BASELINE TECHNETIUM-99m TETROFOSMIN MYOCARDIAL PERFUSION STUDY IN PREDICTING THE MANAGEMENT OUTCOME OF PATIENTS WITH NEWLY DIAGNOSED MYOCARDIAL INFARCTION

BY

DR SITI NOORAEIN YASER

Dissertation Submitted In Partial Fulfilment
Of The Requirements For The Degree Of
Master Of Medicine (Nuclear Medicine)

ADVANCED MEDICAL AND DENTAL INSTITUTE
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ACKNOWLEDGEMENT

Alhamdulillah, Praise to the Almighty for his blessings onto my health and throughout every seconds of my life. My sincere thank and acknowledgment to the Ministry of Health Malaysia and Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia (USM) for allowing me to be involved in this Masters programme that leads me to the writing of this dissertation and strolled me into tremendous Nuclear Medicine journey.

My sincere gratitude and respect to my lecturers and clinicians in USM and Hospital Sultanah Aminah Johor Bahru (HSAJB) who had guided me with their valuable knowledge, point of views and skills in this field. This is in particular to Dr Khadijah Abdul Hamid and Dr Ng Chen Siew for being my supervisors for this dissertation as well as Dr Noorsuzana binti Mohd Shariff and En. Nizuwan Azman for their advices on statistical analysis. Of course not forgetting the teaching sessions and sharing of experience by other specialists, nurses, technologists, pharmacists, physicists and the rest of the crew with whom I worked with. Thank you very much to my dear colleagues especially Dr Lee Yeong Fong and Dr. Fatin Hayyani Mohamad Najib for knowledge sharing on my dissertation writing.

A special and million thanks to my family especially my dearest husband Mohammad Noorzayni Iyni for his incredible and unstoppable emotional support through my rough times. Heartful gratitudes to my parents as well for being understanding and supportive throughout my extended journey.

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ABBREVIATIONS

ACE-I	Angiotensin converting enzyme inhibitor
ACS	Acute Coronary Syndrome
ARB	Angiotensin receptor blocker
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CMR	Cardiac magnetic resonance imaging
DM	Diabetes mellitus
ECG	Electrocardiogram
GTN	Gliceryl trinitrate
HPT	Hypertension
HSAJB	Hospital Sultanah Aminah Johor Bahru
IHD	Ischaemic heart disease
iv	Intravenous
LAD	Left ascending artery
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MBq	Mega Becquerel
MI	Myocardial infarction
MPS	Myocardial Perfusion Study
MREC	Medical Research Ethics Committee
MRI	Magnetic Resonance Imaging
NCVD-ACS	National Cardiovascular Disease Database-Acute Coronary Syndrome
NYHA	Ney York Heart Association
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery

QGS	Quantitative Gated SPECT
RCA	Right coronary artery
SDS	Summed Difference score
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	Single photon emission computed tomography
SDS	Summed difference score
SRS	Summed rest score
SSS	Summed stress score
STEMI	ST segment elevated myocardial infarction
Tc-99m	Technetium-99m
WHO	World Health Organization

ABSTRAK

Pendahuluan: Rawatan trombolisis merupakan salah satu kaedah bagi merawat ST elevasi infarksi miokardium (STEMI) meskipun intervensi koronari perkutaneus (PCI) diketahui merupakan rawatan piawaian yang mantap. Kajian perfusi myokardium (MPS) merupakan salah satu modaliti diagnostik yang boleh digunakan bagi stratifikasi risiko selepas STEMI. Oleh itu, kajian ini secara khusus dijalankan untuk melihat pesakit dengan sejarah thrombolysis selepas STEMI dan hasil pengurusan mereka, 12 bulan selepas MPS asas.

Objektif: Untuk mengkaji peranan MPS dalam meramalkan hasil pengurusan pesakit dengan STEMI yang baru didiagnosis.

Kaedah: Pesakit yang telah didiagnosis STEMI dengan rawatan thrombolisis yang dirujuk untuk MPS disertakan dalam kajian ini. Keputusan MPS termasuk analisa separa kuantitatif keterukan ischaemia, jumlah perbezaan skor (SDS), pecahan ejeksi ventrikel kiri (LVEF), volum akhir diastolik (EDV), dan volum sistolik akhir (ESV) diperolehi. Susulan dilakukan 12 bulan selepas MPS asas dijalankan. Hasil primer pada pengurusan dengan hasil sekunder dikaji berkaitan dengan penemuan MPS.

Keputusan: Tujuh orang pesakit mengalami serangan jantung kritikal (cardiac hard events) 12 bulan selepas MPS asas. Kesemuanya adalah lelaki dengan purata umur 54.3 tahun. Analisa keputusan MPS dan hasil primer mendapati iskemia sederhana dan teruk, SDS bernilai 5 - 6 (OR = 49.875; 95% CI 11.30 – 220.16), SDS bernilai ≥7 (OR = 39.35; 95% CI 10.51 – 147.35), dan LVEF ≥35% mempunyai peluang peningkatan tidak disesuaikan yang signifikan untuk revaskularisasi. Iskemia sederhana dan teruk (OR = 285.8; 95% CI 28.15 - 2902.08) dan LVEF ≥ 35% (OR = 54.04; 95% CI 6.10 – 478.56) mempunyai peluang peningkatan yang signifikan untuk revaskularisasi apabila diselaraskan kepada factor-faktor lain yang mengelirukan

dalam analisis multivariasi. Sementara itu, LVEF of 23.7% dengan julat 17-29% (OR = 0.593; 95% CI 0.39 – 0.9), EDV of 172.6 ml dengan julat 155-197 mls (OR = 1.13; 95% CI 1.05 – 1.21), dan ESV of 130.9 ml dengan julat 110-141 mls (OR = 1.16; 95% CI 1.03 –1.31) mempunyai peluang peningkatan tidak disesuaikan yang ketara dalam kejadian serangan jantung kritikal.

