause of apoplexy, distinguishing it as a hemorrhagic stroke. He also recognized the carotid and vertebral arteries as the primary blood vessels supplying the brain and identified blockages in these vessels as the cause of ischemic stroke (Nwankwo & Makachi, 2014). Stroke can result from either blockage (ischemic stroke) or bleeding (hemorrhagic stroke) (Gomes & Wachsman, 2013b).

1.1.2 Stroke definitions

World Health Organization (WHO) defined stroke as a rapidly developing clinical symptoms of focal (or generalized) brain dysfunction that continue longer than 24 hrs. or cause death but have no other apparent explanation besides vascular origin (Coupland et al., 2017). A stroke occurs when there is a disruption in the blood flow to the brain, leading to damage to the brain tissue. Most strokes, accounting for approximately 85% of cases, are ischemic. These typically result from the presence of thrombi, which are small blood clots that block a brain artery. Another significant cause of ischemic stroke is emboli, commonly originating from the heart or carotid arteries, causing a reduction in blood supply to specific brain areas. The remaining 15% of stroke cases are composed of subarachnoid and intracerebral hemorrhage, highlighting the diverse nature of stroke etiology (Gomes & Wachsman, 2013a). An immediate brain scan using Computed brain tomography (CT) and magnetic resonance imaging (MRI) enables timely treatment and improves stroke outcomes (Hasan et al., 2018). Hemorrhagic stroke, which often results in death, especially in the acute and

subacute phases, is thought to have a worse overall prognosis than ischemic stroke (Salvadori et al., 2020).

1.1.3 Stroke epidemiology

Approximately 75% of all strokes are first-time (Benjamin et al., 2018). Stroke is more likely to occur at an older age but can happen at any age (Pliskin & Sworowski, 2020). Additionally, over the past 20 years, the burden of stroke in those under 65 has increased significantly (Mira Katan & Andreas Luft, 2018). Stroke trends vary depending on race and ethnicity: initial stroke risks are twice as high in African Americans as in Caucasians (Barthels & Das, 2020). Stroke rates are rising in developing nations, including Malaysia, with a population of around 30 million. The percentage of stroke-related fatalities in Malaysia ranged from 6.6 to 34.0% (Chen et al., 2019; Loo & Gan, 2012). Of all stroke cases, ischemic stroke represented 79.4%.

1.2 Acute Ischemic stroke management

Stroke diagnosis and treatment options have dramatically improved over the last ten years. Early detection and triage using established methods are crucial in treating stroke (Phipps & Cronin, 2020b; Waqas et al., 2019). Stroke management involves many approaches and is influenced by the type of stroke and other clinical traits (Phipps & Cronin, 2020b). Acute ischemic stroke patients require complex, multimodal care that involves early interventions to limit brain damage, general life support techniques, and therapies for avoiding or treating acute neurological sequelae (Phipps & Cronin, 2020a).

The purpose of acute general management in stroke is to decrease mortality and functional disability by offering supportive care and treating immediate complications. In stroke management, it is crucial to focus on preventing and treating a range of complications that may arise, including pressure ulcers, seizures, venous thromboembolism, dysphagia, aspiration pneumonia, infections, and, at times, the management of increased intracranial pressure. By actively addressing these complications, healthcare professionals can optimize patient care, improve outcomes, and support recovery following a stroke. The National Institute of Health Stroke Scale (NIHSS) is one example of a validated neurological scale that can be used to monitor neurological states.

The acute management of ischemic stroke includes, in particular, recanalization techniques using intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) to reperfuse the ischemic area, neuroprotective techniques intended to preserve the penumbral tissues, and techniques to increase the time window for revascularization procedure (Zerna et al., 2018). Alteplase, an approved thrombolytic therapy for acute ischemic stroke, is administered as a 10% bolus followed by a 90% infusion over an hour following stroke symptoms within 3 - 4.5 hours. Tenecteplase can be administered intravenously in cases where an acute stroke occurs within 4.5 hours and imaging reveals symptoms of a major arterial occlusion.

1.2.1 Guideline key performance indicators

Clinical guidelines guide standardized care by recommending the most recent best evidence for the prevention, diagnosis, prognosis, and treatment of a particular medical condition (Murad, 2017). In the last decade, guidelines for stroke care have been developed locally and internationally. Stroke guidelines, which first appeared in

the US, are replicated worldwide, revised, and updated with advances in knowledge (Ormseth et al., 2017; Warner et al., 2019b).

