RISK FACTORS OF CARDIOVASCULAR DISEASE AMONG ST-ELEVATION MYOCARDIAL INFARCTION MALE PATIENTS IN MALAYSIA FROM 2006 TO 2013

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Graphical abstract

- Descriptive analysis
- Univariate analysis
- Multivariate analysis
- Obtain the best model
- Assess the goodness of fit of the model
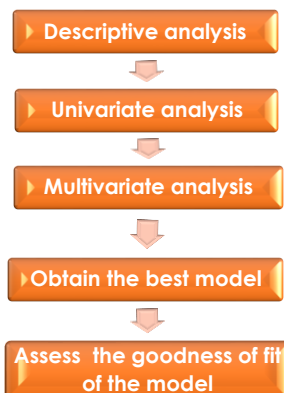
Abstract

Cardiovascular disease is the leading cause of death in Malaysia and globally. This study aimed to identify associated risk factors in cardiovascular disease among ST elevation myocardial infarction (STEMI) male patients and obtain a feasible model to describe the data. A total of 16,673 STEMI male patients from 18 participating hospitals across Malaysia in the National Cardiovascular Disease Database-Acute Coronary Syndrome (NCVD-ACS) registry year 2006-2013 were analysed. Univariate analysis was conducted. Significant variables from the univariate analysis were further analysed by a multivariate logistic analysis to identify the prognostic factors. The most prevalent risk factor for male patients was smoking (79.3%), followed by hypertension (54.9%) and diabetes mellitus (40.4%). At univariate level, this study is consistent with the findings from the Malaysian National Health and Morbidity Survey (NHMS) where smoking is a significant risk factor. After adjustment in multivariate logistic model, the risk factors for cardiovascular death among male patients are related to age, premorbid condition such as diabetes mellitus, hypertension, family history of CVD, Killip class, type of treatment such as percutaneous coronary intervention (PCI) and relevant comorbidity such as renal disease. Drastic efforts in the management of all risk factors in males is needed to improve adherence outcomes.

Keywords: STEMI, cardiovascular, male, risk factor, regression analysis

Abstrak

Penyakit kardiovaskular adalah punca utama kematian di Malaysia dan di seluruh dunia. Kajian ini bertujuan untuk mengenal pasti faktor-faktor risiko yang berkaitan dengan penyakit kardiovaskular dalam kalangan pesakit lelaki infarksi miokardium ketinggian ST (STEMI) dan mendapatkan model yang sesuai untuk menggambarkan data. Seramai 16,673 pesakit lelaki STEMI dari 18 hospital yang mengambil bahagian di Malaysia bagi tahun pendaftaran 2006-2013 telah direkodkan oleh Pendaftar Penyakit Kardiovaskular-Sindrom Koronari Akut Kebangsaan (NCVD-ACS). Analisis univariat telah dijalankan. Pemboleh ubah signifikan dari analisis univariat dianalisis lagi dengan analisis logistik

multivariat untuk mengenal pasti faktor prognostik. Faktor risiko yang paling lazim bagi pesakit lelaki adalah merokok (79.3%), diikuti dengan tekanan darah tinggi (54.9%) dan kencing manis (40.4%). Pada tahap univariat, kajian ini konsisten dengan penemuan daripada kajian Kesihatan dan Morbiditi Kebangsaan Malaysia (NHMS) di mana merokok adalah faktor risiko yang signifikan. Selepas penyesuaian dalam model logistik multivariat, faktor risiko kematian kardiovaskular dalam kalangan pesakit lelaki berkait dengan usia, keadaan premorbid seperti kencing manis, tekanan darah tinggi, sejarah keluarga, kelas Killip, jenis rawatan seperti PCI dan komorbiditi yang berkaitan seperti sebagai penyakit buah pinggang. Usaha gigih dalam pengurusan semua faktor risiko pada lelaki diperlukan untuk meningkatkan hasil pematuhan.

Kata kunci: STEMI, kardiovaskular, lelaki, faktor risiko, analisis regresi

1.0 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in Malaysia [1] and globally [2]. There is a 5% increase in the number of cases the National Heart Institute (IJN) treats every year, with 10000 cases of cardiology and hypertension and 4000 cases of heart surgery in a year [3]. CVD is defined as a group of disorders of the heart and blood vessels which include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease and congenital heart disease [2,4].

An ongoing prospective registry known as the Malaysian National Cardiovascular Disease-Acute Coronary Syndrome (NCVD-ACS) Registry was first established in 2006, and to date it involves 18 hospitals across the country. The registry was introduced to collect clinical data including in-hospital management and clinical outcome. The Ministry of Health Malaysia has become the main sponsor to the NCVD-ACS Registry with National Heart Association of Malaysia as the co-sponsor [5] where technical support in the form of clinical epidemiology expertise, biostatistics and information and communication technology services are provided by the Clinical Research Centre of Malaysia. The data provide a useful source of information in understanding the trends of CVD among the Malaysian population. The database has information on demographic of the patients as well as medical information.

