ASSOCIATION OF AMBULANCE RESPONSE TIME AND MAJOR ADVERSE CARDIAC EVENTS IN ACUTE CORONARY SYNDROME

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Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree Of Master Of Medicine (Emergency Medicine)

UNIVERSITI SAINS MALAYSIA

2018

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HUBUNG KAIT MASA TINDAK BALAS AMBULAN DAN KESAN BURUK MAJOR JANTUNG DALAM SINDROM KORONARI AKUT

ABSTRAK

Latar Belakang**: Satu prinsip yang lazim dalam perkhidmatan perubatan kecemasan (EMS) menggariskan bahawa masa tindak balas yang lebih cepat adalah setara dengan hasil yang lebih baik pada pesakit yang mempunyai sindrom koronari akut (ACS). Kajian ini meneroka hubungan kait masa tindak balas ambulan (ART) dan kesan buruk major jantung (MACE) pada pesakit yang didiagnosis dengan ACS di Malaysia.* ***Metodologi: *Kajian ini merupakan kajian analisis kohort retrospektif yang dijalankan dari tahun 2014 hingga 2016 yang mana melibatkan dua perkhidmatan perubatan kecemasan (EMS) di Malaysia. Pesakit dewasa yang didiagnosis dengan ACS dan menggunakan EMS untuk ke hospital dikenalpasti untuk menilai MACE dalam tempoh 30 dan 90 hari daripada peristiwa primer. Analisis regresi logistik 'multivariable' telah dijalankan untuk menilai interaksi di antara ART dan MACE.* ***Keputusan:*** *Seratus orang pesakit dengan purata umur 59.7 (SD = 12.7) tahun dimasukkan dalam analisis. Kadar purata ART ialah 21.7 (SD = 10.4) minit. 29 orang pesakit mendapat MACE dalam tempoh 30 hari manakala 40 orang pesakit mendapat MACE pada 90 hari selepas ACS. Kajian menunjukkan tiada hubung kait yang signifikan di antara ART dan berlakunya MACE 30 dan 90 hari selepas ACS (OR = 0.99, 95% CI: 0.95, 1.03; P = 0.679 dan OR = 0.98; 95% CI: 0.95, 1.02; P = 0.446).* ***Kesimpulan:*** *Masa tindak balas ambulans (ART) tidak mempunyai hubung kait yang signifikan dengan MACE dalam tempoh 30 dan 90 hari selepas berlakunya ACS. Hasil kajian ini menggariskan keperluan untuk memastikan pengangkutan pesakit ACS dengan ambulan adalah pada kelajuan biasa dan mematuhi undang-undang jalan raya.*

***Kata Kunci** : Masa tindak balas ambulan, simdrom koronari akut, MACE*

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ABSTRACT

Background: A common tenet in emergency medical service is that a faster response time equates to a better outcome in patients with acute coronary syndrome (ACS). We explored the association between ambulance response time (ART) and major adverse cardiac events (MACE) in patients diagnosed of ACS in Malaysia. **Methods:** This study was a retrospective cohort analysis conducted from 2014 until 2016 involving two emergency medical services (EMS) in Malaysia. Adult patients diagnosed with ACS and utilized the EMS to come to hospital were followed up to assess MACE within 30 and 90 days from the primary event. Multivariable logistic regression analysis was performed to evaluate the interaction between ART and MACE. **Results:** One hundred patients with an average age of 59.7 (SD=12.7) years old were included in the analysis. The average ART was 21.7 (SD=10.4) minutes. 29 patients developed MACE at 30 days and 40 patients developed MACE at 90 days post ACS. No significant association was found between ART and occurrence of MACE 30 and 90 days post ACS (OR= 0.99; 95% CI: 0.95, 1.03; P=0.679 and OR=0.98; 95% CI: 0.95, 1.02; P=0.446 respectively). **Conclusion:** ART was not significantly associated with MACE after both 30 and 90 days onset of ACS. This underscores the need for not driving ambulances with high speeds when responding to ACS cases.

Keywords: Ambulance response time, Acute Coronary Syndrome, Major Adverse Cardiac Event

Chapter 1

Introduction

1.1 Background

According to health facts 2008 from the Ministry of Health, cardiovascular disease is the main cause of death in Malaysia. From 2006-2010, 16872 patients with Acute Coronary Syndrome (ACS) were admitted to 17 tertiary centers in Malaysia.

