A COMPARISON OF PREVALENCE, CLINICAL MANAGEMENT AND TREATMENT OUTCOME OF ISCHEMIC STROKE PRIOR TO AND DURING COVID-19 PANDEMIC IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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AIS	Acute ischemic stroke
NIHSS	National institutes of health stroke scale
MCO	Movement control order
CMCO	Conditional movement control
RMCO	Recovery movement control order
Iv -TPA	Intravenous tissue plasminogen activator
HUSM	Hospital Universiti Sains Malaysia
ED	Emergency department
SARI	Severe acute respiratory infection

ABSTRAK

Pengenalan

Strok iskemik adalah perubatan kecemasan. Risiko keterukan dalam strok meningkat dengan kelewatan semasa mendapatkan rawatan. Pandemik Covid-19 memberi kesan yang besar terhadap pengurusan strok yang boleh mengakibatkan strok yang lebih teruk. Kajian ini bertujuan untuk menentukan kesan pandemik Covid-19 terhadap jumlah kemasukan pesakit strok iskemik, penjagaan dan hasil strok standard.

Metodologi

Ini merupakan kajian semakan rekod retrospektif. Data pesakit yang disahkan secara radiologi atau klinikal dengan AIS di HUSM yang didiagnos dari 1 Mac 2019 hingga 28 Februari 2021 telah direkodkan.

Keputusan

Seramai 229 pesakit telah didaftarkan; 114 (49.8%) pesakit ialah daripada kumpulan pra-Covid-19, dan 115 (50.2%) pesakit ialah daripada kumpulan semasa Covid-19. Skor NIHSS awal ialah serupa, 5.3 ± (4.18) pada 2019 dan 5.9 ± (4.42) pada 2020. Masa serangan sehingga ketibaan ke hospital dalam minit ialah 1875.2(2034.72) ketika pra-Covid berbanding dengan 1827.1(2163.95) ketika Covid-19 (ujian.t 0.17 nilai-p 0.863). Masa berjumpa doktor di kecemasan dalam minit ialah 25.3 (30.21) ketika pra covid-19 berbanding 22.6(16.48) ketika Covid-19 (ujian.t .48 nilai-p 0.402). Waktu ketibaan ke mesin otak CT dalam minit ialah 83.8 (58.91) berbanding dengan 92.4 (120.20) pra-Covid-19 dan kemudiannya ketika Covid-19 (ujian t -.69 nilai-p 0.493). Bagi pesakit yang menerima terapi trombolisis; 7(6.1%) ialah ketika pra-Covid-19 berbanding dengan 4

(3.5%) ketika Covid-19 (nilai-p>0.5). Metrik strok lain termasuk fisioterapi, terapi pekerjaan, penilaian terapi pertuturan dan pakar diet, keputusan adalah ;(77.2% lwn 81.7% nilai-p >.05) (76.3% lwn 81.7% nilai-p >.05) (50% lwn 59.1% nilai-p >.05) (43.9% lwn 45.2% nilai-p >.05) untuk fisioterapi, terapi pekerjaan, terapi pertuturan dan pakar pemakanan. Untuk hasil rawatan, tempoh tinggal di hospital ialah [(6.4 ± 4.5 lwn. 7.56.74) (ujian t - 1.36, nilai-p 0.175)] ketika pra-Covid-19 dan semasa Covid-19. Manakala skor MRS semasa dibenarkan keluar ialah [(2.8(1.38) lwn. 2.9(1.49) (ujian t .33 nilai-p 0.742)] ketika pra-Covid-19 dan semasa Covid-19.

Keputusan

COVID-19 tidak memberikan kesan yang ketara ke atas pengurusan strok di HUSM. Perbandingan faktor risiko strok, subjenis dan keterukan, semasa ketibaan ke penyuntikan dan permulaan kepada penyuntikan untuk trombolisis secara statistik adalah tidak signifikan. Hasil pengurusan strok adalah serupa bagi skor MRS, tempoh kemasukan ke hospital, jangkitan yang diperoleh di hospital dan kematian 7 hari.

ABSTRACT

Introduction

Ischemic stroke is a medical emergency. Risk of poor outcomes in stroke increases with delay in time to treatment. Covid-19 pandemic had a significant impact on stroke management resulting in more severe stroke. This study aims to determine the impact of Covid-19 pandemic on the total number of ischemic stroke patients admissions, stroke standards of care and outcome.

Methodology

This is a retrospective record review study. Data of patients with radiologically or clinically confirmed AIS in HUSM diagnosed from 1st March 2019 until 28th February 2021 were included.