Kesimpulan: MPS mempunyai peranan dalam meramalkan hasil pengurusan pesakit yang baru didiagnosis STEMI 12 bulan selepas MPS asas.

ABSTRACT

Background: Thrombolytic therapy is one of the treatment modality in ST elevation myocardial infarction (STEMI) although percutaneous coronary intervention (PCI) is an established gold standard treatment. Myocardial Perfusion Study (MPS) is one of the diagnostic modalities that can be used for risk stratification post STEMI. The purpose of this research is to study the role of MPS in predicting the management outcome in newly diagnosed STEMI patients.

Methods: Post STEMI with thrombolytic treatment referred for MPS were included in this study. MPS findings including semi quantitative analysis of severity of ischaemia, automated summed difference score (SDS), left ventricular ejection fraction (LVEF), end diastolic volume (EDV) and end systolic volume (ESV) were obtained. Follow up was done 12 months after baseline MPS. Primary outcome on types of management with secondary outcome were studied in relation to MPS findings.

Results: Seven patients had encountered cardiac hard events 12 months after the baseline MPS. All were male with mean age of 54.3 years old. Analysis of MPS findings and primary outcome found that moderate to severe ischemia, SDS of 5 - 6 (OR = 49.875; 95% CI 11.30 – 220.16), SDS of ≥7 (OR = 39.35; 95% CI 10.51 – 147.35), and LVEF ≥35% had significant unadjusted increased chance for revascularisation. Moderate to severe ischemia (OR = 285.8; 95% CI 28.15 - 2902.08) and LVEF ≥ 35%(OR = 54.04; 95% CI 6.10 – 478.56) had significant increased chance for revascularisation when adjusted to other confounding factors in multivariate analysis. Meanwhile LVEF of 23.7% with range 17-29% (OR = 0.593; 95% CI 0.39 – 0.9), EDV of 172.6 ml with range 155-197 mls (OR = 1.13; 95% CI 1.05 – 1.21), and ESV of 130.9 ml with range 110-141 mls (OR = 1.16; 95% CI 1.03 –1.31) had significant unadjusted increased chance of cardiac hard events.

Conclusion: MPS has a role in predicting the management outcome of patients with newly diagnosed STEMI post thrombolysis, 12 months after baseline MPS.

Keywords: Tc-99m Tetrofosmin Myocardial Perfusion Imaging, Myocardial infarction, cardiac death, heart failure.

1.0 INTRODUCTION

Myocardial infarction (MI) is defined as myocardial cell death due to prolonged ischaemia. It is one of the five main manifestations of coronary artery disease. Acute MI is classified into two groups, which are ST elevation MI (STEMI), and Non STEMI. Other manifestations include stable angina, unstable angina, heart failure and sudden death. Raising numbers of acute ST elevation myocardial infarction (STEMI) in Malaysia is associated with morbidity and mortality where is has contributed 20-25% of all deaths in public hospitals (Zambahari and Selvadurai, 2014).

Current treatment of STEMI is depending on the availability of percutaneous coronary intervention (PCI) at the hospital. In a PCI center hospital, the recommendation is to do primary PCI within 120 minutes following an acute MI. Thrombolytic treatment is given to patients in non PCI center or patients presented more than 120 minutes from time of diagnosis(Zambahari and Selvadurai, 2014). Thrombolytic treatment works by lysing infarct artery thrombi and achieving reperfusion thus restricting the infarct size, preserving the ejection fraction, and improving survival (White and Van de Werf, 1998). Within ninety minutes of presentation, thrombolytic treatment is at its most efficient to achieve infarct artery patency in around 50% of patients (White and Van de Werf, 1998).

Primary PCI is recommended over thrombolytic therapy but if PCI cannot be performed, thrombolytic therapy can be given within 12 hours of onset of symptoms with persistent ST segment elevation on the electrocardiogram (ECG) (White and Van de Werf, 1998). Thrombolytic treatment have improved survival at long term follow up yet the therapy is not always followed by reperfusion of the artery or thrombus dissolution which may cause the incidence of post infarction angina or recurrent ischemia. Delayed selective angiography plays a role after thrombolysis on haemodynamically unstable patients or residual ischaemia (Zambahari and Selvadurai,

2014).

Early and late risk stratification is divided into clinical and non invasive imaging. Clinical risk stratification using thrombolysis in myocardial infarction (TIMI) score or Global Registry of Acute Coronary Events (GRACE) calculator is done to estimate the prognosis of the patient and to weigh whether patient might benefit from intervention (Zambahari and Selvadurai, 2014). Therefore, it is essential to re-stratify patients post STEMI after thrombolytic treatment. Risk stratification post MI is assessed using Multi-sliced Computed Tomography (MSCT), Cardiac Magnetic Resonance Imaging (CMR), Myocardial Perfusion SPECT (MPS) or Positron Emission Tomography (PET-CT)(Zambahari and Selvadurai, 2014). It is done to prognosticate the risk of cardiac death by assessing the left ventricular ejection fraction (LVEF) and detection of residual myocardial ischemia (Zambahari and Selvadurai, 2014).