The mean age of presentation for the different ACS presentations were 56 years (SD 12) for ST Elevation Myocardial Infarction (STEMI), 62 years (SD 12) for Non ST Elevation Myocardial Infarction (NSTEMI) and 61 years (SD 12) for unstable angina. Compared with the large, multicenter GRACE Registry and other Western registries, patients in Malaysia were younger (mean age in GRACE for STEMI: 65 years; NSTEMI: 68 years; unstable angina 66 years)

Referring to the Malaysian 5th National Cardiovascular Disease Database on ACS (NCVD-ACS) registry from 2006 to 2010, majority of patients presented with STEMI (48%), followed by NSTEMI (30%) and unstable angina (22%). The same registry shows that patients with ACS had a male preponderance over female (76% male, 24% female).

Acute coronary syndrome defined as a clinical spectrum of ischemic heart disease which depending on the acuteness and severity of coronary vascular occlusion will cause either unstable angina, non ST segment elevation myocardial infarction or ST segment myocardial infarction.[1]

Overall, amongst the 4,000 or so STEMI patients, between years 2006-2010 in Malaysia, the median pain-to-needle time was 240 minutes (4 hours), whereas the median door-to-needle (DNT) was 50 minutes. The difference of pre-hospital pain-to-door time was approximately 190 minutes (three hours).[2]

The in-hospital mortality rate was highest in STEMI (8-10%), slightly lower in NSTEMI (6-9%), and lowest in UA (1-3%). At 30-day follow-up, the mortality rates were similar for both STEMI and NSTEMI (12% in average), and the rate was lowest in UA (3-6%).The mortality rate of ACS in Malaysia was higher than the mortality rates in several other global and regional ACS registries within the similar period. The expanded Global Registry of Acute Coronary Events (GRACE 2) from 2001 to 2007 reported in-hospital mortality rate of 6.2% in STEMI, 2.9% in NSTEMI and 1.7% in unstable angina patients.

The National Cardiovascular Disease Database 2010 also mentioned that the in-hospital and 30-day mortality following STEMI is also high at 10% and 14% respectively. These show the high disease burden of cardiovascular diseases.

1.2 Literature Review

So far, the economic burden of Acute Coronary Syndrome in Malaysia is not well known but a study in Korea in 2009, shows the prevalence of ACS in Korea was 6.4 persons per 1,000 population members and the associated mortality rate was 20.2 persons per 100,000 population members. The total cost of ACS in 2009 was USD 918.2 million. Of the total, direct medical cost was USD 425.3 million, direct non-medical cost was USD 11.4 million, and cost associated with morbidity and mortality was USD 481.5 million.[3] According to statistics from the American Heart Association (AHA), approximately 18% of men and 23% of women over the age of 40 will die within 1 year of having an initial recognized MI. The economic burden of ACS is also very high, costing Americans more than $150 billion, according to AHA estimates. Approximately 20% of the ACS patients are re hospitalized within 1 year, and nearly 60% of the costs related to ACS result from re hospitalization.[4] In view of the high economic cost of ACS, efficient and effective treatment and prevention of ACS must be set in

place to reduce ACS mortality morbidity that plaques patients after the initial episode of Acute Coronary Syndrome. [5]

A difference in gender will also predict the severity of MACE in ACS. It was found that women with non-obstructive Coronary Artery Disease (CAD) had a higher risk of MACE than men with non-obstructive CAD (adjusted HR 2.43, 95% CI 1.08-5.49). [6]

There are multiple co-morbidities that influence outcome for ACS. Data from observational studies and secondary analyses of randomized controlled trials (RCTs) have emerged that suggest that anemia is associated with higher rates of mortality, re-infarction, and other adverse outcomes after ACS. A systemic review and meta analysis by Lawler et al.[7] show that among clinical studies almost 20% of subjects with ACS has anemia. The presence of anemia is associated with a clinical and statistical increased risk for mortality after ACS which could be attributed at increased risk of re-infarction. Furthermore, there is evidence that as anemia worsen the outcome also worsen. Thus correction of anemia could improve short and long term outcomes.

In a retrospective study conducted using Western Denmark health care database, there was an association that suggest significantly worse outcome for patient with STEMI who undergo Percutaneous Coronary Intervention (PCI) with underlying Diabetes Mellitus (DM) compared to those who do not have DM. All-cause mortality was 23.7% in patients with DM, vs. 12.7% in patients without DM (adjusted HR 2.03, 95% CI 1.59–2.59).[8] These findings might suggest that more aggressive treatment and vigilance be given to those patients who present with ACS and underlying DM.