Clinical guidelines compliance is the observable application of the defined recommendations used generally in the literature to refer to all elements that may affect the adoption of advised best practices in light of the best and most recent data (Donnellan et al., 2013). According to studies, following evidence-based recommendations is a vital sign of high-quality hospital care for stroke patients (Donnellan et al., 2013; Warner et al., 2019b). Furthermore, studies have shown that quality improvement initiatives like the Get-With-The-Guidelines-Stroke (GWTG-Stroke) enhance stroke outcomes (Ormseth et al., 2017; Warner et al., 2019b).

The most recent clinical practice guideline (CPG) for the treatment of ischemic stroke in Malaysia was released in 2020; the first and second versions, meanwhile, were released in 2006 and 2012, respectively (Al-Temimi et al., 2020; Zariah A Aziz et al., 2015; McMahon et al., 2020). Prompt intervention greatly improved stroke outcomes (Al-Temimi et al., 2020). This recommendation was developed as a manual for best clinical practice based on the most up-to-date evidence. Nine (9) key performance indicators were recommended and adopted by the Malaysian National Stroke Registry to assess the quality of stroke care. The minimum requirements for adherence to the guidelines in eligible patients with acute ischemic stroke include; thrombolytic therapy within 4.5 hours (≥65%), antithrombotic therapy within 48 hours (≥90%), dysphagia screening (≥80%), deep vein thrombosis prophylaxis (≥80%), anticoagulation for atrial fibrillation (≥80%), stroke education (≥90%), rehabilitation assessment (≥90%), antithrombotic therapy upon discharge (≥80%), cholesterol reducing medication upon discharge (≥90%).

1.2.2 Clinical prediction models

Various outcomes for stroke patients can be predicted using prediction models. Certain models have employed costs and length of stay as their main outcomes (García-Rudolph et al., 2020), which can have health economic or policy implications but minimal clinical significance for guiding decisions about urgent care. Although they are significant to the underlying disease process, other models that predict radiological outcomes such as infarct magnitude, post-treatment bleeding, or quality of reperfusion are not directly indicative of a patient's fate (Bourcier et al., 2019; Jiang et al., 2020; Ko et al., 2021). There are ample prediction models in the prognostic research literature, but with limited clinical utility, particularly in long-term care (Fahey et al., 2018). Clinicians often frown upon using risk scores in practice (Fahey et al., 2017). Many think there isn't enough evidence to show the model's repeatability and transferability to another population (Fahey et al., 2017). A risk score must be accurate (properly calibrated with good discriminative ability), general, and clinically trustworthy to be useful (validated). The selection of a prediction model is still debatable because no one model is likely to be appropriate for all circumstances or subgroups.

Clinical prediction models use patient data and treatment processes to calculate the likelihood of a specific event or result in the future (prognosis) (Chen, 2020). These models have proven valuable in stroke care as clinicians set goals and reach shared decisions based on an estimated probability (Chen, 2020). Models such as the Framingham Score for risk of coronary heart disease (2008) (D'Agostino et al., 2008), QRISK for cardiovascular disease risk (2007) (Hippisley-Cox et al., 2007), Reynolds men for cardiovascular disease risk in men (2008) (Ridker et al., 2008), Reynolds women or cardiovascular disease risk in women (2007) (Ridker et al., 2008), and

EURO-SCORE for risk of mortality after cardiac surgery (Roques et al., 2003) have been used in stroke to help clinical decision-making, diagnostic workup, and treatment selection, to guide health service planning and stratified care (Fahey et al., 2018).

1.2.3 Stroke economic evaluation

Stroke imposes a significant economic burden on both individuals and society. Stroke accounts for approximately 3.4% of global healthcare expenditure, reflecting substantial financial commitment (T. N. Rochmah et al., 2021). The economic impact of stroke is substantial; approximately 1.7-4% of total healthcare expenditures are stroke-related (Luengo-Fernandez et al., 2020). The economic burden of stroke in Asia varies significantly across countries (Turana et al., 2021). In China, the estimated average cost per capita for patients with high-risk stroke in 2010 was $517.8 per year (Turana et al., 2021). A review in 2019 compared stroke costs in Indonesia, Malaysia, and Singapore, revealing variable costs of $135.55 per day care (3.88% of GDP per capita), $227.53 per day care (2.11% of GDP per capita), and $366.76 per day care (0.65% of GDP per capita), respectively (Wijaya et al., 2019b).