Results

A total of 229 patients were included; 114 (49.8%) patients in the pre -covid-19, and 115 (50.2%) patients during covid-19. Initial NIHSS score was similar, 5.3 ± (4.18) in 2019 and 5.9 ± (4.42) in 2020. Onset to door time in minutes was 1875.2(2034.72) in pre-Covid-19 vs 1827.1(2163.95) in Covid-19 group (t. test 0.17 p-value 0.863). Time to see emergency doctor in minutes was 25.3 (30.21) in pre covid-19 vs 22.6(16.48) in Covid-19 group (t. test .48 p-value 0.402). Door to CT brain time in minutes 83.8 (58.91) vs 92.4 (120.20) in pre-covid-19 and Covid-19 group subsequently (t. test -.69 p- value 0.493).

For patients received thrombolytic therapy; 7(6.1%) pre covid-19 vs. 4 (3.5%) during covid-19 period (p-value>0.5). Other stroke metrics including physiotherapy,

occupational therapy, speech therapy assessment and dietician, results were ;(77.2% vs 81.7% p-value >.05) (76.3% vs 81.7% p-value >.05) (50% vs 59.1% p- value>.05) (43.9% vs45.2% p-value>.05) for physiotherapy, occupational therapy, speech therapy and dietician subsequently. For treatment outcome, duration of hospital stay was [(6.4 ± 4.5 vs. 7.56.74) (t. test - 1.36, p-value0.175)] in pre Covid-19 and during covid-19 respectively. While MRS score at discharge was [(2.8(1.38) vs. 2.9(1.49) (t. test .33 p-value 0.742)] in pre -Covid-19 and during Covid-19 respectively.

Conclusion

Covid-19 had no significant impact on stroke management in HUSM. Comparison of stroke risk factors, subtypes and severity, door to needle time and onset to needle time for thrombolysis were statistically insignificant. Stroke management outcomes were similar for MRS score, duration of hospitalization, hospital acquired infection and 7 days mortality.

Keywords: *Acute ischemic stroke; Covid-19 pandemic; stroke admission rate; management; outcome.*

CHAPTER 1

INTRODUCTION

Background of Stroke

Stroke was reported by the World Health Organization (WHO) more than 40 years ago as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin‖ (1-3). The American Heart Association's Stroke Council established a writing group to create an expert consensus document for an updated definition of stroke for the twenty-first century. Central nervous system infarction is defined as cell death in the brain, spinal cord, retina caused by ischemia, as determined by neuropathological, neuroimaging, and/or clinical evidence of irreversible injury. Ischemic stroke particularly refers to central nervous system infarction accompanied by overt symptoms, where as silent infarction by definition causes no recognized symptoms. Stroke also includes intracerebral and subarachnoid haemorrhages. The new definition of stroke encompasses clinical and tissue criteria and may be used in practice, research, and public health evaluations. (4).

Global burden of stroke

In 2005, an estimated 16 million people worldwide experienced their first stroke, with an estimated 62 million stroke survivors. In the absence of effective clinical or public health treatments, this figure is predicted to rise to an estimated 23 million first-ever strokes, with 7.8 million fatalities, by 2030. Every year, around 56 million people die throughout the world, with vascular illness accounting for roughly one- quarter of these fatalities. Ischemic heart disease (7.2 million deaths per year) and stroke (5.5 million

deaths per year) are the world's leading causes of death. Stroke is responsible for around 9.7 percent of all deaths globally (5).

Stroke mortality is a leading cause of death in developed countries, with stroke incidence being relatively high. For instance, stroke is still the third-leading cause of death in the United States, killing more than 140,000 people each year. Furthermore,795,000 people in the United States have a stroke each year, with 600,000 of these strokes being first-time attacks (6). The total stroke incidence in the United States is about 269 per 100,000 people (7). These figures are equivalent to those seen in Europe, where the yearly stroke incidence for women is 94.6 per 100,000 population and 141.3 per 100,000 population for men (8). In 2006, the prevalence of stroke was estimated to be 0.3 percent among Malaysians (9), However, in 2011, the prevalence grew to 0.7 %;1.7 % among those aged 55-59 years, 2 % among those aged 60-64 years, 3 % among those aged 65-69 years, 3.5 % among those aged 70-74 years, and 7.8 % among those aged 75 and more (10).

The gross number of worldwide fatalities attributed to stroke is predicted to expand exponentially as the epidemiological shift of illnesses spreads throughout emerging countries around the world (11). Already, between 2000 and 2008, the estimated stroke incidence in low- and middle-income nations surpassed that of high-income countries for the first time. (11).

Common risk factors of stroke

To far, only one big study has catalogued the influence of various risk variables on the global incidence of stroke. The INTERSTROKE study included 3000 patients and an equivalent number of age- and sex-matched controls in 22 countries across three years, using a standardized case-control study design (12). Patients who presented within five

days of an acute, first-time stroke were designated as cases; control individuals had no history of stroke. The 22 countries included representatives from each of the WHO's six low- to middle- income regions as well as high-income nations.

After screening for a plethora of risk variables, ten risk factors were shown to have a statistically meaningful, positive connection with stroke development. These factors included both social (such as smoking, regular alcohol use, poor diet, and physical inactivity) and individual (such as hypertension, elevated waist-to-hip ratio, diabetes, psychosocial factors such as depression, a history of cardiac disease, and elevated apolipoprotein B to A1 ratios) factors (12).