In the VALIANT (Valsartan in Acute Myocardial Infarct Trial) Trial it was found that decreasing Gomerular Filtration Rate (GFR) was associated with increasing mortality rates.[9] It was concluded that preexisting renal disease was a common and

significant independent risk factor for adverse events in patients who had had a myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both.[10]

In regards to heart failure severity in ACS, the Killip classification is an important independent predictor of 30 day mortality. Higher Killip class was associated with higher mortality at 30 days (2.8% in Killip class I vs 8.8% in class II vs 14.4% in class III/IV; $P<.001$) and 6 months (5.0% vs 14.7% vs 23.0%, respectively; $P<.001$).[11]

Advancement in treatment of Acute Myocardial Infarction (AMI) has enabled health care providers to reduce the high mortality that was used to be associated with AMI. Survival rates from AMI are improved by 50% if reperfusion with Alteplase is achieved within 1 hour of symptom onset and 23% if achieved within 3 hours of symptoms onset.[12]

Time is of the utmost importance as more time passes more ischaemic myocardium get irreversibly damage and results in worsen outcome. Every minute delay in treatment of patients with STEMI does influence 1 year mortality, not only in thrombolytic therapy but also in primary angioplasty. The risk of 1-year mortality is increased by 7.5% for each 30-minute delay. Therefore all efforts should be made to shorten the total ischemic time, not only for thrombolysis but also for primary angioplasty. [13]

In a study to see factors influencing emergency department arrival and in hospital management of AMI, the median delay was from onset of symptoms to hospital arrival was 110 minutes (approximately 2 h). Only 22% of patients arrived to the hospital within the first hour. According to the results of this study, many patients with AMI who may be eligible for reperfusion therapy miss the "golden hour" because of late hospital arrival. Some groups of patients (i.e., elderly, women, those with

diabetes) were especially late in arriving.[14] As such any delay in the treatment of patients with AMI must be identified and rectified.

The mean ambulance response time of Emergency Medical Services team of Hospital Universiti Sains Malaysia (HUSM) was 15.2 minutes in 2004-2005.[15] This is below the standard mean ambulance time of 8 minutes recommended by international standards. [16,17]

The recommended eight minute cut off time for ambulance response time originated from the study by Eisenberg et al. in 1978. Eisenberg found that survival from witnessed out of hospital cardiac arrest of medical origin was maximized if the time from cardiac arrest to start of CPR was four minutes and the time from cardiac arrest to definitive care (eg. Defibrillation) was eight minutes.[18] This time was later extended to all life threatening events whether medical or traumatic in origin which is currently the international cut off point for good ambulance response time.

For any health emergencies that require the ambulance services, is it assume that the faster the ambulance response time, the better the patient outcome especially in regards to survival to hospital discharge. However, a study by Blanchard et al. in 2012 shows that ambulance response time does not have an association with survival outcome in life threatening events. For patients with a response time $\geqslant$ 8 minutes, 7.1% died, compared with 6.4% for patients with a response time $\leqslant$ 7 minutes 59 seconds (risk difference 0.7%; 95% confidence interval [CI]: –0.5%, 2.0%). The adjusted odds ratio of mortality for $\geqslant$ 8 minutes was 1.19 (95% CI: 0.97, 1.47).[16] Another study by Pons and colleagues [19] also states that paramedic response time within eight minutes was not associated with improved survival to hospital discharge even after controlling for several important confounders, including level of illness severity. However the due to the diverse number of diseases that the pre-hospital services attend to, the authors

also concluded that more studies must be done to ascertain whether there are particular diseases that truly does benefit from speedy ambulance response time.

As the phrase, Time is Myocardium is used frequently to denote rapid medical intervention can help to limit the severity of damage to the ischaemia myocardium in Acute Coronary syndromes, it is worthwhile to study whether a true association exist between faster ambulance response time and presence of adverse cardiac events in patients who has Acute Coronary Syndrome.

The economic burden to maintain a pre-hospital service that has rapid response to all life threatening conditions can be reduced if there are more selective in choosing cases that truly warrant immediate pre-hospital activation instead of having to strain all the resources to respond to all cases quickly all the time.

Acute Coronary Syndrome is a time sensitive disease with worse outcome when the time from onset of symptoms to arrival to Emergency Department becomes longer. This study is to establish whether there is any association between ambulance response time and occurrence of MACE among ACS patient who used the ambulance services.