Technetium-99m Tetrofosmin MPS with stress and rest study is currently a valuable prognostic test in coronary artery disease (CAD)(Hendel et al., 2009). Studies have shown that MPS is able to prognosticate future cardiac events (Nishimura et al., 2008). Generally, it also served as a diagnostic tool to determine the necessity for catheterisation (Hachamovitch et al., 2006). Therefore MPS has been a routine modality for patients with diagnosed CAD. However, in this PCI era, not much literature was done to look at the patients' post thrombolytic treatment who did not underwent PCI during the acute phase. This study is specifically carried out to look at the patients with history of STEMI post thrombolysis and their management outcome 12 months after baseline MPS.

2.0 LITERATURE REVIEW

2.1 Overview of Myocardial Infarction

Myocardial infarction (MI) is caused by a sudden ischaemic death to the myocardial tissue. It is commonly due to thrombotic occlusion of a coronary vessel caused by rupture of a vulnerable plague (Frangogiannis, 2015). Meanwhile, myocardial ischaemia occurred due to imbalance between oxygen supply and demand. In severe atherosclerosis with >75% luminal narrowing, it does not cause any reduction of blood flow during rest. Type 1 MI or spontaneous MI resulting from coronary atherosclerotic disease complicated by superimposed thrombosis plague is the most common cause of thrombosis as a gap in fibrous cap of a vulnerable plague exposes the necrotic core to the blood stream and has potent thrombogenic response (Frangogiannis, 2015).

There are a few other clinical classifications of MI including Type 2 MI which is secondary to an ischemic imbalance. It is a condition where myocardial injury with necrosis causing imbalanced between myocardial oxygen supply and demand is contributed by other than factors of CAD such as coronary endothelial dysfunction, coronary artery spasm, coronary embolism, arrhythmias, anemia, respiratory failure, hypotension, and HPT with or without LV hypertrophy(Zambahari and Selvadurai, 2014, White et al., 2014).

Acute coronary syndrome is a clinical spectrum ranging from unstable angina (UA) or Non STEMI (NSTEMI) to STEMI. Clinical presentation is usually based on the severity of coronary occlusion. It is a clinical diagnosis based on the presence of myocardial injury or necrosis as indicated by a rise and fall of serum cardiac biomarkers. It should beforehand present with clinical history consistent with chest pain of ischaemic origin, ECG changes of ST segment elevation or presumed left bundle

branch block (LBBB). In unstable angina, cardiac biomarkers are normal but increased in NSTEMI. The distinct clinical feature separating unstable angina or NSTEMI with STEMI is the presence of ST segment elevation in ECG. Both spectrum of disease has different ways of management. While thrombolytic treatment is essential for patients with STEMI, it is contraindicated for patients with unstable angina or NSTEMI. (Wessler et al., 2015).

Chest pain of STEMI starts at sudden onset and should lasts >30minutes. It is centrally located and may radiate to the jaw and down to the left arm. The characteristics of pain is usually described as a pressure, squeezing or severe crushing pain with associated sweating, nausea and shortness of breath. In the elderly, females and diabetic patients may present with atypical symptoms where clinician should put their high suspicion towards these high risk group (Zambahari and Selvadurai, 2014).

Troponins have near absolute specificity and high sensitivity for myocardial infarction where it rises 3-4hours of onset of MI and more likely to be positive after six hours. However to date, troponins namely cardiac troponin T(cTnT), cardiac troponin I (cTnI) were the best cardiac biomarkers for diagnosing MI and usually combined with creatine kinase-MB (CKMB) and myoglobin (Ahmad and Sharma, 2012). A more comprehensive definition of MI which utilises newer cardiac biomarkers such as heart type fatty acid binding protein, high sensitivity cardiac Troponin (hs-Tn) and copeptin together with imaging technique is more sensitive in diagnosing MI (Zambahari and Selvadurai, 2014).

Patients with acute coronary syndrome present at a mean age of 59±12years, 6 years younger than those in Global Registry of Acute Coronary Events (GRACE) (Zambahari and Selvadurai, 2014). Age is one of the significant predictor to outcome of survival at 1-year post MI. According a study, the mean age of 61(51,59) survived whilst mean age of 70(62,79) died after 1 year of diagnosis (Califf et al., 2000). CAD

generally affects men more than women although women had higher 6 month mortality if affected (Seong and John, 2016). From National Cardiovascular Disease-Acute Coronary Syndrome (NCVD-ACS) registry, 75.8% out of patients diagnosed ACS were male while another 24.2% were female(Lu et al., 2014).

Based on race, Indians were over represented in comparison to the general proportion of the ethnicities. (Seong and John, 2016). The prevalence of diabetes mellitus among Asians is more common compared to Caucasians in the two studies done in Birmingham and Kuala Lumpur (Seong and John, 2016). Seong et al. 2016 also reviewed that Chinese had higher prevalence of hypertension and dyslipidaemia whilst the Indians had higher rates of diabetes mellitus. (Seong and John, 2016).

A study measuring BMI in patients post MI revealed that increasing BMI has increased risk of recurrent coronary events. Mild overweight (BMI 25 to 27.4) has relative risk of 0.93 and it has increased to 1.8 for class II-III obesity (BMI>35)(Rea et al., 2001).

