Iran J Public Health, Vol. 49, No.9, Sep 2020, pp.1642-1649

Original Article

Risk Factors of Mortality among Male Patients with Cardiovascular Disease in Malaysia Using Bayesian Analysis

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(Received 15 Jan 2019; accepted 25 May 2019)

Abstract

Background: Identifying risk factors associated with mortality is important in providing better prognosis to patients. Consistent with that, Bayesian approach offers a great advantage where it rests on the assumption that all model parameters are random quantities and hence can incorporate prior knowledge. Therefore, we aimed to develop a reliable model to identify risk factors associated with mortality among ST-Elevation Myocardial Infarction (STEMI) male patients using Bayesian approach.

Methods: A total of 7180 STEMI male patients from the National Cardiovascular Disease Database-Acute Coronary Syndrome (NCVD-ACS) registry for the years 2006-2013 were enrolled. In the development of univariate and multivariate logistic regression model for the STEMI patients, Bayesian Markov Chain Monte Carlo (MCMC) simulation approach was applied. The performance of the model was assessed through convergence diagnostics, overall model fit, model calibration and discrimination.

Results: A set of six risk factors for cardiovascular death among STEMI male patients were identified from the Bayesian multivariate logistic model namely age, diabetes mellitus, family history of CVD, Killip class, chronic lung disease and renal disease respectively. Overall model fit, model calibration and discrimination were considered good for the proposed model.

Conclusion: Bayesian risk prediction model for CVD male patients identified six risk factors associated with mortality. Among the highest risks were Killip class (OR=18.0), renal disease (2.46) and age group (OR=2.43) respectively.

Keywords: Cardiovascular disease; Myocardial infarction; Male; Risk factors; Bayesian

Introduction

It has been established that the deadliest disease in the world is the cardiovascular disease (CVD) (1,2). Known as a group of disorders of the heart and blood vessels, CVD include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease and congenital heart disease (1). Over the last decade, global number of deaths from CVD has increased by 12.5% (3). Worldwide, 17 million people die over a year and it was estimated that 23.6 million people will die by the year 2030 due to coronary heart disease and stroke (4). In Malaysia, CVD accounted for

98.9 deaths per 100,000 population in 2012, or 29,400 deaths which is 20.1% of all deaths (1). Even more so, CVD remains as a principal cause of death in Malaysia for the last ten years, from 2005 to 2014 (5). The commonly known risk factors associated with mortality of CVD worldwide and in Malaysia are smoking, hypertension, diabetes mellitus, unhealthy diet and regular alcohol consumption (1,6).

The National Cardiovascular Disease Database-Acute Coronary Syndrome (NCVD-ACS) registry, a service supported by the Ministry of Health Malaysia (MOH), plays an important role in collecting information about CVD across Malaysia. The database of NCVD-ACS has information on incidence of CVD, clinical variables and types of treatment among others. In this study, only the data of patients who were diagnosed with ST-Elevation Myocardial Infarction (STEMI) were analysed as STEMI is the fatal type of acute coronary syndrome (7). Also, we considered only the male patients as STEMI were more prevalent in males which accounts for approximately 85% in the NCVD-ACS registry dataset compared to females. This is in line with few studies worldwide where majority of the STEMI patients were males with more than 80% (8,9).

Bayesian approach rests on the assumption that all model parameters are random quantities and hence can incorporate prior knowledge. Its use in predicting risk of mortality in CVD has been rather underutilized even though this method is widely used for predictive analysis in other medical applications such as modelling risk of death in an intensive care unit (10), identify risk genes for schizophrenia and neurodevelopmental disorders (11), and multiple treatment comparisons in female urinary incontinence (12).

We aimed to develop a reliable model to identify risk factors associated with mortality among STEMI male patients using Bayesian approach. The novelty of this approach is that Bayesian probabilistic framework can incorporate prior distribution in the model building.

Materials and Methods

Data Collection

As mentioned earlier, the analysis utilise the data from the NCVD-ACS registry. It has the information on patients' characteristics, comorbidities, in-hospital treatment and clinical outcome. The mortality status was obtained through a cross check with the national death registry. This study is retrospective in nature as data from the year 2006 until 2013 are used in the analysis.