Various methods have been developed and introduced to measure the cost of care, including assessing healthcare providers' or societal perspectives. However, comparing countries remains unsuccessful as countries worldwide are different in clinical practice and assessment of unit costs (Grieve et al., 2001). The length of hospital stay mainly determines the total stroke-associated cost. However, factors such as gender, age, co-morbid conditions, and the severity of the stroke might significantly contribute to the overall costs of stroke care (Asil et al., 2011; Gioldasis et al., 2008; Grieve et al., 2001).

Despite increasing stroke admissions, investigations into the economic impact of stroke care are limited in Malaysia (Kooi et al., 2016; Rajsic et al., 2019). Some studies evaluated the cost of treating acute stroke using a case mix at tertiary hospitals (Aznida et al., 2012; Nur & Sulong, 2012). Other studies determined the cost of out-patients stroke care, particularly the rehabilitation (Hejazi et al., 2015), and more recently, a study that estimated the cost of stroke from the healthcare provider perspective (Lee et al., 2017). Therefore, assessing the economic burden of stroke by advancing interventional therapies would provide a more useful cost estimation that would allow better planning and utilization of limited resources.

Cost of illness studies plays a vital role in quantifying the economic impact of a disease, encompassing various aspects of care and associated costs (Strilciuc et al., 2021). These studies aim to estimate the expenses related to inpatient, outpatient, and other types of care and the indirect costs resulting from productivity loss due to prolonged rehabilitation, temporary or lifelong disabilities, and mortality. Although intangible costs are also relevant, they are often challenging to measure and, thus, not typically included in the cost of illness studies. Such studies are valuable tools for estimating disease-specific expenditures and informing health financing policies. They help reconstruct patient pathways, compare theoretical and real-world care pathways, identify key stakeholders and cost components, and estimate the societal costs attributed to the disease.

Additionally, cost of illness studies gather data on various cost categories, including direct medical costs associated with inpatient, outpatient, and home care, direct non-medical costs such as social services and transportation, and indirect costs stemming from productivity losses, cognitive/physical impairments, and mortality. The economic perspective adopted in the study determines which cost components

will be included and quantified. In contrast, the study scope defines the setting (institutional, regional, national, international) where the research will be conducted. Other study design components, such as the prospective or retrospective time direction and the epidemiological approach (incidence/prevalence), shape the data selection and collection process (Strilciuc et al., 2021).

1.3 Acute ischemic stroke outcomes

The lesion's type, size, and location affect the stroke's prognosis. Stroke types, ischemic and hemorrhagic, have a greater fatality rate (Singh et al., 2018). Ischemic stroke tends to have the least neurological and functional recovery (Valery L Feigin et al., 2021). The patients' outcomes after stroke are time dependent. The number of stroke patients who survive longer has increased due to treatment advancement in acute stroke care (Grefkes & Fink, 2020).

1.3.1 Mortality after acute ischemic stroke

Stroke remains a leading cause of death and disability worldwide (Valery L Feigin et al., 2021). Studies have shown that the highest risk of mortality following a stroke occurs during the first 30 days, while the average annual mortality rate after that is reported to be around 10% (Singh et al., 2018). Following an initial stroke, approximately one-third of the patients didn't survive beyond three years (Koton et al., 2014). Additionally, according to data from previous studies in Malaysia, the overall mortality was 37%, and most patients died within the first month following stroke (34%) (W. Y. Hwong et al., 2021; Jaya et al., 2001). Another study found that the mortality rate was 11.4% in the first month following the stroke attack, with half of the fatalities occurring in the first week (Cheah et al., 2016). In addition, deterioration

of the Glasgow coma scale (GCS), middle cerebral artery (MCA) infarct, atrial fibrillation (AF), diabetes (DM), and severe disability were associated with increased mortality rate after acute ischemic stroke (El Hajj et al., 2023). Nonetheless, timely and proactive interventions to prevent further cardiovascular events can significantly enhance long-term survival rates after a stroke (Lip et al., 2022). By actively and consistently applying practical measures for cardiovascular event prevention, individuals can substantially improve their prognosis and overall quality of life following a stroke (Koton et al., 2014).