1.3 Research Questions

1. What is the current mean ambulance response time for complaints of chest pain or symptoms that suggest cardiovascular diseases?
2. Is there any association between ambulance response time and occurrence of MACE for among patient with ACS who used the ambulance services?
3. Is there any association between gender, anemia, renal failure, dyslipidemia, heart failure and occurrence of MACE in ACS patients who used the ambulance services?

1.4 Study Objectives

i. General Objective:

To identify ambulance response time within the areas covered by Hospital Universiti Sains Malaysia and Hospital Raja Permaisuri Bainun (HRBP) in regards to patients with ACS.

ii. Specific objectives:

1. To determine the average ambulance response time for patients with ACS for HUSM and HRPB.
2. To determine the association between ambulance response time and MACE in ACS who used ambulance services.
3. To determine factors associated with occurrence of MACE in ACS patients who used the ambulance services.

1.5 Methodology

Study Population

This is a retrospective cohort study from January 2014 until December 2016. The study will be conducted in two major capital cities in Malaysia, namely Kota Bharu and Ipoh where the EMS system were based in Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Permaisuri Bainun (HRPB) respectively. Kota Bharu has a total population of 491,234 while that of Ipoh has 659,892.[20]

All the ambulance units are equipped with Advanced Cardiac Life Support (ACLS) equipment and manned by dedicated ambulance driver and 2 ACLS trained EMS providers. Convenient sampling will be used in this study where all 999 calls with symptoms of ACS during the study period were included. Trained EMS call takers who determined ACS symptoms from a written EMS directive handled all the covered calls.

The study includes all EMS cases with the age of above 18 years old that were diagnosed as having ACS. The ART will be obtained from the dispatcher information sheet. Patients' age, gender, co-morbidities, admission diagnosis, treatments given, and event of MACE will be obtained from patients' in-hospital record. MACE was determined at 30 and 90 days after initial presentation.

The sample size was determined based on the objective of estimating the average ART in our study population. Based on a previous study, the ART was 15.22 minutes (SD=4.6 minutes).[15] To estimate the average ART with type I error of 5% and precision of estimation of ± 1 minute, and the required sample size was 103 after accounting for 20% drop out.

Statistical analysis

Data entry and analysis will be conducted using Statistical Package for Social Sciences (SPSS) version 22. The data will be explored to look for errors in data entry and to determine the pattern of distribution of numerical variables (age and ART). Based on histogram and test of normality which showed normal distribution of these numerical variables, they will be presented as mean (SD). Categorical variables will be presented as number and percentage (%). Simple and multiple binary logistic regression analysis will be applied in determining factors associated with the probability of developing MACE at 30 and 90 days post-ACS. At univariable analysis, variables with $p<0.25$ were selected to be included in the multivariable analysis for variable selection using forward and backward LR method. Multicollinearity of all independent variables will be checked using correlation matrix, and interaction will be checked using a multiplicative method. The Model fitness was then analyzed using the Hosmer-Lemeshow goodness of fit χ^2 test, classification table, and area under Receiver

Operation (ROC) curve. Categorical variables are presented in numbers (n) and percentages (%), and continuous variables in means with the standard deviation (SD).

References

1. Guidelines MCP. UA/NSTEMI. wwwacadmedorgmy/view_filecfm?fileid=414. 2011.

2. W.A Wan Ahmad KHS. Annual Report of the NCVD-ACS Registry. National Cardiovascular Disease Database. 2009 & 2010.

3. Kim J, Lee E, Lee T, Sohn A. Economic burden of acute coronary syndrome in South Korea: a national survey. BMC cardiovascular disorders [Internet]. 2013 2013; 13:[55 p.]. Available from: http://europepmc.org/abstract/MED/23924508

http://europepmc.org/articles/PMC3751132?pdf=render

http://europepmc.org/articles/PMC3751132

http://www.pubmedcentral.nih.gov/picrender.fcgi?tool=EBI&pubmedid=23924508&action=stream&blobtype=pdf

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=EBI&pubmedid=23924508

http://dx.doi.org/10.1186/1471-2261-13-55.

4. Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. Am J Manag Care. 2009;15(2 Suppl):S36-41.

5. Tarride J-E, Lim M, DesMeules M, Luo W, Burke N, O'Reilly D, et al. A review of the cost of cardiovascular disease. Canadian Journal of Cardiology. 2009;25(6):e195-e202.

6. Sedlak TL, Lee M, Izadnegahdar M, Merz CNB, Gao M, Humphries KH. Sex differences in clinical outcomes in patients with stable angina and no obstructive coronary artery disease. American Heart Journal. 2013;166(1):38-44.