2.2 Management of Myocardial Infarction

In acute setting, primary PCI remains the gold standard of treatment in treating STEMI. However, the efficacy of PCI has always been limited when there is delayed in restoration of the infarcted coronary artery. The ideal time for reperfusion strategy either by primary PCI or thrombolytic treatment, from the onset of angina is 180 minutes (Zambahari and Selvadurai, 2014). Although primary PCI is more effective than thrombolysis, the advantage of primary PCI is exceptionally prone to treatment delays (Gershlick et al., 2013). A multivariate analysis which adjusted for other predictors of mortality recommend that system delay is independantly associated with mortality (Terkelsen et al., 2010). Another study on the other hand concluded that primary PCI is associated with significantly reduced 30 day mortality compared with

fibrinolysis irrespective of treatment delay and therefore despite logistic issues, the standard approach should be PCI for all patients with STEMI (Boersma, 2006). Meanwhile, other studies showed that patient who came earlier within 2 hours of angina symptoms and received early thrombolysis had no significant reduction in 1 year mortality rates compared with patients who came in early and treated with PCI (Lambert et al., 2010, Armstrong, 2006, Westerhout et al., 2011). Another study recommended that thrombolysis should be carried out early preferably at pre hospital level to patients with no contraindications and followed by coronary angiography (within 24 hours) or rescue PCI for those thrombolytic failure (Bonnefoy et al., 2002). A study showed that more than 70% of patients receiving early thrombolysis had TIMI flow grades of 2-3 compared with 20% of those arriving for primary PCI which means thrombolysis has a role to reduce the infarct size in STEMI (Armstrong et al., 2013).

According to Malaysian guidelines, the suitable and timely use of some form of reperfusion treatment is more vital than the selection of therapy. Patients presented 3 hours of onset of angina are at low risk where both treatment strategies appear to have similar benefit (Zambahari and Selvadurai, 2014). In majority of hospital in Malaysia, thrombolysis is more readily available and plays as the main reperfusion strategy in patients with STEMI (Zambahari and Selvadurai, 2014). There are two options for thrombolytic treatment which are intravenous (i.v) Streptokinse or Tenectaplase/Metalyse. Being the most popular, Streptokinase which is not a fibrin specific agent results in a lower patency rate of occluded vessel at 60 minutes compared to fibrin specific agents (Zambahari and Selvadurai, 2014). Tenectaplase/Metalyse on the other hand results to a more rapid restoration of the infarcted artery than streptokinase. Heparin or enoxaparin should also be given following completion of thrombolysis therapy (Zambahari and Selvadurai, 2014).

While optimum management of STEMI with primary PCI is still controversial,

very limited study had shown the role of MPS for decision making of revascularisation (Meliga et al., 2011). A study of patients using Tc-99m Sestamibi MPS was done looking at the viability of the myocardium post thrombolysis where the study found that redistribution of regional wall and improvement of wall motion indicate viable myocardium (Javadi et al., 2011).

Antiplatelet agents such as Aspirin is indicated in all patients at diagnosis and should be continued unless contraindicated. Clopidogrel with aspirin have shown to reduced risk of death, reinfarction without increasing the risk of bleeding or cerebrovascular disease (group, 2005). Other drugs of choice include β blockers, Angiotensin converting enzyme inhibitor (ACE-I) and Angiotensin Receptor Blocker (ARB) (if ACE-I intolerant). β blockers which was already established as a beneficial long term treatment in the prethrombolytic era is indicated in patients with heart failure or LV dysfunction. ACE-I should be considered in the treatment and when there is intolerance it can be replaced with ARB (Zambahari and Selvadurai, 2014, O'Gara et al., 2013). Lipid lowering therapy is also initiated regardless of initial cholesterol levels and is to continue indefinitely (Pedersen et al., 2005). A study showed that with optimal medical therapy in patients who survived the acute phase of STEMI regardless whether PCI was commenced, reduced the mortality rates in 2 years follow up (García-García et al., 2017).

2.3 Prognostication of Myocardial Infarction

Patients with history of STEMI are at increased risk of subsequent morbidity and mortality due to complications such as heart failure and late onset arrhythmias. Therefore continuous risk stratification using dynamic TIMI risk score in patients with STEMI is essential. It is a significant clinical tool to estimate 1 year mortality. A review

on dynamic TIMI risk scoring estimated 1 – 5% mortality in one year among low to moderate risk patients with TIMI score of ≤5; and 8 – 25% mortality among patients with TIMI risk score of >5 (Amin et al., 2013). Risk stratification of patients post STEMI is necessary for prognostication and to identify further management. Patients who were not managed with coronary angiography should be risk stratified early. Myocardial perfusion study is one of the modalities to look at the left ventricular function and the presence of myocardial ischemia (Zambahari and Selvadurai, 2014, O'Gara et al., 2013).

Nishimura T (2008) has classified the cardiac outcome in his study into presence of cardiac hard events or no hard events. The cardiac hard events include death, severe heart failure or myocardial infarction. The result showed 2.4% encountered cardiac hard events during 3 year follow up. Hachamovitch et al (2003) also defined the outcome as presence of cardiac events i.e death, myocardial infarction, severe heart failure whilst no hard events is defined as asymptomatic of cardiac disease. CAD was the main cause of heart failure (49.5%) followed by hypertension (18.6%). (Seong and John, 2016).

2.4 Role of Nuclear Cardiology

Myocardial perfusion study (MPS) is one of the non-invasive images of the myocardium. Two most common used isotopes are Thallium-201 and Technetium-99m and imaging acquisition used is SPECT. MPS using SPECT have been largely replacing the previous multiple views planar images due to its superiority in the standpoint of localisation, quantification and image quality. MPS is done at rest and during stress to produced images of myocardial regional uptake that reflect relative regional myocardial blood flow (Gibbons, 2000). During stress vasodilator, myocardial blood flow is typically increased three to five fold compared to rest. With significant to coronary stenosis myocardial perfusion will not increase appropriately in the territory

supplied by the artery with the stenosis (Ziessman et al., 2013).