According to the findings, these ten major determinants were responsible for up to 90% of the population - attributable risk for stroke worldwide. Hypertension and smoking were the two variables that conferred the greatest attributable risk. Hypertension is responsible for around 54 percent of strokes globally, with rising rates of hypertension shown in especially in India and China (13). The dose-response association shown between the numbers of cigarettes smoked per day and the risk of stroke in the majority of nations in the study appears to emphasize the need of implementing smoking- cessation programmes globally in the coming years.

Management of stroke

The three fundamental concepts of acute stroke care are: (1) prompt recanalization of the occluded artery and reperfusion of the ischemic tissue, (2) optimization of collateral flow, and (3) avoidance of further brain damage.

The majority of acute stroke therapy is recanalization and reperfusion, which can reduce infarct size and restore neurologic impairments (9). The degree of reopening of the

occluded artery defines recanalization. The degree of flow reaching the previously hypoperfused brain area is utilized to calculate reperfusion. Opening the occluded artery works because, in most circumstances, when the occlusion occurs, a region of brain tissue gets hypoperfused but is not immediately infarcted. This area of brain tissue represents the ischemic penumbra, which can be rescued if enough blood flow is quickly restored. Donnan et al. (2009), used advanced brain imaging with CT perfusion or magnetic resonance (MR) diffusion / perfusion to visualize this at risk region (penumbra imaging). Mechanical embolectomy with chemical thrombolysis with recombinant tissue plasminogen activator (rtPA), commonly known as alteplase and mechanical thrombectomy with a retrievable stent are the two evidence – based strategies to achieve reperfusion (14).

Collateral flow is responsible for keeping the ischemic penumbra viable. It provides enough flow to prevent critical ischemia and infarction but not sufficient flow to maintain normal cellular function. This explains why the acute neurologic deficits exceed what would be expected for the established infarct core at the time of presentation and why neurologic function can improve after reperfusion. This collateral flow, however, is often tenuous and can sustain viability only for a limited period of time. Thus, without recanalization, the ischemic penumbra is destined to progress to infarction. Collateral flow can be protected by avoiding blood pressure drops and supported by the administration of IV fluids. The value of keeping the head of the bed flat for patients with acute ischemic stroke is being investigated in the ongoing Head Position in Stroke Trial (Head Post) and should be weighed against the risk of aspiration (15).

Avoidance of secondary insults is a form of neuroprotection. Hypoglycemia can

exacerbate energy failure and should be strictly averted. Hyperglycemia might also be deleterious; so far, we know it associated with poorer results after an ischemic stroke, but there is no evidence that correcting it improves outcomes (14). Because fever is associated with poor clinical outcomes, treating fever may be helpful. The benefit of hypothermia is still being researched. Preventing infections (including dysphagia evaluation prior to any oral intake) and early recurrence strokes are important priority in the management of the acute stroke patient (16).

There have been considerable attempts in recent years to create and implement clinical practice recommendations for the care of individuals with acute stroke (17). A recognized strategy to assisting the translation of research evidence into clinical practice through the use of standardized performance indicators (18), often known as quality indicators, process of care measurements, or key performance indicators (KPIs).

Acute ischemic stroke (AIS) is a life-threatening condition (19). The likelihood of bad stroke outcomes increases when treatment is delayed (20). Intravenous recombinant tissue plasminogen activator (rtPA) is an FDA-approved medication for AIS that should be administered between 3-4.5 hours after the commencement of the stroke (21). Clinical data supports the need of quick diagnosis and therapy start for improved stroke outcomes (22). Data from the Get with the Guidelines-Stroke (GWTG-Stroke) initiative show that stroke care in the United States has improved significantly and sustainably (23). However, therapy of AIS has largely remained conservative, with conventional clinical practice frequently falling short of guideline-established targets and only a tiny minority of patients benefiting.

Although Malaysia lacks stroke units, it has KPIs in place to monitor the quality of stroke healthcare services. To assess the compliance rate of stroke care delivery, nine

KPIs are used, adapted from the Centers for Disease Control and Prevention's Paul Coverdell Nation al Acute Stroke Registry: (1) thrombolytic therapy administration,(2) antiplatelet therapy within 48 hours of admission, (3) venous thromboembolism prophylaxis, (4) anticoagulation therapy for atrial fibrillation, (5) discharge on antiplatelet therapy, (6) discharge on statin medication, (7) dysphagia screening, (8) stroke education, and (9) rehabilitation (24). The performance indicators are standards of care that demonstrate insufficiency if eligible patients do not obtain that care standard. As a result, these indicators are used to monitor compliance with guidelines, and support transfer of new evidence into routine practice (25).