The objective of this study is to identify the risk factors associated with mortality among CVD patients. In particular, we utilised the NCVD-ACS Registry to identify the associate risk factor among ST-elevation myocardial infarction (STEMI) male patients. Interestingly, STEMI was more prevalent among males compared to females [6,7,8]. In this dataset, the percentage of male patients is approximately 85.6% compared to female patients. Using the covariates available in the data, we attempted to identify the risk factors using logistic regression analysis. The organisation of this paper is as such; it starts with the overview of the CVD, NCVD-ACS registry and the methodology used, the descriptive statistics of the variables and the proposed logistic regression model. This is followed by a discussion and the implication of the findings of the analysis.

2.0 METHODOLOGY

2.1 Materials

Anonymized patient data were obtained from the NCVD-ACS registry for the years 2006 to 2013. In this study, only data of patients who were diagnosed with ACS ST-elevation myocardial infarction (STEMI) from 18 participating hospitals across Malaysia were selected from the NCVD-ACS registry. In this context, STEMI was defined as persistent ST segment elevation ≥ 1 mm in two contiguous electrocardiographic leads, or the presence of a new left bundle branch block in the setting of positive cardiac markers [7].

Data was collected from the time the patient with STEMI was admitted to the hospital till discharge from hospital. Follow-up was done 30 days after hospital discharge through phone call or when the patient came to the clinic for a review. Mortality status verification was also done by a cross check with the the Malaysian National Registration Department (NRD). The patients' characteristics and clinical presentation, in-hospital treatment and clinical outcome were recorded. Data was then entered into the NCVD website after verification. The operation of the NCVD is supported by a comprehensive information and communications technology system to ensure functional efficacy and effectiveness.

Demographic variables available from the data are ethnicity and age group. The patients' ethnicity was determined based on self-report and their national identity cards. As for the age, the patients were categorized into two groups; age < 65 years and age ≥ 65 years. The cut-off age of 65 years was chosen based on the local medical practice [7]. The risk factors were diabetes mellitus, hypertension, smoking status, dyslipidaemia and family history of CVD. While the comorbid variables were myocardial infarction (MI) history, chronic lung disease, cerebrovascular disease, peripheral vascular disease

and renal disease. Clinical presentation known as Killip class was divided into four classes. The Killip classification predicts the chances of survival within 30 days in patients with an acute heart attack, with a higher class having a higher chance of dying. Killip IV is the highest class [9]. As for the treatment, the variables were percutaneous coronary intervention (PCI) and cardiac catheterization. PCI or formerly known as angioplasty is a non-surgical procedure that uses a catheter to place a small structure called a stent to open up blood vessels in the heart that have been narrowed by the buildup of atherosclerotic plaque [10]. While cardiac catheterization is the insertion of a catheter tube and injection of contrast dye usually iodine-based into the coronary arteries [11].

2.2 Methods

Categorical variables were presented as percentage. Significant variables from the univariate analysis were further analysed by the logistic multivariate analysis to identify the prognostic factors. The goal of logistic regression was to find the best fitting model to describe the relationship between the dichotomous characteristic of dependent variable and a set of independent variables. Logistic regression generated the coefficients of a formula to predict a logit transformation of the probability of presence of the characteristic of interest. In other words, logistic regression analysis estimated the log odds of an event. Mathematically, logistic regression estimated a multiple linear regression function defined as:

$$\text{logit}(p) = \log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_n x_n \qquad (1)$$

where p is the probability of presence of the characteristic of interest, β_i is the logistic regression coefficients and x_i is the independent variables for $i = 1,..., n$.

Stepwise regression analysis was chosen in the model building procedure. It is a method that allowed the move in direction, removing or adding variables at the various steps. Addition of variable was based on the significance of the score statistic, and removal of variable was based on the probability of a likelihood-ratio statistic based on the maximum partial likelihood estimates. Statistical significance was considered if the p-value was less than 0.05. Goodness of fit was performed using the Hosmer and Lemeshow test [12] which determined the variation of the outcome, and Spearman rank test to check on multicollinearity. All analyses were conducted using SPSS statistical software (version 22, IBM SPSS Statistics, USA).

3.0 RESULTS AND DISCUSSION

From the descriptive analysis presented in Table 1, STEMI patients were predominantly ethnic Malay with more than 50.0%, and followed by Chinese of about 18.0%. This proportion is a reflection of the population in Malaysia where more than 50% are Malay [13]. The majority of male patients fell into the less than 65-year-old age group. Simply put, males had a greater risk of suffering CVD, and they also had attacks earlier in life [7, 14]. According to the IJN (2016), patients as young as in their 20s had undergone bypass surgery due to clogged arteries [3].