Many types of coronary vasodilators can be used for stress the heart pharmacologically. Dypiridamole for instance, is practically used in this study acts by blocking the cellular re-uptake of adenosine thus resulting in coronary vasodilatation and subsequent increased in coronary blood flow. Therefore in a significant coronary stenosis, the vasodilator would reduce perfusion at the sclerotic area (steal phenomenon) without inducing true ischemia(Ziessman et al., 2013, De Carvalho et al., 2017). Contraindications include second or third degree heart block, bronchospasm such as bronchial asthma and chronic obstructive airways disease. Dobutamine on the other hand is used when patients are contraindicated to Dypiridamole. It is a sympathomimetic drugs that mainly acts on β_1 cardiac receptors causing positive inotropic and chronotropic effects. Apart from its short half life (2min), and slight vasodilatory effect due to less β_2 receptor mechanism, patients on β-blockers need to witheld their medication 24-48hours since it will interfere with Dobutamine efficacy(De Carvalho et al., 2017, Ziessman et al., 2013).

Tc-99m-1,2-bis[bis(2-ethoxyethyl) phosphino] ethane (tetrofosmin) has been used for SPECT study in which the pharmacokinetics is similar to Tc-99m-2-methoxyisobutylisonitrile (sestamibi). It is a cationic complex that diffuses passively through the capillary and cell membrane. It then trapped in the mitochodria and retention is based on the intact mitochondria reflecting viable myocytes. Tetrofosmin is cleared rapidly from blood and approximately 1.2% of the administered radiotracer is taken up by the myocardial cells (Hesse et al., 2005, Ziessman et al., 2013). It is also known that the Tc-99m agents have better characteristics compared to Thallium (Tl-201) which is already out of market. Tc-99m agents have higher energy (140kEV) and hence resulting better image quality due to less attenuation and scatter. Having short half life approximately 6 hours, it also has low radiation exposure towards patient (Ziessman et al., 2013, Hesse et al., 2005).

Semi quantitative analysis of SPECT used short axis, horizontal long axis and vertical long axis tomography divided into 17 segments. Each segment was scored by consensus of two expert observers using five-point scoring system namely 0=normal; 1=equivocal; 2=moderate; 3=severe; 4=absence of tracer uptake (Cerqueira et al., 2002). It is reported to be a known comparable prognostic value to that of automatic quantitative analysis (Berman et al., 1998). Another automated semiquantitative analysis, summed difference score (SDS) reflected the burden of ischaemia in MPS. It is derived from the difference between summed stress score (SSS) and summed rest score (SRS). An SDS of ≥7 defined large amount of ischaemia and patient should undergo revascularisation (Hachamovitch et al., 2003).

Although cardiac stress MRI is the preferred and best method due to its detailed anatomical description, MPS is comparable to the standard in evaluating the myocardial perfusion (De Carvalho et al., 2017). A study has found that MPS has equivalent value compared to cardiac MRI in terms of sensitivity and specificity for detection of angiographically significant stenosis (Cremer et al., 2014). Other nuclear imaging such as cardiac perfusion Positron Emission Tomography/Computed Tomography (PET/CT) and Multi-sliced Computed Tomography (MSCT) is another known modality for perfusion evaluation (Ziessman et al., 2013, Okada et al., 2010). Other modalities such as stress echocardiography has similar negative predictive value as SPECT MPS which is around 94-99%(Metz et al., 2007).

A study by Sharir et al (2001) found that with large amount of ischemia with severe left ventricular dysfunction; left ventricular ejection fraction (LVEF) of less than 30% would increased cardiac death rate to >4% per year. The author also provided a risk stratification by post stress LVEF and amount of inducible ischemia (Sharir et al., 2001). Meanwhile another study has concluded that LVEF more than 50% predicted low event rate of less than 5% in 1 year and the rate increased to 27% in those with LVEF of less than 20%(Mahmarian et al., 2006).

Patients with severe coronary artery disease, angina, viable myocardium and reversible ischaemia with mild LV dysfunction (LVEF more than 35%) are more likely to benefit from revascularisation (Zambahari and Selvadurai, 2014). Medical therapy showed a survival advantage over patients undergoing revascularisation in the setting of no or mild ischaemia, whereas patients undergoing revascularisation had an increasing survival benefit over patients undergoing medical therapy when moderate to severe ischaemia was detected. Patients with more than 20% ischaemic myocardium showed that revascularisation had a lower cardiac mortality compared with medical therapy (Hachamovitch et al., 2003). Hachamovitch et al (2003) also stated that revascularisation does not improve survival over medical therapy in patients without ischemia or viable myocardium. A study by Mahmarian et al. (2006) concluded that patient with small perfusion defect less than 10% and LVEF more than 35% were discouraged from undergoing coronary angiography unless symptomatic or hemodynamically unstable. Infarct free survival at 1 year was calculated to be >95% in low risk patient(Mahmarian et al., 2006). Another study also found that revascularisation is associated with lower incidence of MI by 5.6% compared to conventional treatment (Madsen et al., 1997).

