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Gender differences in mortality among ST elevation myocardial infarction patients in Malaysia from 2006 to 2013

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BACKGROUND: Coronary artery disease (CAD) is one of the leading causes of death in Malaysia. However, the prevalence of CAD in males is higher than in females and mortality rates are also different between the two genders. This suggest that risk factors associated with mortality between males and females are different, so we compared the clinical characteristics and outcome between male and female STEMI patients.

OBJECTIVES: To identify the risk factors associated with mortality for each gender and compare differences, if any, among ST-elevation myocardial infarction (STEMI) patients.

DESIGN: Retrospective analysis.

SETTINGS: Hospitals across Malaysia.

PATIENTS AND METHODS: We analyzed data on all STEMI patients in the National Cardiovascular Database-Acute coronary syndrome (NCVD-ACS) registry for the years 2006 to 2013 (8 years). We collected demographic and risk factor data (diabetes mellitus, hypertension, smoking status, dyslipidaemia and family history of CAD). Significant variables from the univariate analysis were further analysed by a multivariate logistic analysis to identify risk factors and compare by gender.

MAIN OUTCOME MEASURES: Differential risk factors for each gender.

RESULTS: For the 19 484 patients included in the analysis, the mortality rate over the 8 years was significantly higher in females (15.4%) than males (7.5%) (P<.001). The univariate analysis showed that the majority of male patients <65 years while females were ≥65 years. The most prevalent risk factors for male patients were smoking (79.3%), followed by hypertension (54.9%) and diabetes mellitus (40.4%), while the most prevalent risk factors for female patients were hypertension (76.8%), followed by diabetes mellitus (60%) and dyslipidaemia (38.1%). The final model for male STEMI patients had seven significant variables: Killip class, age group, hypertension, renal disease, percutaneous coronary intervention and family history of CVD. For female STEMI patients, the significant variables were renal disease, smoking status, Killip class and age group.

CONCLUSION: Gender differences existed in the baseline characteristics, associated risk factors, clinical presentation and outcomes among STEMI patients. For STEMI females, the rate of mortality was twice that of males. Once they reach menopausal age, when there is less protection from the estrogen hormone and there are other risk factors, menopausal females are at increased risk for STEMI.

LIMITATION: Retrospective registry data with inter-hospital variation.

Coronary artery disease (CAD) is the number one cause of mortality and morbidity in Malaysia and globally for both males and females.[1,2] Even worse, CAD has remained the principal cause of death for the ten years from 2005 to 2014.[3] In CAD, which is also known as ischemic heart disease, a waxy substance called plaque builds up inside the coronary arteries.[4]

CAD, traditionally considered a male disease, is also a major threat to females nowadays. In general, females

with CAD have a worse outcome than their male counterparts when no adjustments are made for other characteristics and comorbidities.[5,6] Although females tend to present with CAD later in life, the outcome can be severe.[6] Even when they present young, they tend to receive less evidence-based treatment than their male counterparts.[7]

An ongoing prospective registry known as the Malaysian National Cardiovascular Disease-Acute Coronary Syndrome (NCVD-ACS) registry was first established in 2006. Starting with only 8 hospitals in 2006, it now includes 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 of the NCVD-ACS Registry with National Heart Association of Malaysia as the co-sponsor.[8] 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 database is a useful source of information such as demographic values of patients as well as medical information, which are helpful in understanding the trends of CAD among the Malaysian population.

In one way or another, CAD affects all Malaysians. Most adults at increased risk of CAD have no symptoms or obvious signs, especially females, but they may be identified by assessment of risk factors. Therefore, the main aim of the study was to identify the risk factors associated with mortality for each gender and compare differences, if any, among acute coronary disease patients, particularly ST-elevation myocardial infarction (STEMI) patients.