7. Lawler PR, Filion KB, Dourian T, Atallah R, Garfinkle M, Eisenberg MJ. Anemia and mortality in acute coronary syndromes: A systematic review and meta-analysis. American Heart Journal. 2013;165(2):143-53.e5.

8. Saghafi O. Influence of Diabetes Mellitus on Clinical Outcomes Following Primary Percutaneous Coronary Intervention in Patients with ST-Segment Elevation Myocardial Infarction: Jensen LO, Maeng M, Thayssen P, et al. Am J Cardiol 2012;109:629–35. The Journal of emergency medicine. 2012;42(6):749.

9. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004;351(13):1285-95.

10. Anzai A, Anzai T, Naito K, Kaneko H, Mano Y, Jo Y, et al. Prognostic Significance of Acute Kidney Injury After Reperfused ST-Elevation Myocardial Infarction: Synergistic Acceleration of Renal Dysfunction and Left Ventricular Remodeling. Journal of Cardiac Failure. 2010;16(5):381-9.

11. Khot UN, Jia G, Moliterno DJ, Lincoff AM, Khot MB, Harrington RA, et al. Prognostic importance of physical examination for heart failure in non–ST-elevation acute coronary syndromes: the enduring value of Killip classification. Jama. 2003;290(16):2174-81.

12. Moser DK, Kimble LP, Alberts MJ, Alonzo A, Croft JB, Dracup K, et al. Reducing delay in seeking treatment by patients with acute coronary syndrome and stroke: a scientific statement from the American Heart Association Council on cardiovascular nursing and stroke council. Circulation. 2006;114(2):168-82.

13. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109(10):1223-5.

14. Ayrik C, Ergene U, Kinay O, Nazli C, Unal B, Ergene O. Factors influencing emergency department arrival time and in-hospital management of patients with acute myocardial infarction. Advances in therapy. 2006;23(2):244-55.

15. Shah CH, Ismail IM, Mohsin SS. Ambulance response time and emergency medical dispatcher program: a study in Kelantan, Malaysia. Southeast Asian J Trop Med Public Health. 2008;39(6):1150-4.

16. Blanchard IE, Doig CJ, Hagel BE, Anton AR, Zygun DA, Kortbeek JB, et al. Emergency medical services response time and mortality in an urban setting. Prehosp Emerg Care. 2012;16(1):142-51.

17. Blackwell TH, Kaufman JS. Response Time Effectiveness:Comparison of Response Time and Survival in an Urban Emergency Medical Services System. Academic Emergency Medicine. 2002;9(4):288-95.

18. Eisenberg MS, Bergner L, Hallstrom A. Cardiac resuscitation in the community: Importance of rapid provision and implications for program planning. Jama. 1979;241(18):1905-7.

19. Pons PT, Haukoos JS, Bludworth W, Cribley T, Pons KA, Markovchick VJ. Paramedic response time: does it affect patient survival? Acad Emerg Med. 2005;12(7):594-600.

20. Malaysia DoS. 2010.

Chapter 2

Study Protocol

2.1 Document submitted for ethical approval

Study proposal

Topic: Association of Ambulance Response Time and Major Adverse Cardiac Events in Acute Coronary Syndrome

Sponsor: Self-funding

Principle Investigator: Dr. Jeremiah Ding Deck Shen

Institution: Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia

Introduction

According to health facts 2008 from the Ministry of Health, cardiovascular disease is the main cause of death in Malaysia. From year 2006 to year 2010, 16872 patients with Acute Coronary Syndrome (ACS) were admitted to 17 tertiary centers in Malaysia.

The mean age of presentation for the different ACS presentations were 56 years (SD 12) for ST Elevation Myocardial infarction (STEMI), 62 years (SD 12) for Non ST Elevation Myocardial Infarction (NSTEMI) and 61 years (SD 12) for unstable angina. Compared with the large, multicenter GRACE Registry and other Western registries, patients in Malaysia were younger (mean age in GRACE for STEMI: 65 years; NSTEMI: 68 years; unstable angina 66 years)

Referring to Malaysian 5th National Cardiovascular Disease Database on ACS (NCVD-ACS) registry (NCVD-ACS) registry from 2006 to 2010, majority of patients presented with STEMI (48%), followed by NSTEMI (30%) and unstable angina (22%).

The same registry shows that patients with ACS had a male preponderance over female (76% male, 24% female).