In many nations, stroke mortality has decreased in both men and women of all ages suffering from ischemic or hemorrhagic stroke during the last several decades. This is due to the implementation of stroke units, which provide coordinated stroke treatment and improved control of stroke risk factors, resulting in milder strokes.

Stroke outcome

Up to one third of patients with acute ischemic stroke (AIS) will clinically deteriorate during the first few days after hospital admission. Although this process may be reversible depending on the etiology of deterioration, it places patients at higher risk of poor functional outcome and mortality. One such etiology of neurologic deterioration (ND) is infection, either present on admission (POA) or hospital-acquired infections. (22)

Stroke prognosis could be understood under three different and complementary points of view: vital, neurological and functional outcome. Monitoring of the neurological function is of special interest during the acute and subacute phase of stroke, by providing an objective measure that alert physicians about neurological worsening. The National

Institutes of Health Stroke Scale (NIHSS) is the most widely used scale for this purpose. It is usually evaluated at least every 24 h in the acute stroke setting, as well as before and after revascularization procedures. Variations in four points or more in the score along time are usually considered as neurological improvement, when the score decreases, or deterioration, when there is an increment. (20)

Perhaps the most important issue in the prediction of stroke outcome and the main end-point for stroke clinical trials is the functional status. Data from the World Health Organization indicates that about half of stroke survivors are left with some degree of physical or cognitive impairment, and a 20% of them will require institutional care. This situation ranks stroke to the second leading cause of disability in Europe, which entails a 6.3% of total DALYs. The modified Rankin Scale (mRS) is a 7-point scale grading the capacity of performing basic activities of daily living, recommended as clinical end-point for stroke trials . The mRS score is usually dichotomized into ≤ 2 or > 2 points to report good or poor functional outcome, respectively. (15)

Stroke and Covid-19 Association

A review by a panel of the World Stroke Organization reported that the risk of ischemic stroke during COVID-19 is around 5% (95% confidence interval [CI]: 2.8–8.7%). The median time from diagnosis to ischemic stroke in one small single-center study was 10 days (IQR: 1–19) among 50 patients with ischemic stroke admitted in Wuhan, China, there was more comorbidity, lower platelet counts and leukocyte counts, and the patients had higher levels of D-dimers, cardiac troponin I, NT probrain natriuretic peptide, and interleukin-6.(26)

Three main mechanisms appear to be responsible for the occurrence of ischemic strokes in Covid-19. These include a hypercoagulable state, vasculitis, and cardiomyopathy.

Thachil et al. published guidance on recognition and management of coagulopathy in Covid-19 from the International Society for Thrombosis and Haemostasis. They recommended monitoring of prothrombin time, D-dimer, platelet count, and fibrinogen and prophylactic anticoagulation with low-molecular weight (LMW) heparin in all patients with Covid-19. (29) Increasing evidence suggests a potential link between coronavirus disease 2019 (COVID-19) infection and thromboembolism, which could affect a range of organs resulting in myocardial infarction (MI), ischemic stroke, and pulmonary embolism (PE).

SARS-CoV-2 causes clinical Covid-19 by its affinity for the ACE2 receptors that are expressed in the lungs, heart, kidneys, and small bowel. These receptors are also abundant in the vascular endothelium, where infection elicits an inflammatory response (a lymphocytic "endotheliitis") that has been postulated as one of the substrates for the thrombotic complications of this infection. (29)

There are a number of mechanisms for cardiac involvement in Covid-19 patients. There may be direct invasion by the virus, causing a myocarditis, with resultant injury and even death of cardiomyocytes. The consequent intracardiac thrombus formation, possibly compounded by the hypercoagulable states, raises the risk of subsequent cardioembolic stroke. (26)

Problem statement and study rationale

Acute Ischemic Stroke (AIS) is successfully managed when it is recognized early in the prehospital setting and diagnosed promptly in the Emergency Department (ED). Intravenous thrombolysis (IVT) has been recognized as an essential causal treatment for AIS to reopen a stenosed cerebral vessel and for which clinical benefit has been

demonstrated in a time window of 4.5–9.0 hours in numerous randomized controlled trials. In addition, interventional catheter thrombectomy as an adjunct to IVT, used in cases of large vessel occlusion (LVO) in specialized neurovascular centers, is becoming increasingly important. For functional outcomes after AIS, the time to recanalization is significant, as further brain tissue death threatens with each passing minute. For this reason, time management is of paramount importance in stroke care ("time is brain"). Given the proven high efficacy, however, still, too few patients have access to these forms of therapy; especially in rural regions, there is an underutilization of this patient group. This is mainly due to delays in the prehospital phase, resulting in patients not reaching the clinic in time for causal treatment. Therefore, prompt diagnosis, implementation of appropriate procedures is crucial for a patient with a stroke, and time plays the most vital role here. The pandemic of coronavirus disease has changed how health care is provided and has a significant impact on healthcare delivery. The problems that occurred during Covid-19 pandemic that has affected stroke care can be categorized into two main factors, including health care workers factor and patient's factor. WSO members report reallocation of neurology and stroke physicians, nurses, and other stroke healthcare-related workers to look after COVID-19 patients. As a result, several groups reported that stroke care suffered from a shortage of services and delays in time-dependent treatments and diagnostic work-up since the onset of the pandemic. Furthermore, in preparation for the suspected influx of COVID-19 patients, many healthcare systems have reduced or stopped provision of "non-urgent" care which will particularly impact on stroke prevention and follow-up. Regarding patients role in stroke care, observational studies showed a marked and unexplained reduction in the number of patients admitted in hospital, due to delays in hospital admission or referrals, total lockdown with difficult transportation, or patients preferring not to enter