PATIENTS AND METHODS

Anonymised patient data were obtained from the NCVD-ACS registry for the 8-year period from the years 2006 to 2013. The registry enrols patients presenting with STEMI, non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). However, in this study, only the data of patients who were diagnosed with STEMI from 18 participating hospitals across Malaysia were selected from the NCVD-ACS registry. Among the different types of acute coronary syndrome, STEMI has the worst outcome.[1] In this setting, 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.[9]

Data was collected from the time the patient with STEMI was admitted to the hospital until discharge. Each patient was assigned a unique national identifica-

tion number to avoid duplication. Follow-up was done 30 days after hospital discharge via phone call or when the patient came to the clinic for a review. To verify the mortality status, a cross check was done with the national death registry. Patient characteristics and clinical presentation, in-hospital treatment and clinical outcome were recorded. After verification, data was then entered into the NCVD website. An extensive information and communications technology system is maintained to ensure functional efficacy and effectiveness in the NCVD operation.

In addition to gender, other demographic variables such as ethnicity and age group are available. The ethnicity was determined based on national identity cards and self-report. In this study, patients were categorised into two age groups based on local medical practice namely age <65 years and age ≥65 years.[9] The risk factors were diabetes mellitus, hypertension, smoking status, dyslipidaemia and family history of CAD. Comorbid variables included 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 odds of survival within 30 days in patients with an acute MI, with a higher class having a higher odds of dying whereby Killip IV is the highest class.[10] Treatment variables were percutaneous coronary intervention (PCI) and cardiac catheterisation. This NCVD registry study was approved by the Medical Review & Ethics Committee, Ministry of Health Malaysia in 2007 (Approval Code: NMRR-07-20-250). MREC waived informed consent for NCVD.

Results are presented in the form of descriptive statistics, followed by univariate analysis and a multivariate logistic regression model. Categorical variables are described as percentages. Chi-square tests were used to test the association between factors by gender. Stepwise logistic regression was used to explain the relationships of all independent variables to mortality. A P value of less than .05 was considered statistically significant. A Hosmer and Lemeshow test was used to determine the goodness of fit. The variable inflation factor test is a test of multicollinearity. The -2log-likelihood is used to measure how well the model actually fits the data and the change in fit of the model to data if a variable is removed or added to the model. All analyses were conducted using SPSS statistical software (version 22, IBM SPSS Statistics, Armonk, NY, USA).

RESULTS

For females, the mortality rate (15.4%) was significantly higher than for males (7.5%) (P<.001) over the 8-year

period. Nevertheless, the percentage of female patients affected with STEMI (14.4%) was fewer than males (85.6%). The patient population was mainly ethnic Malay (more than 50.0% for both male and female patients) (**Table 1**). The majority of male patients were ≤65 years while females were mostly ≥65 years. For females ≥65 years, the incidence of CAD was twice that of males. The most prevalent risk factors for male patients were smoking (79.3%), followed by hypertension (54.9%) and diabetes mellitus (40.4%), while the most prevalent risk factors for female patients were hypertension (76.8%), followed by diabetes mellitus (60%) and dyslipidaemia (38.1%). MI history was the most common comorbidity followed by renal disease and cerebrovascular disease for both male and female patients.

The 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 frequent procedure followed by PCI for both male and female patients. All variables showed a statistically significant difference between males and females except for chronic lung disease (*P*=.472) and peripheral vascular disease (*P*=.444).

In the univariate analysis, all variables were significant for males (data not shown). Among the most significant were Killip class (odds ratio (OR=15.9), age group (OR=3.2) and renal disease (OR=3.9) for male patients. In the multivariate model for males (**Table 2**), seven variables were significant: diabetes mellitus, hypertension, family history of CAD, renal disease, PCI,

Table 1. Demographic and clinical characteristics by gender for 19 484 patients from the National Cardiovascular Database-Acute coronary syndrome registry for the years 2006 to 2013.