Patients were divided into four major ethnic groups namely Malay, Chinese, Indian and others according to the Malaysian population. Two age groups namely age < 65 yr and age ≥ 65 yr were used in this study. The cut off 65-yr was chosen based on the local medical practice (13). Diabetes mellitus, hypertension, smoking status, dyslipidaemia and family history of CVD were classified as risk factors. While myocardial infarction (MI) history, chronic lung disease, cerebrovascular disease, peripheral vascular disease and renal disease were classified as the comorbid variables. Clinical presentation known as Killip class was divided into four classes. The Killip classification predicts the chances of survival within 30 d in patients with an acute heart attack, with a higher class having a higher chance of dying (14). Percutaneous coronary intervention (PCI) and cardiac catheterisation were categorised as the treatment variables.

Ethical approval

This NCVD-ACS registry study was approved by the Medical Review & Ethics Committee (MREC), Ministry of Health (MOH) Malaysia in 2007 (Approval Code: NMRR-07-20-250). MREC waived informed consent for NCVD-ACS.

Study Subject

Overall 7180 male patients with STEMI was identified for this study. Among them, 5026 patients' data were classified as training set, leaving behind 2154 patients' data as validation set. In this context, STEMI was known as persistent ST segment elevation ≥ 1 mm in two contiguous electrocardi-

ographic leads, or the presence of a new left bundle branch block in the setting of positive cardiac markers (13).

Statistical analysis

In the development of Bayesian model in this study, the likelihood is specified as a Bernoulli-distributed outcome with the parameter μ, explicitly defined as a logistic model with "1" indicative of death and "0" alive or otherwise. After the likelihood been specified, prior distributions are specified for the regression coefficients β. Non-informative priors were used due to lack of information on the regression parameters.

In order to monitor convergence of the chains, three multiple parallel chains with different starting points were applied in all simulation work. The univariate models were developed by running the multiple chains for 10,000 iterations each with the initial 1000 burn-in. Significant variables were then fitted into the Bayesian multivariate logistic model. Selection of variables in the Bayesian model was based on the purposeful selection method (15). Multivariate model was developed by running the three multiple parallel chains for 100,000 iterations each, with the initial 10,000 samples were discarded from the analysis to eliminate some effect of the initial values of the parameters (10). Convergence of the Markov Chain Monte Carlo (MCMC) algorithm was also monitored through Convergence Diagnosis and Output Analysis (CODA). All analysis were done using Just another Gibbs Sampling (JAGS) in R interface.

Model discrimination was assessed through the area under receiving operating characteristics (ROC) curve (AUC) (16). An AUC value 1.0 implied perfect discrimination, while model calibration was measured through the Hosmer-Lemeshow goodness-of-fit test. The patients were by default divided into 10 groups using equally spaced cut points based on the predicted risk of death. The agreement between predicted and observed mortality rates in these groups was measured by computing the Pearson Chi-squared statistics from the 2×10 table of observed and estimated expected frequency of death and alive (17). Deviance Information Criterion (DIC) a hierarchical modelling generalization of the familiar Akaike Information Criterion (AIC) (18), was used to evaluate the model overall goodness of-fit of the model.

Results

Descriptive analysis on male patients' baseline characteristics are shown in Table 1. These analyses revealed that almost 60% of the STEMI patients are from ethnic Malay. This was followed by Chinese (18.5%) and Indian (17.7%). Male patients with the age group less than 65 yr accounted for more than 80% of the total admission.

Smoking was the most prevalence risk factor for STEMI male patients with more than 70%. This was followed by hypertension (48.6%) and diabetes mellitus (35.5%). The most relevant comorbidity was myocardial infarction (MI) followed by renal disease. The majority of male patients fell into the Killip class I or II on presentation. Cardiac catheterisation was the most undergone procedure followed by the percutaneous coronary intervention (PCI).

At the univariate level, a variable is considered significant if the *P*-value for the likelihood ratio test is less than 0.25 and the 75% credible interval must not contain zero (15). Nine variables were found to be significant at univariate level namely diabetes mellitus, hypertension, family history of CVD, chronic lung disease, Killip class, age, cerebrovascular, peripheral and renal disease. The nine significant variables are then fitted into Bayesian multivariate model. The final model consisted of six significant variables (Table 2) namely diabetes mellitus, family history of CVD, chronic lung disease, renal disease, Killip class and age group. The odds ratio (OR) suggested that mortality for diabetic male patients were 1.61 times higher than that of non-diabetic patients. Interestingly, patients with family history of CVD were less likely to die (OR=0.53).