Table 1 Patients' characteristics

Characteristic			Percentage (%) (n= 16,673)
Demographic	Ethnicity	Malay	59.3
		Chinese	17.9
		Indian	16.3
		Others	6.5
	Age group	<65	80.9
		≥65	19.1
Risk factor	Diabetes Mellitus	No	59.6
		Yes	40.4
	Hypertension	No	45.1
		Yes	54.9
	Smoking status	Never	20.7
		Active/ former	79.3
	Dyslipidaemia	No	65.0
		Yes	35.0
	Family history of CVD	No	83.9
		Yes	16.1
Comorbidities	MI History	No	86.3
		Yes	13.7
	Chronic lung disease	No	97.5
		Yes	2.5
	Cerebrovascular disease	No	97.2
		Yes	2.8
	Peripheral vascular disease	No	99.7
		Yes	0.3
	Renal disease	No	96.5
		Yes	3.5
Clinical presentation	Killip Class	Class I	64.4
		Class II	21.0
		Class III	4.3
		Class IV	10.3
Treatment	PCI	No	69.9
		Yes	30.1
	Cardiac catheterization	No	65.6
		Yes	34.4

The most prevalent risk factor for STEMI male patients was smoking (79.3%), followed by hypertension (54.9%) and diabetes mellitus (40.4%). Myocardial infarction (MI) was the most relevant comorbidity followed by renal disease and cerebrovascular disease. Majority of the STEMI patients were in Killip class I or II on presentation. As part of their continuing medical care, cardiac catheterization was the most undergone procedure followed by the percutaneous coronary intervention (PCI).

Using dependent variable of patient status whether died or alive, univariate analysis was performed and it found that all variables were significant. Among the highest were Killip class, age group and renal disease. Patients with Killip class IV were 15.9 times more likely to die than those from Killip class I. The odds of dying for patients from the age group ≥ 65 were 3.2 times higher than those from the age group < 65. Those with renal disease were 3.9 more likely to die than those without it.

All significant variables as listed in Table 1 were used in the multivariate model where stepwise regression analysis was performed and the result of the best model is given in Table 2.

Table 2 Variables in the Final Model

Variable	β	S.E.	df	p-value	Odds ratio (95% C.I)
Diabetes mellitus	0.294	0.107	1	0.006	1.342 (1.088, 1.655)
Hypertension	0.479	0.113	1	0.000	1.615 (1.295, 2.014)
Family history of CVD	-0.373	0.171	1	0.029	0.689 (0.493, 0.963)
Renal disease	0.858	0.198	1	0.000	2.358 (1.598,3.478)
Killip class I			3	0.000	
Killip class II	0.720	0.143	1	0.000	2.054 (1.553, 2.717)
Killip class III	2.208	0.167	1	0.000	9.095 (6.556, 12.617)
Killip class IV	2.792	0.128	1	0.000	16.314 (12.685, 20.981)
PCI	-0.359	0.114	1	0.002	0.698 (0.558, 0.873)
Age (≥ 65)	0.861	0.110	1	0.000	2.365 (1.905, 2.935)
Constant	-4.031	0.123	1	0.000	0.018

Of the fifteen variables, seven variables were found to be significant in the multivariate model namely diabetes mellitus, hypertension, family history of CVD, renal disease, PCI, Killip class and age group of the patients.

The odds ratio suggests that patients with diabetes mellitus were 1.3 times more likely to die than those without it. The odds of dying also increased for patients with hypertension (OR=1.6) and patients with renal disease (OR=2.4). Whereas, patients with family history of CVD were less likely to die (OR=0.7). The regression coefficients, β for all Killip class were significant, indicating that increasing affluence is associated with increased odds of dying. Surprisingly, the odds of dying for patients with Killip class IV were 16.4 times higher than those from Killip class I. In addition, the risk of mortality for male patients from the age group ≥ 65 was 2.4 times higher than those from the age group < 65. Patients who had undergone PCI were significantly less likely (OR=0.7) to die than those without it.

As for model checking, -2log-likelihood was used in the logistic regression. This statistic was used to indicate how well the model actually fits the data and the change in fit of the model to data if a variable is removed from the model. There was a significant decrease in the -2log-likelihood value for the final model as shown in Table 3 compared to the -2log-likelihood value for the null model. This indicates the absolute fit of the final model to the data.