2.5 Myocardial Perfusion SPECT in Malaysia

Currently in Hospital Sultanah Aminah Johor Bahru (HSAJB), patients with STEMI are managed using the guidelines from Management of STEMI 2014 produced by Academy of Medicine of Malaysia which mainly focused on spontaneous MI (MI type 1) with ST segment elevation on ECG. Patients with high risk TIMI score (score 6 or more) are appointed for in patient or early coronary angiography. Primary PCI is established as a potent reperfusion strategy compared to thrombolytic treatment in patients with STEMI with its ability to reduced short term death from 9% to 7% (Keeley et al., 2003). However, this practice is still limited by facilities and expertise at our

center. The NCVD-ACS report 2011 by Lu et al (2014) found that utilisation rates for elective and emergency PCI and CABG was low and the predominant treatment of choice for STEMI was thrombolytic treatment which accounted for >70% of patients.

Most of the time those with low and moderate risk TIMI score (score 5 or less) were referred for other imaging modalities as outpatients for risk re-stratification in which MPS was one of the most feasible procedure to be done. MPS has been a routine method and has become the gatekeeper prior to any cardiac intervention. Therefore this study was done to assess the usefulness of MPS particularly in patients post STEMI.

3.0 OBJECTIVES

3.1 GENERAL OBJECTIVES

1. To study the role of MPS in predicting the management outcome in patients with newly diagnosed STEMI, 12 months after baseline MPS.

3.2 SPECIFIC OBJECTIVES

1. To determine the association between severity of myocardial ischemia, LVEF, EDV, ESV and SDS noted on MPS and the management of patients, 12 months after baseline MPS
2. To determine the proportion of cardiac hard events among patients, 12 months after baseline MPS
3. To determine the correlation between the management of patients, 12 months after baseline MPS and the presence of cardiac hard events.

3.3 RESEARCH HYPOTHESIS

3.3.1 Null hypothesis

Tc-99m Tetrofosmin myocardial perfusion study (MPS) has no role in predicting the management outcome in patients with newly diagnosed STEMI, 12 months after baseline MPS.

3.3.2 Alternate hypothesis

Tc-99m Tetrofosmin myocardial perfusion scan (MPS) has a role in predicting the management outcome in patients with newly diagnosed STEMI, 12 months after baseline MPS.

3.4 RATIONALE OF THE STUDY

This study is to determine whether MPS is a useful modality for the referring team in decision making for revascularisation in patients with history of STEMI.

3.5 BENEFIT OF THE STUDY

This study is to establish risk stratification for patients with history of STEMI.

4.0 METHODOLOGY

4.1 RESEARCH DESIGN

A retrospective and prospective cohort study was carried out in Department of Nuclear Medicine, Hospital Sultanah Aminah Johor Bahru (HSAJB) from March 2015 till December 2016.

4.2 PATIENT SELECTION

Patients with history of STEMI referred for MPS in HSAJB, who fulfilled the inclusion and exclusion criteria and consented to participate in this study were included. 33 patients were retrospectively recruited and 70 patients were prospectively enrolled in this study.

4.3 SAMPLE SIZE CALCULATION

Sample size calculation was done based on study by Nishimura T (Prognostic study of risk stratification among Japanese patients with ischaemic heart disease using gated MPS: J-Access study). This study needed 91 patients to achieve 5.0% precision in estimating prevalence which may be about 6.7% (3) with CI=95%. Sample size calculation Software : SSCPS version 1.0.03-3.xls

Formula with Finite Population Correction:

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

where n' = Sample size with finite population correction,
N = Population size,
Z = Z statistic for a level of confidence,
P = Expected proportion (If the prevalence is 20%, $P = 0.2$), and
d = Precision (If the precision is 5%, then $d = 0.05$)

Reference:
Daniel WW (1999). Biostatistics: A Foundation for Analysis in the Health Sciences. 7th edn. New York: John Wiley & Sons.

SAMPLE SIZE CALCULATOR FOR PREVALENCE STUDIES

* USING RANDOM (NOT CLUSTER) SAMPLING

Level of Confidence =	95%
Expected *P* =	0.067
Population Size (*N*) =	1,500

* Suggested precision (d) is 0.034.

Sample Size Table

Precision (*d*)	Sample Size (*n*) No FPC	Sample Size (*n*) With FPC	Suggestion for FPC application	Assumption (Normality)
± 0.01	2402	924	◄ n/N>0.05. FPC should be applied.	OK
± 0.02	601	429	◄ n/N>0.05. FPC should be applied.	OK
▼ ± 0.03	267	227	◄ n/N>0.05. FPC should be applied.	OK
▲ ± 0.04	151	137	◄ n/N>0.05. FPC should be applied.	OK
± 0.05	97	91	◄ n/N>0.05. FPC should be applied.	OK
± 0.06	67		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.07	50		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.08	38		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.09	30		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.10	25		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.11	20		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.12	17		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.13	15		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.14	13		◄ n/N≤0.05. FPC is NOT needed.	Not OK
± 0.15	11		◄ n/N≤0.05. FPC is NOT needed.	Not OK

Enter desired precision here.

FPC = Finite Population Correction

4.4 INCLUSION AND EXCLUSION CRITERIA

4.4.1 Inclusion Criteria

- First episode of STEMI, evidenced by typical/atypical chest pain, ECG changes (ST segment elevation or new onset LBBB) and increased in cardiac enzymes level.

- Post intravenous thrombolysis with either intravenous (i.v) Streptokinase or i.v Metalyse.
- Referred to Nuclear Medicine Department HSAJB for MPS.

4.4.2 Exclusion Criteria

- Patients who had undergone Coronary Artery Bypass Surgery (CABG) or Percutaneous Coronary Intervention (PCI).
- Patients with congestive heart failure, vulvular heart disease or congenital heart disease.
- Patients with other complications such as chronic kidney failure, cerebrovascular disease.
- Normal or infarction with no ischaemia in MPS findings.