1.3.2 Disability after acute ischemic stroke

Depending on the part(s) of the central nervous system affected, a stroke can have various manifestations of the disability. The most common manifestations include focused weakness and sensory difficulties, speech and swallowing disorders, loss of vision or neglect, cognitive problems with inattention or memory loss, and emotional problems with mood or worry. Therefore, early stroke therapy by medical, surgical, or rehabilitation measures is crucial to lowering the severity of the disability, the risk of subsequent complications, and the likelihood of lifelong deficits (Powers et al., 2018).

Because the degree of disability immediately following a stroke affects how patients may recover long-term (Pettersen et al., 2002; Meijer et al., 2003), providing a quantitative prognosis following the attack requires the use of a repeatable, valid measure of impairment. However, disability rather than mortality accounts for the majority of the burden of stroke for patients and their families (Valery L Feigin et al., 2021). Functional outcome measures play a prominent role in stroke studies, with the modified Rankin Scale (mRS) being the most used outcome measure for acute

ischemic stroke. The mRS is preferred due to its ease of administration, high repeatability, and minimal floor or ceiling effects (Broderick et al., 2017). A ceiling effect occurs when a measurement tool cannot capture further improvements in patients who have reached a high level of functional recovery. In the case of the mRS, it effectively assesses functional outcomes across a wide range of stroke severities, including patients with minimal impairment. This characteristic ensures that the mRS can detect and measure changes in functional status even in individuals with relatively mild strokes or those who have achieved a high level of recovery. Furthermore, the mRS captures the outcome of death, making it possible to examine death and disability as a single outcome (Ganesh et al., 2017).

1.3.3 Cost of acute ischemic stroke care

Stroke is the most common cause of serious long-term impairment and has a major financial impact on the patient, family members, health system, and society. In the United Kingdom (UK), the significant human burden caused by stroke is paralleled by the substantial cost of providing healthcare to stroke patients. Stroke care alone accounts for approximately 3-5% of the total healthcare expenditure in the country (Xu et al., 2018). Stroke costs in the United States (US) totaled $103.5 billion in 2016, with indirect costs from underemployment and premature death accounting for 68.5% of the overall cost ($68.5 billion) (Khan et al., 2021).

The prevalence of diseases in a population can be determined through several measures. Life expectancy, death rates, and the number of new and existing instances of a particular disease are epidemiological indicators (Thinni Nurul Rochmah et al., 2021). Epidemiological indicators quantify the impact of an illness on quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs). The severity of the

disease and the monetary losses suggested by absenteeism from work, usage of medical facilities, and other costs are represented by using inpatient and outpatient services. Direct medical costs, direct non-medical costs, and indirect costs of disease and health spending methods are some of the economic elements that were calculated (Thinni Nurul Rochmah et al., 2021).

1.4 Problem statement and rationale of the study

Stroke incidence is rising in low- and middle-income nations. (Feigin et al., 2017). The main causes of high mortality and disability following stroke are thought to be risk factors and care quality (Wijaya et al., 2019a). Improving stroke care following evidence-based guidelines greatly improves patient outcomes in high-income countries (Bayley et al., 2015; Ormseth et al., 2017). However, nations significantly differ in how acute strokes are generally treated and how they turn out (Wu et al., 2019). Based on the most recent, highest-quality research, this recommendation was created as a manual for optimum clinical practice. It was attempted to achieve local relevance using local data and publications. The best clinical outcome for each patient's care may not always result from following this recommendation. Each healthcare provider is accountable for managing their patients based on the local clinical presentation and therapy options.

Developing countries like Malaysia have wide variations in stroke care quality (Yaria et al., 2021). Malaysia faces additional difficulties in providing the best possible stroke care given its low resources, which may not be available to most of the population. More recently, a stroke care unit, intravenous thrombolysis therapy, and endovascular thrombectomy have been developed (Chia et al., 2020). Addressing these gaps could be facilitated by stroke care quality improvement strategies that ensure

timely and effective implementation of evidence-based guidelines with attendant benefits to the patients and entire health systems. However, there is minimal research on how adherence to standardized quality-of-care indicators affects stroke outcomes, especially in emerging nations like Malaysia with diverse racial/ethnic populations and healthcare systems.