Characteristics			Female (n=2811)	Male (n=16673)	*P* value
Demographic	Ethnicity	Malay	1540 (54.8)	9887 (59.3)	<.001
		Chinese	523 (18.6)	2984 (17.9)	
		Indian	595 (21.2)	2718 (16.3)	
		Others	152 (5.4)	1084 (6.5)	
	Age group	<65	1465 (52.1)	13488 (80.9)	<.001
		≥65	1346 (47.9)	3185 (19.1)	
Risk factor	Diabetes mellitus	Yes	1687 (60.0)	6736 (40.4)	<.001
	Hypertension	Yes	2159 (76.8)	9153 (54.9)	<.001
	Smoking status	Active/former	309 (11.0)	13221 (79.3)	<.001
	Dyslipidaemia	Yes	1071 (38.1)	5836 (35.0)	<.007
	Family history of CAD	Yes	304 (10.8)	2684 (16.1)	<.001
Comorbidities	MI history	Yes	315 (11.2)	2284 (13.7)	<.001
	Chronic lung disease	Yes	62 (2.2)	417 (2.5)	.472
	Cerebrovascular disease	Yes	135 (4.8)	467 (2.8)	<.001
	Peripheral vascular disease	Yes	11 (0.4)	50 (0.3)	.444
	Renal disease	Yes	183 (6.5)	584 (3.5)	<.001
Clinical presentation	Killip class	Class I	1574 (56.9)	10737 (64.4)	
		Class II	677 (24.1)	3501 (21.0)	<.001
		Class III	180 (6.4)	717 (4.3)	
		Class IV	351 (12.5)	1717(10.3)	
Treatment	PCI	Yes	697 (24.8)	5019 (30.1)	<.001
	Cardiac catheterization	Yes	807 (28.7)	5736 (34.4)	<.001

Killip class and age group. The adjusted odds ratio suggests that patients with diabetes mellitus are 1.3 times more likely to die than those who are not diabetic. Also, male patients with hypertension and renal disease have 1.6 and 2.3 times respectively higher mortality risk than those without it, whereas, patients with a family history of CAD are less likely to die (OR=0.7). The regression coefficients, for all Killip class are significant, indicating that increasing affluence is associated with an increased odds of death. Also, Killip class IV are 16.5 times more likely to die than Killip class I males (base category). Moreover, the risk of mortality is 2.4 times higher for male patients from the age group ≥65 than from the age group <65. The mortality of patients who had undergone PCI were significantly less with an OR of 0.69 as compared to those without PCI.

In the univariate analysis on females, all variables were also significant. Among the highest were Killip class (OR=12.8), renal disease (OR=2.6) and age group (OR=2.5). The best-fitting multivariate model for females is given in **Table 3**. Of the 15 variables, only 4 were statistically significant in the multivariate model: smoking, renal disease, Killip class and age group. The

adjusted odds ratio suggests that females who smoked are less likely to die (OR=0.49), while the mortality of female patients is 2.2 times higher with renal disease than those without renal failure. The effect of Killip class in the model is also significant, indicating that those with Killip class IV are 14.6 times more likely to die than those from Killip class I. Equally important is the age group where the risk of mortality is 3.4 times higher in female patients from the age group ≥65 years than those from the age group <65 years.

The -2log-likelihood values obtained by comparing the final model with the null model with no covariates, showed a significant decrease in the -2log-likelihood. Likewise, the Hosmer and Lemeshow tests of the goodness of fit found that both final models fit well to the data as the P values were greater than .05. The degree of accuracy of both models was 93.3% and 87.5%. Also, the variable inflation factor test indicates an absence of multicollinearity in the variables for both males and females.

DISCUSSION

CAD is the leading cause of mortality among both males

Table 2. Variables in the regression model for male patients.

Variable	Characteristic	β	Standard error	P value	Adjusted odds ratio (95% CI)
Diabetes mellitus	No				Reference
	Yes	0.294	0.107	.006	1.342 (1.088, 1.655)
Hypertension	No				Reference
	Yes	0.479	0.113	<.001	1.615 (1.295, 2.014)
Family history of CAD	No				Reference
	Yes	-0.373	0.171	.029	0.689 (0.493, 0.963)
Renal disease	No				Reference
	Yes	0.858	0.198	<.001	2.358 (1.598,3.478)
Killip classification	Class I				Reference
	Class II	0.720	0.143	<.001	2.054 (1.553, 2.717)
	Class III	2.208	0.167	<.001	9.095 (6.556, 12.617)
	Class IV	2.792	0.128	<.001	16.314 (12.685,20.981)
PCI	No				Reference
	Yes	-0.359	0.114	.002	0.698 (0.558, 0.873)
Age group	<65				Reference
	≥65	0.861	0.110	<.001	2.365 (1.905, 2.935)

-2 log-likelihood: 2803.447, Hosmer and Lemeshow P=.202

Table 3. Variables in the regression model for female patients.