4.5 STUDY PROTOCOL

Patients with history of STEMI post thrombolysis and referred for MPS were identified. Explanation regarding the protocol of MPS was carried out after inclusion and exclusion criterias were determined.

Patients background and clinical history were obtained. Demographic datas such as age, gender and race were confirmed from patients' identification cards. Patients' weight in kilogram(kg) and height in meter(m) were then measured. Detail background medical illnesses including history of STEMI, diabetes mellitus (DM), hypertension (HPT), dyslipidaemia, bronchial asthma or chronic obstructive airways disease were obtained. Smoking history and family history of IHD were also obtained.

Variables definitions

- Age/Gender/Race – confirmation from identification cards
- BMI – Formula of Weight(kg) divided by Height(m) x Height(m)
- Diabetes Mellitus – Confirmation by medical records or diabetic drugs or

prescriptions brought by patients.

- Hypertension – Confirmation by medical records or antihypertensive drugs or prescriptions brought by patients.
- Dyslipidemia - total cholesterol level more than 5.2mmol/l, High density lipoprotein cholesterol (HDL-C) less than 1.0 mmol/L (males) less than 1.2 mmol/L (females) and/or Triglycerides (TG) more than 1.7 mmol/L (Zambahari and Rajadurai, 2017).
- Smoking history - Active smoker defined as smoking >100 cigarettes (including hand rolled cigarettes or cigars) in their lifetime and has smoked in the last 28 days. Non smoker or no history of smoking is someone who has not smoked greater than 100 cigarettes in their lifetime and currently not smoking (Zealand, 2015)
- Family history of IHD - obtained from patients' history of family either parents, offspring or siblings who suffered from premature CAD (men less than 55years old and women less than 65years old).

4.5.1 Stress study

All patients were given counselling and provided with a brochure containing instructions and preparation checklist before the MPS**.** Fasting for at least 4 hours prior to the study was mandatory. Patients need to withold caffeine intake, medications such as Aminophylline, Nitrates and β blockers (Ziessman et al., 2013). Pharmacological stress test with iv Dypiridamole 142mcg/kg/min was used. However, when contraindicated in patients with history of bronchial asthma or chronic obstructive airways disease, iv Dobutamine 10mcg/kg/min and was titrated till 40mcg/kg/min was used instead. Patients were attached to vital signs (blood pressure and electrocardiogram) monitoring before the study started. Slow bolus injection of

Dypiridamole will take place for about 4 minutes. Subsequently, injection of radiopharmaceutical (Tc-99m Tetrofosmin 250MBq-400MBq) was given at 8th minute from the time the procedure started. Instead, when the iv Dobutamine was used, it was infused until the targeted heart rate of the patients were achieved, before the radiopharmaceutical being injected. Targeted heart rate should be achieved at 80 % of maximum targeted heart rate. The maximum heart rate was calculated with formula of 220 minus by age. The adverse effects of the drugs were observed, and presence of chest pain and shortness of breath was observed and recorded.

Patients were acknowledged regarding the risk of ACS characterised by chest pain with or without ECG changes (ST segment elevation or new onset LBBB) during stress study which is 2 in 10000. The ST segment depression is also recorded if at all present in this study. If patients were to have the adverse effects, after iv Dypiridamole, a reversal drug (iv Aminophylline 250mg stat) was given. Meanwhile, if the patients injected with iv Dobutamine encountered adverse effects, the procedure would be abandoned and subjects were treated accordingly. The overall time taken for the study is about 15 minutes with vital signs monitoring every 3 minutes. Stress imaging was performed 60 minutes after the pharmacological stress study was done.

4.5.2 Rest study

Meanwhile rest study was done on the same day following the stress study. Patients were given sublingual glyceryl trinitrate (GTN) 10-15min before injection of 400MBq-500MBq Tc-99m Tetrofosmin three hours after the stress study. GTN was given to reduce resting hypoperfusion and especially in patients with severe defect during stress study (Hesse et al., 2005, Strauss et al., 1998). Rest imaging was done on dual head gamma SPECT camera with three chest lead electrodes used for ECG gating 60 minutes after the injection of radiopharmaceutical

4.5.3 Imaging Acquisition

Imaging was performed with dual head gamma camera (Siemens Symbia E) which was equipped with low energy, high resolution collimator (LEHR) and an energy interval of 140±7.5%keV in a 128x128 matrix resolution. Myocardial images were acquired in a 180° orbit with 25 seconds readings every 3° producing raw data projections. Transverse reconstruction is automatically applied in the quantitative Gated SPECT (QGS) process using ramp filter, and 180 filtered back projections. The SPECT images recorded post acquisition were reviewed by the primary investigator or medical officers in the Nuclear Medicine department to exclude any possible technical error or imaging artefacts that might interfere with the end result.

4.5.4 Imaging Interpretation

The semiquantitative visual SPECT interpretation was done using short axis, vertical long axis and horizontal axis views tomograms by two experienced Nuclear Medicine physicians. If there is disagreement, a discussion is held and a final conclusion or diagnosis pertaining to the image interpretation is obtained. The 17 segment model is used for image interpretation with a five point score for each segment: 0 = Normal; 1 = Mildly reduced; 2 = Moderately reduced; 3 = Severely reduced; 4 = Absent tracer uptake. Inducible ischaemia or reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest images in two or more contiguous segments or slices. (Sarullo et al., 2002, Ziessman et al., 2013).