To enhance clinical decision-making and develop effective risk prediction models, there is a need for a deeper understanding of risk factors and biomarkers. Current data on predicting stroke outcomes show that prediction models based solely on clinical criteria exhibit limited discrimination between individuals (Shipe et al., 2019). Researchers have been studying stroke survivors' functional status and mortality since the 1980s, and the number of studies in this area has significantly increased (Vieira et al., 2021). Recent advancement saw the discovery of at least 63 multivariate models of functionality prognosis and the identification of more than 195 predicted variables for post-stroke functional recovery (Fahey et al., 2018). However, it is still debatable which predictive model should be employed because there isn't one that can be applied to all situations, subgroups, or evaluation dates. Predictive models of inpatient death from acute stroke were created and internally verified using the GWTG-Stroke database. A risk score, including the NIHSS score, showed excellent discrimination and calibration (Sun et al., 2019). However, its application to Malaysian patients suffering from acute ischemic stroke is still questionable.

Despite rising stroke admissions, there has not been much research regarding the financial impact of stroke care in Malaysia (Kooi et al., 2016; Rajsic et al., 2019). Some of the studies evaluated the cost of treating acute stroke using a case-mix at tertiary hospitals (Aznida et al., 2012; Nur & Sulong, 2012), while other studies determined the cost of out-patients stroke care, particularly the rehabilitation (Hejazi

et al., 2015), and more recently a study that estimated the cost of stroke from the healthcare provider perspective (Lee et al., 2017). Therefore, assessing the economic burden of stroke by advancing interventional therapies would provide a more useful cost estimation that would allow better planning and utilization of limited resources.

1.5 Significance and benefits of the study

Studies on stroke and its pathological forms, including information on epidemiology, are crucial for allocating resources and developing evidence-based stroke care plans. Comprehensive descriptions of stroke epidemiology have been developed largely due to population-based research. Studies have mostly concentrated on defining stroke patterns and clinical characteristics according to sociodemographic and risk variables and ascertaining the relationship between these variables and patient outcomes (Higashida et al., 2013). Stroke registries were started more recently to close a critical gap regarding the relationship between patient outcomes and adherence to key performance metrics. It is crucial to understand how acute stroke medications, such as thrombolysis, affect patient outcomes to increase adherence to the indicators and enhance patient outcomes (Appelros et al., 2014; Cadilhac et al., 2016).

The findings of this study can be utilized to prioritize these interventions based on a country's needs and to allocate resources for evidence-based planning, prevention, and treatment of stroke and its pathological manifestations. By evaluating the risk-attributable burden of various stroke types in different geographic areas, this study can be utilized to establish location-specific strategies for reducing the burden of stroke. Public health research should prioritize expanding evidence-based preventative interventions that reduce exposure to stroke risk factors. Reduced disparities in acute and chronic stroke prevention, screening, and treatment between high-income and

low- to middle-income nations are also essential. Furthermore, it is vital to prioritize epidemiological studies on the prevalence and risk of stroke in various populations and countries.

Accurate prediction of outcomes in acute ischemic stroke is crucial as it enables clinicians to make timely informed decisions (Chavva et al., 2022). Understanding acute ischemic stroke's potential long-term health and financial impacts is vital for patients, families, and society. A precise prognosis ensures adequate resources are allocated to meet the needs of stroke survivors. Furthermore, it enables the evaluation of the long-term implications of comprehensive strategies focused on ischemic stroke awareness, prevention, and treatment, including the importance of structured stroke unit care and rehabilitation. By predicting outcomes effectively, healthcare professionals can optimize patient care and facilitate appropriate planning for post-stroke management and support (Lin et al., 2018). Furthermore, knowledge of the factors related to functional recovery and mortality is essential for patient evaluation and developing preventive strategies. Setting goals for managing acute stroke and identifying predictors of stroke outcomes are crucial steps in creating a secondary prevention strategy.

1.6 Research questions

1. What are the relationships between guideline adherence and mortality in patients with first-ever acute ischemic stroke?
2. What are the relationships between guideline adherence and functional disability in patients with first-ever acute ischemic stroke?
3. What are the socio-demographic and clinical characteristics that are predictive of mortality in patients with first-ever acute ischemic stroke?

4. What are the socio-demographic and clinical characteristics that are predictive of functional disability in patients with first-ever acute ischemic stroke?
5. What are the direct economic implications of inpatient care in patients with first-ever acute ischemic stroke?

1.7 Objectives of the study

1.7.1 General objective

The main objective of this study is to evaluate the impact of guideline adherence, associated risk factors on mortality and functional disability, and direct costs of inpatient care in patients with first-ever acute ischemic stroke.