Table 3 Model Checking

Model	-2log-likelihood	p-value
Null model	2977.450	0.000
Final model	2803.447	0.202

In other words, the final model with the listed covariates shown in Table 2 has a better fit than the null model. Also, the Hosmer and Lemeshow test of the goodness of fit suggests all the models are good fit to the data as p > 0.05. The degree of accuracy of this model was 93.3%. Additionally, multicollinearity was assessed by the variable inflation factor (VIF). The result suggested weak multicollinearity in the variables as all the VIF values were less than 5 [15, 16].

As mentioned earlier, CVD remains the main cause of mortality and morbidity in Malaysia. The NCVD-ACS 2009-2010 reported that in-hospital mortality rates remained constant with an overall average of 7% over the five-year period from 2006 to 2010 [6]. It is worthwhile to note that mortality of STEMI patients was 9% which was higher compared to a few other global and regional ACS registries [6]. Similar to other studies, male patient population was predominantly ethnic Malay with more than 50% [8, 17, 18]. Patients from the age group less than 65 years old have strong dominancy with more than 85%. This is supported by the NCVD-ACS registry which showed that Malaysians are having acute coronary syndrome (ACS) at a younger age, with a mean age of between 55.9 to 59.1 years compared to mean ages of between 63.4 to 68 years in most developed countries [18].

As stated earlier, the motivation of the study was to identify the risk factors on mortality among STEMI male patients in Malaysia. The most prevalent risk

factor was smoking (79.3%), followed by hypertension (54.9%) and diabetes mellitus (40.4%) and is consistent with those reported in the NCVD database registry Annual reports [6]. In addition, more than 95% of patients had at least one well-known cardiovascular risk factor namely hypertension, diabetes mellitus, smoking, and dyslipidaemia on their admission [6]. Also, an earlier case-control study by Suleiman *et al.* [19] noted that smoking and hypertension were significant risk factors of CVD diagnosis.

The result of this study is also similar to previous studies by Lim *et al.* [20] and Venkatason *et al.* [21] which suggested that males have the highest prevalence of smoking in Malaysia. In another study, Chiam *et al.* [22] retrospectively reviewed the risk factor prevalence in 302 coronary artery bypass grafting patients. Their study found that the prevalence of diabetes mellitus and hypertension was 45.7% and 78.8%, respectively. Malays and Chinese most commonly presented with hypertension, while Indians had the highest tendency of having both risk factors. The findings of their study are also supported by the recent study of Musa *et al.* [23]. In addition, according to the National Health and Morbidity Survey [24], the prevalence of hypertension in Malaysia was 34.6% in 2006, 33.6% in 2011, and 35.3% in 2015. Hypertension is highly associated with chronic diseases such as myocardial infarction, stroke and heart failure.

Another significant finding from this study is associated with renal disease. Patients with renal disease were 2.3 times more likely to die than those without it. This is supported by the finding of other studies where renal disease is a strong and independent predictor of all-cause mortality in CVD [25, 26, 27]. As for clinical presentation, patients with Killip class IV were 16.5 more likely to die than patients with Killip class I. From this study, only 16% of the patients had family history of CVD. The odds ratio suggest that those associated with positive family history of CVD were less likely to die than those without it (OR=0.7). In contrast, Muda *et al.* [28] retrospectively reviewed the medical records of patients in Hospital Universiti Sains Malaysia with angiographically proven CVD from 2002 to 2004 found 55% of the patients had family history of CVD.

Percutaneous coronary intervention (PCI) is one of the common treatments of CVD. This study, found that patients who had undergone PCI were less likely to die than those without it (OR=0.7). Thus, this suggests that PCI is an effective treatment in reducing morbidity and mortality. As suggested by Chen *et al.* [29] and Zuhdi *et al.* [7], primary PCI is the preferred treatment due to its better outcome. They suggested that even if the outcome of elderly patients after PCI is not as good as that of non-elderly patients, there were still some mortality benefits to be gained from PCI invasive treatment for elderly patients. For this reason, a greater Kuala Lumpur STEMI network was initiated in 2015 by the Ministry of Health, in conjunction with the Ministry of Education and IJN [8]. This network refers acute STEMI patients between government hospitals, teaching university hospitals and the IJN directly to PCI capable centres.

4.0 CONCLUSION

In conclusion, smoking, hypertension and diabetes mellitus are established risk factors for CVD specifically STEMI male patients. Intensive efforts must be made towards educating the public to change risky lifestyle such as smoking and to increase awareness of healthy living such as regular exercise and healthy diet to reduce the prevalence of CVD in the country. In fact, much effort is needed to improve cardiology services in the country especially the provision of primary PCI facilities in all major cities. Earlier instituting of proper treatment has been shown to lead to better outcomes. Also, logistic regression model is the most suitable to describe the relationship between dichotomous characteristic of dependent variable and a set of independent variables in the NCVD-ACS data in this study.

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