A variety of coronary risk factors exist for ACS. Of patients with ACS, it is noted 33% were active smokers, 22% were former smokers, while 39% never smoked. On the same note, 33% were previously diagnosed with dyslipidaemia, 61% with hypertension, 43% with diabetes and 11% had a family history of premature coronary artery disease.

The Emergency Medical Services (EMS) of HUSM is one of the services provided by HUSM to cater for the demands of transporting patients who require medical assistance to the Emergency Department for further treatment. The total coverage area of HUSM services is 65,000 km^2 with a total of 9 functioning ambulances to serve the needs of the community during emergencies. The mean ambulance response time of EMD team was 15.2 minutes in 2004-2005.[1] On the same note, mean ambulance response time in Singapore was 15 minutes and UK was 7-11 minutes.

Literature review

Acute coronary syndrome (ACS) defined as a clinical spectrum of ischemic heart disease which depending on the acuteness and severity of coronary vascular occlusion will cause either unstable angina, non ST segment elevation myocardial infarction or ST segment myocardial infarction.[2]

Overall, amongst the 4,000 or so STEMI patients, between years 2006-2010 in Malaysia, the median pain-to-needle time was 240 minutes (4 hours), whereas the median door-to-needle (DNT) was 50 minutes. The difference of pre-hospital pain-to-door time was approximately 190 minutes (three hours).[3]

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In a retrospective study conducted using Western Denmark health care database, there was an association that suggest significantly worse outcome for patient with STEMI who undergo PCI with underlying Diabetes Mellitus (DM) compared to those who do not have Diabetes Mellitus. All-cause mortality was 23.7% in patients with DM, vs. 12.7% in patients without DM (adjusted HR 2.03, 95% CI 1.59–2.59).[9] This finding might suggest that more aggressive treatment and vigilance be given to those patients who present with ACS and underlying DM.

In the VALIANT (Valsartan in Acute Myocardial Infarct Trial) Trial it was found that decreasing Glomerular Filtration Rate (GFR) was associated with increasing mortality rates.[10] It was concluded that preexisting renal disease was a common and significant independent risk factor for adverse events in patients who had had a

myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both.[11]

Patient population with chest pain and ACS comes to the emergency department with a myriad of underlying co morbidities that will influence the clinical outcome. Thus risk scoring systems such as TIMI (Thrombolysis in Myocardial Infarction) will help to predict the outcomes of such patients. The TIMI risk score at ED presentation successfully risk-stratified this unselected cohort of chest pain patients with respect to 30-day adverse outcome, with a range from 2.1%, with a score of 0, to 100%, with a score of 7. The highest correlation of an individual TIMI risk indicator to adverse outcome was for elevated cardiac biomarker at admission.[12]

In regards to heart failure severity in Acute Coronary Syndrome, the Killip classification is an important independent predictor of 30 day mortality. Higher Killip class was associated with higher mortality at 30 days (2.8% in Killip class I vs 8.8% in class II vs 14.4% in class III/IV; $P<.001$) and 6 months (5.0% vs 14.7% vs 23.0%, respectively; $P<.001$).[13]

Advancement in treatment of Acute Myocardial Infarction has enabled health care providers to reduce the high mortality that was used to be associated with Acute Myocardial Infarction (AMI). Survival rates from AMI are improved by 50% if reperfusion with Alteplase is achieved within 1 hour of symptom onset and 23% if achieved within 3 hours of symptoms onset.[14]

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shorten the total ischemic time, not only for thrombolysis but also for primary angioplasty. [15]

In a study to see factors influencing emergency department arrival and in hospital management of AMI, the median delay was from onset of symptoms to hospital arrival was 110 minutes (approximately 2 hours). Only 22% of patients arrived to the hospital within the first hour. According to the results of this study, many patients with AMI who may be eligible for reperfusion therapy miss the "golden hour" because of late hospital arrival. Some groups of patients (i.e. elderly, women, those with diabetes) were especially late in arriving.[16] As such any delay in the treatment of patients with AMI must be identified and rectified.

One of the reasons that results in delay of treatment will be access to transportation. In a study in East Tennessee, approximately 15% of the study population did not have timely geographic accessibility to emergency cardiac care. Populations with poor access were located in rural areas.[17] This reflects the area surrounding HUSM which is still considered a rural area. Also as distance from hospital increases, MACE and mortality rates among ACS patients become higher.[18]

The mean ambulance response time of EMS team of HUSM was 15.2 minutes in 2004-2005[14] which is below the standard mean ambulance time of eight minutes recommended by international standards.[19,20]

The recommended eight minute cut-off time for ambulance response time originated from the study by Eisenberg et al. in 1978. Eisenberg found that survival from witnessed out of hospital cardiac arrest of medical origin was maximized if the time from cardiac arrest to start of CPR was four minutes and the time from cardiac arrest to definitive care (eg. Defibrillation) was eight minutes.[21] This time was later

extended to all life threatening events whether medical or traumatic in origin which is currently the international cut-off point for good ambulance response time.