1.7.2 Specific objectives

The current study was carried out with the following objectives:

1. To investigate the impact of adherence to guidelines key performance indicators on mortality in patients with first-ever acute ischemic stroke.
2. To investigate the impact of adherence to guidelines key performance indicators on functional disability in patients with first-ever acute ischemic stroke.
3. To develop and validate clinical prediction models of mortality in patients with first-ever acute ischemic stroke.
4. To develop and validate clinical prediction models of functional disability in patients with first-ever acute ischemic stroke.
5. To evaluate the direct costs of inpatient care of patients with first-ever ischemic stroke.

CHAPTER 2

LITERATURE REVIEW

2.1 Stroke general background

Stroke, a cerebrovascular disorder, is a brain disorder resulting from reduced blood supply to underlying tissues (Engelhardt, 2017). The term "stroke" signified an acute neural dysfunction (Moskowitz et al., 2010). It evolved from the ancient term "apoplexy", a Greek word that means "struck down with violence" (Schutta & Howe, 2006). The first person to describe the phenomena of abrupt paralysis frequently linked to ischemia was Hippocrates (460–370 BC). To describe the stroke occurrence, he used the phrase "apoplexy" (Karenberg, 2015; Thaakur, 2019). In his 1658 book Apoplexia, Johann Jacob Wepfer (1620-1695) suggested that apoplexy victims had a cerebral hemorrhage, identifying the cause of hemorrhagic stroke. Wepfer identified the carotid and vertebral arteries as the main blood vessels supplying the brain and the causes of ischemic stroke when he hypothesized that apoplexy would result from a blockage of those blood vessels (Nwankwo & Makachi, 2014). Furthermore, stroke could be caused by blockage (ischemic stroke) or bleeding (hemorrhagic stroke) (Gomes & Wachsman, 2013b).

2.1.1 Stroke global disease burden

Stroke is an important cause of morbidity and mortality, resulting in substantial economic implications (Johnson et al., 2019). Around 6 million people globally die from their first stroke yearly, with roughly 16 million new cases annually (Rajsic et al., 2019). Additionally, individuals over the age of 75 account for more than half of all stroke cases. Although many industrialized countries are experiencing a decline in

the incidence of stroke due largely to better risk factor management, the burden of strokes is still rising due to disability and consequences (Pliskin & Sworowski, 2020). In addition, stroke ranks third in terms of the most frequent causes of mortality, after cancer and heart illnesses, when it is regarded separately from other cardiovascular diseases (Virani et al., 2021).

Although promising data indicates a decrease in stroke rates, the global lifetime risk of stroke is rising due to an aging population and the accumulation of risk factors. From 1990 to 2016, the average global lifetime risk of stroke increased from 22.8 to 24.9% (Virani et al., 2020). Over the past few decades, stroke has become more common in adults under 65. The frequency has increased by 25% worldwide among people 20 to 64 (Mira Katan & Andreas Luft, 2018). Particularly in low- and middle-income countries, the overall burden of stroke is alarmingly shifting towards younger age groups. More youthful people now experience a higher burden of stroke due to the epidemic rise in young adults' cardiovascular risk factors in various countries, including Russia, China, and India (Mira Katan & Andreas Luft, 2018). Compared to Western Europe, the Americas, and Australia, stroke death rates are higher in Asia and Eastern Europe (Venketasubramanian et al., 2017c). Asia, home to more than 60% of the world's population and many of its "emerging" nations has a significant stroke problem. Except for a few countries like Japan, Asia has a higher stroke death rate than Western Europe, the Americas, or Australasia (Feigin et al., 2014).

2.1.2 Stroke burden in Malaysia

Malaysia is a growing nation in Southeast Asia with a total population of roughly 30 million people who are primarily Malays (63%), Chinese (25%), Indians (7%), and other ethnic groups (5.0%) (Shahar et al., 2019). In Malaysia, cerebral

vascular disease ranks third among the leading causes of mortality (Tan & Venketasubramanian, 2022). Between 2008 and 2016, the incidence of stroke increased by 4.9% in males but decreased by 3.8% in women. The 28-day all-cause death rate decreased in both sexes by 13.1 and 10.6%, respectively (Wen Yea Hwong et al., 2021). The study also showed that despite a decrease in mortality, there had been a notable increase in the number of individuals experiencing functional disabilities associated with stroke.