the hospital at all with fear of contracting Covid-19 infection (26). It correlates with a preliminary survey done by Malaysia Stroke Council involving 47 public and private hospitals (pending publication) which shows reduction in stroke admission and challenges in managing stroke services in view of the current pandemic.

The movement control order (MCO) and social distancing campaign has possibly contributed to reduction in the number of stroke admissions worldwide and in the majority of the hospitals in Malaysia based on our preliminary survey (27). This public aversion of stroke patients admission towards hospitals may lead to delay in arrival and seeking treatment which subsequently results in more severe stroke with higher morbidity and mortality (28).

Patients with stroke who require hospitalization during this pandemic are at an increased risk of suboptimal outcomes. There is currently no published study for impact of covid-19 on ischemic stroke care in Malaysia. This study aims to compare standard of care for ischemic stroke before and during Covid-19 pandemic.

LITERATURE REVIEW

In December 2019, a novel viral infection emerged in Wuhan, China, which rapidly attracted worldwide attention (29). Later in January 2020, the World Health Organization (WHO) recognized this new viral infection as Novel Coronavirus 2019 which was subsequently named as Coronavirus Disease (Covid-19). The genomic analysis of the virus has shown that Covid- 19 is similar to the SARS-like coronavirus (26). Coronavirus disease-2019 (Covid-19), has infected more than 105 million persons and caused more than 2.3 million deaths worldwide as of 5 February 2021. The Covid-19 infection, which is commonly associated with respiratory symptoms, has been reported to also be associated with neurological manifestations that may precede respiratory complaints and in more severe Covid-19 cases, 5.9% suffered an ischemic stroke.

Zhao et al., (2020) conducted a retrospective study from China's big data observatory platform for stroke, which included 280 hospitals across the country, nearly half of which were assigned hospitals for Covid-19. The study found that, hospital admissions related to stroke decreased by 40%, thrombolysis and thrombectomy cases decreased by 25%, but the actual time for prehospital or in- hospital delays (door-to-needle time) was not determined. The author believes that these findings might be attributed to a variety of causes, the most important of which is that patients or patients' relatives are less inclined to visit the hospital, resulting in a lower hospital admission rate and fewer thrombolysis and thrombectomy instances. The author clearly highlighted the impact of Covid-19 on the stroke patients care management in different hospitals (30).

While the results of Chen et al., (2020) were somewhat different, he conducted retrospective research of 18 Taiwanese hospitals, including seven medical centres and

11 community hospitals. The number of daily stroke admissions reduced by 16 percent in 2020 compared to 2019. The quality indicators were generallycomparable, and certain metrics, including intravenous thrombosis, endovascular thrombectomy, early and discharge antithrombotic usage, and rehabilitation evaluation, even improved in 2020. The authors concluded that there was reported no difference in the stroke management and inclining trend of treatment outcome has been observed in the patients recovery before and after Covid-19 (31).

Similarly, another study was done with a total of 822 patients at 3 hospitals in Connecticut from January 1 to April 28, 2020. Total stroke incidences decreased by 30% during pandemic weeks in 2020 compared to 2019. Age, gender, race/ethnicity, stroke severity, time to presentation, door-to-needle/door-to-reperfusion timings, and discharge modified Rankin Scale did not vary. Furthermore, the study found no difference in stroke severity or early outcomes (32).

Another retrospective multicenter cohort study, with a total of 309 patients, was conducted using data from the prospective stroke registries of three hospitals in Amsterdam. It revealed a 24% decrease in the number of patients with a suspected stroke in the hospitals in the Amsterdam area during the peak of the Covid-19 outbreak compared to a pre-Covid- 19 control period. Although the quality of stroke care characteristics was comparable, this study was unable to give data on long-term functional outcome (33).

J.E. Siegler et al, (2020) conducted a single-center, prospective observational research with 328 patients in a tertiary care centre in New Jersey. New stroke diagnoses decreased by 38% on average. There was no significant delay between the time patients

were last known well and the time they arrived at the ED, computed tomography scan, or thrombolysis. Compared to patients hospitalized before to Covid-19, those treated during Covid-19 had a lower hospital duration of stay(34).