Variable	Characteristic	β	Standard error	P value	Adjusted odds ratio (95% CI)
Smoking status	Never				Reference
	Active/former	-0.793	0.352	.024	0.453 (0.227, 0.903)
Renal disease	No				Reference
	Yes	0.663	0.338	.049	1.941 (1.002, 3.762)
Killip classification	Class I				Reference
	Class II	.860	0.235	<.001	2.364 (1.491, 3.750)
	Class III	1.482	0.336	<.001	4.403 (2.278, 8.511)
	Class IV	2.720	0.235	<.001	15.183 (9.572, 24.081)
Age group	<65				Reference
	≥65	1.003	0.190	<.001	2.727 (1.878, 3.961)

-2 log-likelihood: 800.099, Hosmer and Lemeshow P value=.393

and females in Malaysia. With cancer, tuberculosis, HIV/AIDS, and malaria combined, CAD is still the most common cause of mortality in females worldwide, killing more than 16 per minute.[11] That the percentage of females affected with STEMI was much lower than males is supported by other studies where STEMI is more prevalent among males as compared to females.[9,12,13] However, females had a significantly higher mortality rate as compared to male patients in our study, which is compatible with other findings indicating that females have had higher mortality rates than males annually since 1984 with the cause of death mostly from myocardial infarction and sudden death.[14,15] Females are more resilient to developing CAD, but once they have CAD, they are more likely to experience the worse consequences.[16] Contrary to popular belief, CAD, and not breast cancer, is the main cause of death in women, where there is a two to one ratio of CAD between males and females.[17] Also, females are twice as likely to die of a first MI and notably have a short-term survival as compared with males.[18,19] In addition, since females have smaller coronary vessels than males, females are twice as likely to die as a result from coronary artery bypass surgery.[18,20]

The motivation of this study was to assess whether gender differences exist in risk factors, clinical presentation and outcomes among STEMI patients in Malaysia. This study found that in females aged 65 years and older, the incidence of STEMI is twice of males. This is similar to previous studies which found that larger risk of acute MI and a significantly higher mortality rate in female patients aged 65 years and older.[21,22] Female risk climbs as they age and once females reach menopausal age, there is less protection from the estrogen hormone and together with other risk factors like diabetes mellitus and obesity, menopausal women are at greater risks for CAD.[21,23] Moreover, due to the misconception that acute coronary syndrome is a disease of men; most women lack the awareness and are considered more at risk for breast cancer than for CAD.[18] Contrary to men, atypical symptoms such as numbness of the arms, fatigue, nausea, jaw pain, tightness or pressure, but no pain over the left chest are often present among women with CAD.[18,20] Physicians often fail to distinguish these symptoms in women.[24]

Smoking is the most prevalent risk factor for males (79.3%) followed by hypertension (54.9%) and diabetes mellitus (40.4%). This is supported by the National Health and Morbidity Survey Malaysia which stated that the Malaysian population has a higher prevalence of smoking with the prevalence of adult male smokers being 46.5%.[25,26] This is consistent with the NCVD database registry annual reports.[12] Moreover, a high prevalence of smoking (48.7%) and hypertension (31.7%) among male residents in rural Selangor, Malaysia were found in another study.[27] Even though most of the disease burden caused by active smoking occurs among males, females bear nearly 80% of the total burden from passive smoking.[28] In this context, passive smoking is the inhalation of smoke, called second-hand smoke, or environmental tobacco smoke, by persons other than the intended active smoker.[29] The number of deaths among females caused by passive smoking is about two-thirds of that caused by smoking for CAD and lung cancer.[28] Also, another study stated that passive smoking wives of current or former

cigarette smokers had a higher death rate from isch-emic heart disease than women whose husbands never smoked.[30]