A recent study found that stroke is one of Malaysia's top five leading causes of death. Since 2005, 6 and 8% of deaths in general hospitals have been related to stroke (Loo & Gan, 2012). In 2019, the impact of stroke in terms of its incidence and mortality in Malaysia was significant. There were 47,911 incident cases, resulting in 19,928 deaths. Additionally, the prevalence of stroke was reported at 443,995 cases, and the total burden measured in disability-adjusted life years (DALYs) lost amounted to 512,726 (Tan & Venketasubramanian, 2022). According to the World Health Organization (WHO) study on the global disease burden, Malaysia had 10.8% of the population's DALYs were lost to non-communicable diseases, including stroke (Feigin et al., 2014).

2.2 Stroke pathophysiology

Stroke is a medical condition that shows up as rapidly changing clinical symptoms of a focused (or global, in the case of a coma) impairment of cerebral function that lasts for more than 24 hours or terminates in death without any other apparent cause other than a vascular origin (Sacco et al., 2013). A stroke could majorly be an ischemic or hemorrhagic stroke. In contrast to hemorrhagic stroke, which occurs when a blood vessel ruptures owing to an irregular vascular structure and causes blood

vessels to flood into the cerebral space, ischemic stroke is caused by a blood vessel obstruction that reduces the blood supply to the brain (Chugh, 2019). The type of hemorrhagic stroke will depend on where the blood loss occurred, either intracerebral hemorrhage or subarachnoid hemorrhage. Ischemic strokes comprise about 87%, 10%, and 3% of all stroke cases, respectively, along with intracerebral and subarachnoid hemorrhage strokes (Chugh, 2019).

2.2.1 Mechanisms of ischemia

The most typical kind of stroke, a thrombotic stroke, is brought on by a thrombus that prevents blood flow to specific brain areas. Large-vessel thrombosis may cause atheromatous plaques to burst, resulting in an ulcerated lesion with highly thrombogenic qualities. This can cause metalloproteinases to attack the luminal component of the plaques, causing them to be destroyed (Ay, 2010). During minor vascular thrombosis, asymptomatic tiny lacunar infarcts typically form in arteries with a diameter of less than 200 mm (Labovitz et al., 2007).

When an embolus enters the bloodstream and makes its way to the brain, bigger arteries divide into smaller ones, and it can cause an embolic stroke. The blood supply to the brain is virtually cut off when this blood clot blocks a tiny cerebral artery and reaches a point where it can no longer grow (Allen and Bayraktutan, 2008; Massicotte and Bauman, 2011). Most emboli that could enter the brain come mostly from the heart. Several conditions increase the risk of cerebral emboli, including atrial fibrillation (Doufekias et al., 2008).

2.2.2 Classification, diagnosis and syndromes of acute ischemic stroke

The main classification criteria are pathogenesis and clinical signs of acute ischemic strokes. The two most well-known classification schemes are the Oxfordshire Community Stroke Project (OCSP) and the Trial of Org 10172 in Acute Stroke Treatment (TOAST). The five-category TOAST classification system strongly emphasizes the attack (Jackson and Sudlow, 2005; Kirshner, 2009). The patient's symptoms are combined with diagnostic tests such as echocardiography, duplex imaging of the extracranial arteries, arteriography, and laboratory evaluations for a prothrombotic disease to determine the diagnosis. Scanning the brain with magnetic resonance imaging (MRI) or computed tomography (CT) (Adams et al., 1993).

Using the OCSP classification system, acute ischemic strokes are also separated into groups. Based on the symptoms and indications present at the moment of greatest impairment following a stroke episode, the OCSP category is total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), and posterior circulation infarct (POCI). Using this classification, it is possible to forecast the location and size of cerebral infarction, functional recovery, and post-attack death rates. As a result, it can be used very quickly after an ischemic stroke, even before the infarct appears on a scan (Bamford et al., 1991). Clinical signs of an ischemic stroke vary depending on the damaged artery regions and brain region. However, acute loss of brain functions, such as motor, sensory, language, vision, visuospatial perception, or awareness, is typically evident (Blumenfeld, 2002).

The most prevalent clinical symptom of an ischemic stroke is motor weakness. The face, hand, shoulder, foot, and hip are hemiparetic in about two-thirds of cases. Furthermore, monoplegia, frequently brought on by tiny infarcts in the motor cortex

or centrum semiovale, affects 19% of stroke victims. While facioscapular weakness is commonly brought on by superficial MCA infarcts, distal hemiparesis shows cerebral involvement (Blumenfeld, 2002). Sensory anomalies, the second most prevalent stroke symptom affecting 50% of stroke patients, also impact the arm, leg, trunk, and hemifacial region. The most frequent stroke outcome is pure sensory loss.