Rational of study

For any health emergencies that require the ambulance services, is it assume that the faster the ambulance response time, the better the patient outcome especially in regards to survival to hospital discharge. However, a study by Blanchard et al. in 2012 shows that ambulance response time does not have an association with survival outcome in life threatening events. For patients with a response time $\geqslant$ 8 minutes, 7.1% died, compared with 6.4% for patients with a response time $\leqslant$7minutes 59 seconds (risk difference 0.7%; 95% confidence interval [CI]: –0.5%, 2.0%). The adjusted odds ratio of mortality for $\geqslant$ 8 minutes was 1.19 (95% CI: 0.97, 1.47).[19] Another study by Pons and colleagues [22] also states that paramedic response time within 8 minutes was not associated with improved survival to hospital discharge even after controlling for several important confounders, including level of illness severity. However the due to the diverse number of diseases that the pre-hospital services attend to, the authors also concluded that more studies must be done to ascertain whether there are particular diseases that truly does benefit from speedy ambulance response time.

As the phrase, Time is Myocardium is used frequently to denote rapid medical intervention can help to limit the severity of damage to the ischaemia myocardium in ACS, it is worthwhile to study whether a true association exist between faster ambulance response time and occurrence of adverse cardiac events in patients who has ACS.

The economic burden to maintain a pre-hospital service that has rapid response to all life threatening conditions can be reduced if there are more selective in choosing

cases that truly warrant immediate pre-hospital activation instead of having to strain all the resources to respond to all cases quickly all the time.

Acute Myocardial Infarction is a time sensitive disease with worse outcome when the time from onset of symptoms to arrival to Emergency Department becomes longer. Thus the pre-hospital services can be an avenue to reduce the national pain to needle time which in the end will help to reduce the mortality and morbidity of ACS and also the financial burden of ACS. [23]

Lastly, after knowing the ambulance access time, it will be used to gauge the efficacy of the ambulance services of HUSM and also HRPB in comparison to international standards and also to assess whether there has been any improvement since the last study by Shah et al. 2008.

Research Questions:

1. What is the current mean ambulance response time for complaints of chest pain or symptoms that suggest cardiovascular diseases?
2. Is there any association between ambulance response time and MACE for patient with acute coronary syndromes?
3. Is there any association between gender, underlying comorbidity, ambulance access time and Killip classification to rates of MACE in acute coronary patients?

Hypothesis

1. The faster the response ambulance time, the lower the rate of MACEs.
2. Female gender and higher number of underlying comorbidity have higher rate of MACEs.

Study Objectives

i. General Objective:

To identify ambulance response time within the areas covered by Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Permaisuri Bainun (HRBP) regarding patients with of Acute Coronary Syndrome.

ii. Specific objectives:

1. To determine the average ambulance response time for patients with ACS.
2. To determine the association between ambulance response time and MACE in ACS.
3. To determine factors associated with MACE occurrence in ACS patients who used ambulance services.

Methodology

i. Study design: retrospective study (both exposure and outcome had already occurred prior to the commencement of the study).

ii. Target group: Patients with Acute Coronary Syndrome (UA/STEMI/NSTEMI).

iii. Source population: All patients with acute coronary syndrome presented to HUSM and HRPB who used the ambulance service from 2014-2016.

iv. Location of study: Areas covered by HUSM and HRPB health services.

v. Data collection: Looking through the case notes of patients presented to HUSM and HRPB using the ambulance service with UA/NSTEMI/ STEMI as primary data.

vi. Sampling methods

1. Inclusion criteria: All cases of confirmed Acute Coronary Syndrome admitted to HSUM and HRBP during the study period will be included in the study.
2. Exclusion criteria : Patients not residents of Kelantan and Perak.

vii. Research analysis:

1. Objective1 : Descriptive statistics
2. Objective 2 and 3 : Multiple logistic regression

viii. Sample Size determination

1. Objective 1 : ambulance response time of HUSM

$$n = \left(\frac{Z\sigma}{E} \right)^2$$

-Z = 1.96, CL: 95%
-SD = 4.6 min.[1]
-Precision = 1 min
Sample size = 81 + 20% = 103