Rudilosso et al., (2020) conducted a prospective study at hospital clinic Barcelona, public university hospital. They compared the result of stroke admissions, reperfusions therapies and outcomes in March 2020 in compare with March 2019. The number of stroke admissions reduced to 83 in March 2020 compared to 108 in March 2019 and further decrement was seen during lockdown in Catalonia. The author concluded that, in 2019, less intravenous thrombolysis and thrombectomies were done, but other prehospital or in-hospital workflow measures yielded comparable outcomes (35).

CHAPTER 2

OBJECTIVES OF THE STUDY

2.1 Research questions

The research question of this study is as follow:

1. Does Covid-19 pandemic have an impact on the total admission of acute ischemic stroke patients in HUSM?

2. Is there any difference between the stroke care management (based on National key performance index) prior to and during Covid-19 pandemic?

3. Is there any difference between the clinical outcome of ischemic stroke patients prior to and during the Covid-19 pandemic?

2.2 General and specific objectives

2.2.1 The General Objective of this study

To determine the impact of Covid-19 on the stroke management care.

2.2.2 The Specific Objective of this study

The specific objectives of this study according to the study phases are as follows:

1. To describe the impact of Covid -19 in total number of admissions of patients of acute ischemic stroke prior to and during Covid-19 pandemicin HUSM.

2. To compare the difference between ischemic stroke care management (based on National stroke key performance index) prior to and during Covid-19 pandemic. The National stroke key performance indicators are: (1). Thrombolytic therapy administration, (2) antiplatelet therapy within 48 hours of admission, (3) venous

thromboembolism prophylaxis, (4) anticoagulation therapy for atrial fibrillation, (5) discharge on antiplatelet therapy, (6) discharge on statin medication, (7) dysphagia screening, (8) stroke education, and (9) rehabilitation.

3. To determine the clinical outcome during hospital admission among ischemic stroke patients prior to and during Covid-19 pandemic. The parameter of outcome based on: MRs score on discharge, duration of hospital stay, hospital acquired infection and 7 days mortality.

2.3 Hypotheses

1. H0: there is no impact of Covid-19 pandemic on total number of patients admitted for acute ischemic stroke prior to and during Covid - 19 pandemic in HUSM.
2. H0: there is no difference between ischemic stroke care management (based on National key index) prior to and during the Covid-19 pandemic.
3. H0: there is no difference in clinical outcome of ischemic stroke patients prior to and during the Covid-19 pandemic.

CHAPTER 3

STUDY PROTOCOL

1.1 Study Design

The design of this study is a retrospective record review. It is a method used to retrieve data from patients' medical records unit to address the research question (36). The study was conducted in HUSM, and the medical records of patients admitted with ischemic stroke between 1st of March 2019 – 28th February 2021 was reviewed.

3.2. Study Area

Hospital Universiti Sains Malaysia (HUSM) is where this study was conducted. HUSM is a tertiary care centre and teaching hospital of Universiti Sains Malaysia and a referral centre for the Kelantan state in addition to the nearby states.

3.3. Population and sample

3.3.1. Target population

All patients with ischemic stroke who fulfilled inclusion and exclusion criteria.

3.3.2. Sampling frame

All patients with ischemic stroke admitted to HUSM.

Cases that fulfill inclusion and exclusion criteria was divided into two groups:

1. Prior to Covid19 Pandemic: 1st March 2019- 28th February 2020.
2. During Covid19 Pandemic: 1st March 2020- 28th February 2021.

3.3.3. Source population

Ischemic stroke patients admitted to neurology or medical ward in HUSM between 1st March 2019 – and 28th February 2021.

3.4.1 Subject Criteria

The selection of patients medical records was based on:

3.4.2 Inclusion criteria

1. Age more than 18 years old.
2. Ischemic stroke was diagnosed by clinical findings and supported by neuroimaging (Based on AHA/ASA definition), early findings (within 6 hours) include loss of grey- white matter differentiation, sulcal effacement, obscuration of lateral margins of insula (insular ribbon sign), loss of density of the basal ganglia (vanishing basal ganglia sign) and hyperattenuation of vessels (dense vessel sign or clot sign). After approximately 12-24 hours a well-defined hypodensity may be seen.

3.4.3 Exclusion criteria

1. Hemorrhagic stroke
2. Brain infarct without clinical evidence of stroke syndrome.
3. Neurological deficit due to other causes such as tumor, encephalitis etc.

3.5 Sample size calculation:

3.5.1 Objective One

Objective one was a descriptive analysis for a total number of patients admitted with

ischemic stroke in HUSM prior and during covid-19 pandemic. The sample size calculation for this objective is not needed.