From the multivariate logistic model, smoking is one the significant variables in females. The odds ratio suggests that females who smoke are less likely to die (OR=0.49). This surprising outcome is similar to a previous study whereby active smokers have a tendency to do well at both in-hospital and 30-days post discharge with significantly lesser overall mortality risk compared to those who never smoked.[25] Another study suggested that even though most of the females who die of CAD are past menopausal age, smoking increases the danger in younger females than in older females.[31] In addition, women are less likely to quit smoking than men.[32] In this study, the most prevalent risk factors for females were hypertension (76.8%) followed by diabetes mellitus (60%) and dyslipidaemia (38.1%). A study of the NCVD-ACS registry patients between 2006 and 2008 reported that out of 9702 patients, 24.2% were females with 22.3% being menopausal women, which was associated with diabetes mellitus and hypertension.[33]

The findings of the present study for both males and females are supported by a preceding study whereby on admission, more than 95% of patients having not less than one common cardiovascular risk factor such as hypertension, smoking, dyslipidaemia and diabetes mellitus.[12] Diabetes mellitus has been well recognized in increasing the risk of CAD in both males and females.[34-37] A study on the numerous aspects of gender differences among 10554 PCI patients in the NCVD-PCI registry between 2007 to 2009 found that at presentation, women typically were five years older than men and had a higher prevalence of risk factors.[5] Even more, the in-hospital and six-month mortality were also higher in women.[5] Another study found that among 13591 patients in the NCVD-ACS registry from 2006 to 2010, 24.2% were women and they had more risk factors, were not likely to undergo invasive treatment, and had a higher mortality.[38] Besides, a review of autopsy reports done at the University Malaya Medical Centre from year 1996 to 2005 found that 83 of 936 female deaths were because of cardiac causes.[39] Hypertension, diabetes mellitus and age were the most significant risk factors.

Apart from that, renal disease has become one of the significant findings for both males and females in this study. The mortalities of both male and female patients were twice as high with renal disease than those without it. Another study found that in patients with acute decompensated heart failure, one-year worsening of renal function is a common comorbidity and

strong predictor of all-cause and cardiovascular mortality.[40] As for clinical presentation, male and female patients with Killip class IV were 16.5 and 14.6 times, respectively, more likely to die than patients with Killip class I. This is supported by a previous study where the mortality rate within Killip classes were in descending order from class IV to III, II and I.[16] Apart from that, a family history of CAD is one of the significant variables among males in this study. This is similar to the another study where a family history of CAD was a significant risk factor among patients of ABO blood groups with the majority of patients being males (57.4%).[41]

PCI, also known as coronary angioplasty, is a typical treatment for CAD. In this study, PCI is one of the significant variables in the multivariate logistic model for males. Patients who had undergone PCI had a lower mortality rate than those who had not undergone a PCI (OR=0.7). Therefore, PCI is considered an effective treatment in reducing morbidity and mortality. Primary PCI is the preferred treatment due to a better result.[9,42,43] Moreover, there were mortality advantages gained from PCI treatment for elderly patients even though the outcome of elderly patients after PCI is not as good as that of non-elderly patients.[9] In another study, the lack of PCI treatment in acute MI patients has contributed to the high in-hospital mortality among female patients with 12.3% as compared to 9.5% for males.[44] To overcome this problem, the Malaysian Ministry of Health, together with the Ministry of Education and National Heart Institute, initiated a better Kuala Lumpur STEMI network in 2015. This network plays an important role in referring acute STEMI patients between government hospitals, teaching university hospitals and the National Heart Institute right to PCI capable centres.[13]

In conclusion, gender differences existed in the baseline characteristics, associated risk factors, clinical presentation and outcomes among STEMI patients. Female patients were older and more likely to have hypertension and diabetes mellitus, yet less likely to smoke than male patients. It is obvious that even though females share the same risk factors as males, there are risk factors that relate only to females which may increase their tendency to develop CAD. To date, with the enhancement of health care in general and the cardiac care specialist, understanding possible gender-based differences in baseline characteristics, risk factors, treatments and outcomes will help in improving current management of females with CAD particularly STEMI.

Conflict of interest

All authors have no conflict of interest to declare.

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