Furthermore, brain strokes frequently cause a reduction in discriminative sensations with a relatively high retention of protopathic experiences (Sullivan and Hedman, 2008). Dysarthria occurs in about 8.7% of ischemic stroke victims. Cortical lesions are typically associated with dysarthria that affects speech, whereas pontine involvement is more frequently the cause of dysarthria, affecting other neurological symptoms (Kumral et al., 2007).

2.3 Risk factors of acute ischemic stroke

Numerous ischemic stroke risk factors have been associated with an elevated risk of stroke attack. They are separated into risk factors that can be controlled and those that cannot (Goldstein et al., 2011). Examples of modifiable risk factors include environmental and lifestyle factors, which can be changed with the help of medical experts, treatments, and continued education. However, risk factors associated with hereditary processes cannot be altered because of current knowledge and technology (Allen and Bayraktutan, 2008; Goldstein et al., 2011).

2.3.1 Modifiable risk factors

2.3.1(a) Hypertension

Hypertension, characterized by persistently elevated blood pressure, is recognized as the leading risk factor for stroke. Studies consistently show that a

significant proportion of stroke cases (over 64%) are associated with hypertension (Wajngarten & Silva, 2019). High blood pressure (BP) could damage the blood vessels supplying the brain. Persistent hypertension leads to structural changes, such as vessel thickening and narrowing, increasing the risk of blood clots, blockages, and vessel ruptures. Managing hypertension through lifestyle modifications and appropriate medications is crucial in reducing the incidence of stroke and preventing its devastating consequences (A. J. Webb & D. J. Werring, 2022).

Hypertension is associated with all subtypes of ischemic stroke, including cardioembolic stroke related to atrial fibrillation, large artery stroke caused by carotid stenosis, lacunar stroke in small vessel disease, and less common stroke causes like carotid dissection (A. J. S. Webb & D. J. Werring, 2022). In studies like PROGRESS (The Perindopril Protection Against Recurrent Stroke Study), combination treatment significantly reduced recurrent stroke by up to 43% and intracerebral hemorrhage by 50% (A. J. S. Webb & D. J. Werring, 2022). However, a 10% risk of recurrent events remained. Similarly, in the TIA-Registry, a 5-year follow-up revealed a 14.3% risk of recurrent major vascular events and a 9.5% risk of recurrent stroke (Katsanos et al., 2017), highlighting the ongoing risk despite high-quality secondary prevention efforts.

2.3.1(b) Diabetes mellitus

Diabetes is considered a major risk factor for stroke. Individuals with diabetes are at a higher risk of developing ischemic and hemorrhagic strokes than those without diabetes. The mechanisms underlying this association include the adverse effects of diabetes on blood vessels, leading to atherosclerosis, hypertension, and impaired blood flow regulation. Additionally, diabetes often coexists with other risk factors, such as

obesity, high blood pressure, and high cholesterol, increasing the likelihood of stroke (Maida et al., 2022).

Diabetes has a notable impact on both stroke recovery and occurrence. Individuals with diabetes experience increased mortality rates after a stroke and have double the risk of stroke recurrence (Khanevski et al., 2019). Moreover, recurrent strokes in diabetic patients often carry a poorer prognosis compared to the initial stroke episode. Managing diabetes effectively becomes crucial to mitigate these risks and improve outcomes for individuals who have experienced a stroke (Krinock & Singhal, 2021). Furthermore, it is important to note that around 20 - 40% of acute stroke patients admitted to hospitals experience elevated blood sugar levels, regardless of their diabetes status. Additionally, 25 to 50% of individuals demonstrate undiagnosed glucose tolerance abnormalities, extending beyond those with a diabetes diagnosis (Norhammar et al., 2017).

2.3.1(c) Ischemic heart disease

The history of ischemic heart disease (IHD) was a risk factor for cardioembolic strokes (6.5%) and non-lacunar strokes (5.8%) (Ohira et al., 2006b). Furthermore, it has been found that when carotid plaques grow and build, the risk of an ischemic stroke gradually increases (Amarenco et al., 1994). According to studies, individuals with significant plaques had a 3-fold higher risk of ischemic stroke than those without (Hollander et al., 2002).

2.3.1(d) Atrial fibrillation

Atrial fibrillation (AF) is a heart rhythm disorder characterized by irregular and rapid heartbeat. It significantly increases the risk of stroke due to the formation of