3.5.2 Objective Two

Objective two was to compare Clinical stroke care management before and after Covid-19 pandemic. The sample size was calculated by a sample size calculator (37), comparing two proportions with the following parameters:

1. P0 = proportion of stroke patients who achieved door to CT brain time less than 25minutes before Covid-19 (P0 = 0.836 based on literature) (31).
2. P1 = expected proportion of stroke patients who achieved door to CT brain time less than 25 minutes after Covid-19 (P1 = 0.60 according to expert opinion).
3. Alpha (α) = level of significance at 0.05.
4. $(1-\beta)$ = power of study at 0.8
5. M = ratio of stroke patients who used before and after Covid-19 (M = 1) The sample size (n) for this objective was 56 per group. With addition of 10% dropout, sample size (n) was 124.

3.5.3 Objective three

Objective three was compare the stroke care outcomes in stroke patients beforeand during Covid-19. Sample size for this objective was calculated by sample size calculator (37) using two mean comparison and standard deviation difference formula:

A. Mean mRS score

Standard deviation of difference (σd) for mean mRs score (0-2) = 1.59 based on literature (38).

Expected difference: 0.5 Significance level (α): 0.05 (1−β) = power of study at 0.8

The sample size (n) for this objective was 80 per group. With addition of 10% dropout, sample size (n) was 178.

B. Mean hospital stay:

Standard deviation of difference (σd) for mean mRs score (0-2) = 6.49 based on literature (38).

Expected difference: 2 Significance level (α): 0.05 (1−β) = power of study at 0.8

The sample size (n) for this objective was 83 per group. With addition of 10% drop out, sample size (n) was 185. The largest sample size of this study from the above calculations was 185, depending on objective 3.

3.6 Sampling method

All medical records with completed data required of ischemic stroke patients admitted between 1st March 2019 – 28th February 2021 was selected from the medical record unit. For NIHSS score variable was collected based on data available in the patients file, if not available, recalculation was done based on detailed clinical neurological examination findings that were available in the patients files.

3.7 Research Tool

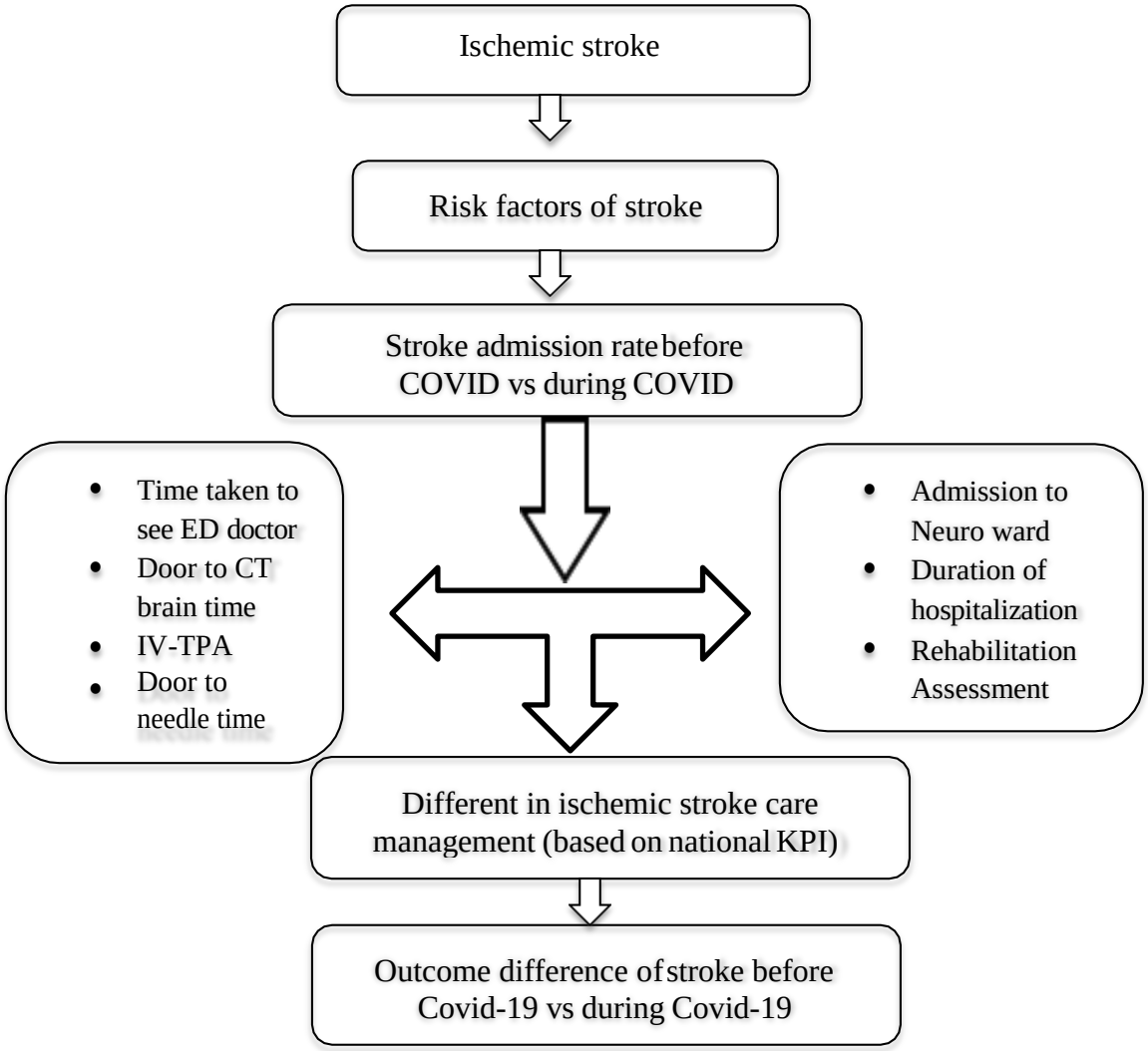
Microsoft Excel spreadsheets were designed to collect the needed data from the HUSM