2. Objective 2: Association of ambulance response time with MACE in ACS, retrospective cohort, 2 proportions
- alpha = 0.05 (2 sided)
- power = 0.8
- ratio : 1
- P0 = 0.06 (proportion of patient with ambulance response time < 8 minutes with mortality).[19]
- P1 = 0.3 (estimated proportion of patient that HUSM ambulance service ambulance response time > 8 minutes with MACE)
- sample size = 78 + 20 % = 94

3. Objective 3: Association of other factors to MACE in ACS

i) gender

- alpha = 0.05 (2 sided)

- power = 0.8

- ratio =1

- P0 = 0.3 (proportion of STEMI who are female).[24]

- P1 = 0.7 (estimated proportion of STEMI who are men)

- sample size = 46 + 20% = 55

ii) anemia

Alpha – 0.05

Power = 0.8

Ratio = 1

P0= 0.01 (proportion of ACS patient who has no anemia and have MACE).[25]

P1 = 0.2 (estiamted ACS patient with anemia and MACE)

Sample size = 80 + 20 % = 100

iii) Diabetes

Alpha = 0.05

Power = 0.8

Ratio = 1

P0 = 0.16(Proportion of patient without diabetes with MACE in post MI).[26]

P1 = 0.5 (estimated proportion of MACE in diabetic patient post ACS)

Sample size = 76 + 20% = 91

ix. Research Instruments: Statistical Package for Social Science (SPSS) 22.

Definition

1. Acute Myocardial Infarction is used when there is evidence of myocardial necrosis in a clinical setting that consistent with myocardial ischaemia. The diagnosis includes biochemical cardiac markers of myocardial necrosis, symptoms consistent with myocardial ischaemia, cardiac imaging, ECG changes and intracoronary thrombus upon autopsy/ angioplasty.[27]
2. ECG criteria for STEMI: ST-segment elevation or presumed new LBBB is characterized by ST-segment elevation in 2 or more contiguous leads Threshold values for ST-segment elevation consistent with STEMI are J-point elevation 0.2 mV (2 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men40 years old); J-point elevation 0.25 mV (2.5 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men 40 years old); J-point elevation 0.15 mV (1.5mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (women).[27]
3. ECG criteria for Unstable Angina/NSTEMI: ST-segment depression 0.5 mm (0.05 mV) or dynamic T-wave inversion with pain or discomfort is classified as UA/NSTEMI. Non persistent or transient ST-segment elevation 0.5 mm for 20 minutes is also included in this category. Threshold values for ST-segment depression consistent with ischemia are J-point depression 0.05 mV (-.5 mm) in leads V2 and V3 and -0.1 mV (-1 mm) in all other leads (men and women).[27]
4. MACE (major adverse cardiac events): Death (not clearly non-cardiac), cardiac arrest, an emergency re-vascularisation procedure, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrio ventricular block needing intervention and acute myocardial infarction within 30 days from primary event, as cited from [28]

5. Ambulance response time: Defined as time taken from receiving the emergency call, till time of arrival to incident site. Includes call processing time, time to prepare a team , time to travel to scene.[29]
6. Time at the scene: The period between ambulance arrival at the scene and ambulance departure from the scene.[29]
7. Transport time: the interval between leaving the scene and arriving at the emergency department.[29]
8. Total run time: response time, scene time and transport time which amount to the total run time.[29]

Conclusion, Discussion, Future Recommendation

Data supporting the association between longer ambulance access time and worse outcomes in Acute Myocardial Infarction will drive more efforts to improve ambulance services and also to get the appropriate funding and supports that it deserves.

References

1. Shah CH, Ismail IM, Mohsin SS. Ambulance response time and emergency medical dispatcher program: a study in Kelantan, Malaysia. Southeast Asian J Trop Med Public Health. 2008;39(6):1150-4.

2. Guidelines MCP. UA/NSTEMI. wwwacadmedorgmy/view_filecfm?fileid=414. 2011.

3. W.A Wan Ahmad KHS. Annual Report of the NCVD-ACS Registry. National Cardiovascular Disease Database. 2009 & 2010.

4. Kim J, Lee E, Lee T, Sohn A. Economic burden of acute coronary syndrome in South Korea: a national survey. BMC cardiovascular disorders [Internet]. 2013 2013; 13:[55 p.]. Available from: http://europepmc.org/abstract/MED/23924508