The automated semiquantitative analysis using Cedar Sinai software was done to generate summed difference score (SDS). SDS was derived as a difference from

summed stress score (SSS) and summed rest score (SRS) which reflected the burden of ischaemia. The classifications of scoring consisted of mild = 2-4; moderate = 5-6, severe = ≥7 (Czaja et al., 2017). From SDS score, percentage of ischemic myocardium can be obtained given formula of SDS divided by 68 times 100. The 17 segments scoring with maximum score of 4 yielded the denominator value of 68.

QGS parameters, which consisted of LVEF, EDV and ESV values were studied for completion of data on MPS findings. These were the normal values used as reference for this study; LVEF = 47-53%, EDV: male = 79 - 161ml; female = 60 – 107ml, ESV: male = 36 – 74ml; female = 25 – 44ml(Lomsky et al., 2008).

4.5.5 Patients Follow up

Patients were followed up after 12 months of MPS were done. This was to evaluate whether patient had undergone revascularization namely Percutaneous Coronary Intervention (PCI) or Coronary Bypass Artery Surgery (CABG). Patients were contacted via phone to assess for any presence of hard events (which includes death, non-fatal myocardial infarction and severe heart failure) or no hard events (uneventful and non of the above).

Cardiac death was confirmed by review of death certificate while non-fatal myocardial infarction was determined with appropriate ECG changes and/or elevated cardiac enzymes level. Degree of heart failure severity was defined with New York Heart Association (NYHA) either NYHA III (Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms) and IV (Unable to carry on any physical activity without discomfort. Symptoms of Chronic Heart Failure present at rest) fall into severe categories (Tonkin et al., 2005, Yancy et al., 2013).

4.6 STUDY OUTCOME MEASURE AND FOLLOW UP

A total of 103 patients who had met the inclusion and exclusion criteria were followed up, 12 months after baseline MPS. They were reached via phone and evaluation of presence of cardiac hard events at 12 months after MPS was recorded. Cardiac hard events include death, recurrent MI and severe heart failure. Types of intervention were also observed, whether the patients had undergone revascularisation or continued with medical therapy.

This study consisted of primary and secondary outcome. Primary outcome consisted of types of management of patients carried out after MPS was done which was either revascularisation or continue with medical therapy. For objective 1, all independent risk factors and variables in MPS findings were analysed in relation to types of management.

For objective 2, prevalence of cardiac hard events, 12 months after baseline was also described.

Secondary outcome on the other hand consisted of presence of cardiac hard events or no cardiac hard events. Therefore, for objective 3, all independent risk factors, variables in MPS findings and types of management were analysed in relation to presence of cardiac hard events.

4.7 DATA ANALYSIS

Statistical analyses were performed using IBM Statistical Package for Social Science software version 22 for Mac (SPSS, 2013). Descriptive statistics were expressed as frequency (percentage), mean ± standard deviation for normal data or median (IQR) for skewed data. Comparison between two groups was performed using Chi-square test, with Fischer Exact's correction where appropriate. For unpaired data, the differences in distribution between two groups were analysed by independent-t test

or Mann-Whitney test according to normal or skewed distribution of the data. *P* value of 0.05 and less was considered as significant.

Univariate analysis using binary simple logistic regression was used to determine the relationship between independent variables and dependant variables. Reference variable is determined when the group has the lowest possible value for what the outcome may be. When the group is identified, the interpretation of significance is made easier. The result would produce crude odds ratio with 95% confidence interval and p value<0.05 is considered to be significant. Those variables with value of p<0.05 in univariate analysis were required for entry into multivariate analysis. The analysis was to predict the probability that end observation that fall of one of two categorics of dichotomous dependant variable based on one or more independent variables that can be either continuous or categorical (statistics.laerd.com).

4.8 ETHICS AND DISCLOSURE

Research procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1964, revised in 2013 (World Medical Association, 2013) and Malaysian Guideline for Good Clinical Practice (National Committee for Clinical Research, 2011). This study had been approved by the Medical Research Ethics Committee (MREC) of the Malaysian Ministry of Health and registered with the National Medical Research Register (NMRR ID: NMRR-15-1991-35487) (APPENDIX H). Written informed consent was obtained from all patients. Confidentiality was strictly maintained, and data rendered anonymous except for the purpose of subject identification during statistical analysis.

The author had no conflicts of interest to disclose, which may influence the impartiality of this study.

RESULTS

5.1 DEMOGRAPHIC RESULTS

A total of 103 patients who fulfilled the inclusion and exclusion criteria were selected. The mean age of patients who were referred for MPS was 55.1 years old. Male patients predominated the female with 79 (76.7%) patients. The ethnic group breakdown were 67 (65.0%) Malay, followed by 26 (25.2%) Chinese and 10 (9.7%) Indian. As for the risk factors, dyslipidaemia was the highest, which accounted for 81 patients (78.6%) followed by HPT 67 patients (65.0%) and DM 60 patients (53.3%). These results were shown in Table 5.1.

Table 5.1: Characteristics of patients with history of STEMI referred for SPECT MPS (*n*=103)

Characteristics	**Category**	**Frequency (%) or Mean(SD)**	**p value**
Age		Mean 55.1(9.0)	0.31
Gender	Male	79(76.7)	0.22
	Female	24(23.3)	
Race	Malay	67(65.0)	0.33
	Chinese	26(25.2)	
	Indian	10(9.7)	
Risk factors			
BMI		Mean 25.0(4.2)	0.06
Diabetes mellitus		60(58.3)	0.33
Hypertension		67(65.0)	0.51
Dyslipidaemia		81(78.6)	0.78
Active smoking		46(44.7)	0.09
Family history		29(28.2)	0.66