Record Unit (APPENDIX A). The collected data included: Demography, Clinical features, stroke type, and characteristics, medical history and comorbidity, clinical examination, Brain CT scan findings, the implemented stroke management protocol, rehabilitation therapy and stroke management outcome.

A comparison of data was performed between these two groups. Additional details descriptions of clinical management and outcome during Covid-19 Pandemic also was performed based on the time of MCO:

1. First MCO
2. First PKPB/PKPP
3. Second MCO
4. Second PKPB/PKPP

3.8 Conceptual Framework



3.9 Operational Definition

1. Ischemic Stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.

2. National KPI for stroke care management, are adapted from the Centers for Disease Control and Prevention's Paul Coverdell National Acute Stroke Registry, are used to assess the compliance rate of stroke care delivery: (1) thrombolytic therapy administration, (2) antiplatelet therapy within 48 hours of admission, (3) venous thromboembolism prophylaxis, (4) anticoagulation therapy for atrial fibrillation, (5) discharge on antiplatelet therapy, (6) discharge on statin medication, (7) dysphagia screening, (8) stroke education, and (9) rehabilitation (39).

3. Stroke outcome during admission until hospital discharge: the parameters of outcome is based on:

- MRs score: is a 6-point disability scale with possible scores ranging from 0 to 5.

A Separate category of 6 is usually used for patients who expire. The MRs score is the most widely used outcome measure in stroke clinical trials.

- Duration of hospital stay

- Hospital acquired infection

4. Covid -19 pandemic time frame: - First case reported in Malaysia January 25 2020.

- First MCO: from 18th of March 2020, until 3rd of May 2020.
- First CMCO: from4th of May 2020, until 9th of June 2020.

- RMCO: from 10th of June 2020, until 31th December 2020.
- Second MCO: 16th of January 2021m until 18th of February 2021.
- Second CMCO: 19th of February until 28th of April 2021.

5. Period of assessment:

- Pre-MCO group period: 01/3/2019-29/02/2020
- MCO group period: 1/03/2020 –28/02/2021

6. Door to see the Emergency doctor time: time from patient arrival in hospital emergency to initial evaluation by an emergency doctor and should be less than 10 minutes, adapted from American heart association guidelines.

7. Door to CT brain time: time from patient arrival in hospital emergency to CT scan brain and should be less than 25 minutes, adapted from American heart association guidelines.

8. Door to needle time: time from patient arrival in hospital emergency to start thrombolysis and should be less than 60 minutes, adapted from American heart association guidelines.

9. Onset to door time: time from onset of stroke signs and symptoms to arrival at hospital emergency and should not exceed 35 minutes, adapted from American heart association.

10. Onset to needle time: time from onset of stroke signs and symptoms until initiation of thrombolysis.

11. HUSM: Hospital Universiti Sains Malaysia is a tertiary level teaching hospital with 950 beds that serves an estimated 1.8 million inhabitants of Kelantan. The hospital

also serves as referral centres for nearby states.

12. Radiological changes in Ischemic stroke:

early findings (within 6 hours) include loss of grey- white matter differentiation, sulcal effacement, obscuration of lateral margins of insula (insular ribbon sign), loss of density of the basal ganglia (vanishing basal ganglia sign) and hyperattenuation of vessels dense vessel sign or clot sign). After approximately 12-24 hours a well-defined hypodensity may be seen.

3.10 Data Collection Method

The list of stroke patients was obtained from the HUSM record unit using the ICD-10 reference of ischemic stroke. The stroke patients medical records were retrieved and reviewed at the medical record office to protect patients confidentiality.

3.11 Data Analysis

The analysis was a descriptive type of analysis after the data is collected. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) Ver 26.0. The categorical variables were described by frequency (n) and percentage (%). Numerical variable was described using mean (SD).

Comparison between categorical variables was analyzed using two tests of difference in proportion, and student T- test for the numerical variables with two levels and one-way Anova test for numerical values with three levels. A p-value of < 0.05 was considered significant.

3.12 ETHICAL CONSIDERATION

3.12.1 Study sample Vulnerability