Table 1: Male patients' characteristics

Characteristic			*Training set n = 5026 (%)*	*Validation set n = 2154 (%)*
Demographic	Ethnicity	Malay	2978 (59.3)	1313 (61.0)
		Chinese	930 (18.5)	376 (17.5)
		Indian	888 (17.7)	297 (13.8)
		Others	230 (4.6)	168 (7.8)
	Age group	<65	4079 (81.2)	1762 (81.8)
		≥65	947 (18.8)	392 (18.2)
Risk factor	Diabetes Mellitus	No	3241 (64.5)	1429 (66.3)
		Yes	1785 (35.5)	725 (33.7)
	Hypertension	No	2584 (51.4)	1049 (48.7)
		Yes	2442 (48.6)	1105 (51.3)
	Smoking status	Never	1145(22.8)	396 (18.4)
		Active/former	3881 (77.2)	1758 (81.6)
	Dyslipidaemia	No	3368 (67.0)	1495 (69.4)
		Yes	1658 (33.0)	659 (30.6)
	Family history of CVD	No	4312 (85.8)	1884 (87.5)
		Yes	714 (14.2)	270 (12.5)
Comorbidities	MI History	No	4352 (86.6)	1942 (90.2)
		Yes	674 (13.4)	212 (9.8)
	Chronic lung disease	No	4923 (98.0)	2106 (97.8)
		Yes	103 (2.0)	48 (2.2)
	Cerebrovascular disease	No	4893 (97.4)	2105 (97.7)
		Yes	133 (2.6)	49 (2.3)
	Peripheral vascular disease	No	5014 (99.8)	2149 (99.8)
		Yes	12(0.2)	5 (0.2)
	Renal disease	No	4870 (96.9)	2093 (97.2)
		Yes	156 (3.1)	61 (2.8)
Clinical presentation	Killip Class	Class I	3364 (66.9)	1493 (69.3)
		Class II	1118 (22.2)	325 (15.1)
		Class III	184 (3.7)	110 (5.1)
		Class IV	360 (7.2)	226 (10.5)
Treatment	PCI	No	3353 (66.7)	1374 (63.8)
		Yes	1673 (33.3)	780 (36.2)
	Cardiac catheterisation	No	3086 (61.4)	1152 (53.5)
		Yes	1940 (38.6)	1002 (46.5)

Table 2: Variables in the final multivariate model for male patients

Variable	*Posterior mean*	*Standard error*	*Odds ratio*	*(95% Credible Interval)*
Diabetes Mellitus	0.479	0.130	1.614	(1.251, 2.079)
Family history of CVD	-0.620	0.221	0.538	(0.344, 0.818)
Chronic lung disease	0.471	0.333	1.602	(0.815, 3.007)
Renal disease	0.901	0.239	2.462	(1.531, 3.904)
Killip class II	0.776	0.171	2.173	(1.553, 3.034)
Killip class III	2.135	0.222	8.457	(5.441, 12.975)
Killip class IV	2.893	0.163	18.047	(13.144, 24.903)
Age (≥65)	0.886	0.140	2.425	(1.842, 3.190)

The mortality of those with chronic lung disease were 1.60 times more than those without it. Patients in Killip class IV were 18.0 times more likely to die than those from Killip class I (base category). Furthermore, the mortality of patients with renal disease were significantly higher with OR 2.46 as compared to those without it. Risk of mortality was 2.43 times higher for male patients from the age group ≥ 65 than those from the age group < 65.

The MCMC convergence diagnostics of final model were assessed through visual inspections using trace and autocorrelation plots. Also, other convergence diagnostic was obtained such as the Gelman-Rubin diagnostic. Although not shown here, the trace plots obtained suggest that there were no specific trends and the mixing of MCMC tends to be good. Similarly, the autocorrelation plots suggested that mild autocorrelations for diabetes mellitus, Killip classes as well as the intercept term in the model. Additionally, the Gelman-Rubin diagnostic value of potential scale reduction factors (PSRF) suggested model convergence where all variables in the model with PSRF equal to 1.0.

Final Bayesian multivariate model was validated using 2154 male patients from the latest few months of the years 2006-2013 NCVD dataset. Model discrimination was assessed through the area under Receiving Operating Characteristics (ROC) curve (AUC) based on nonparametric approach (16) as shown in Fig. 1. Discrimination in male patients' model was fairly good with an AUC of 0.8161 with a 95% confidence interval ranging from 0.75 to 0.83. Model calibration was assessed using Hosmer-Lemeshow goodness of-fit test (15). After calibrating the Bayesian model with the set of predictor variables, the Hosmer-Lemeshow test showed a good fit ($P = 0.90$). The small Brier score (0.049) showed good overall accuracy. Also, the deviance value of 1857.71 produced by the Bayesian model indicated a better-fitting model.

Discussion

This study has shown that Bayesian MCMC approach can be successfully applied as an alternative in determining the risk factors of mortality associated with CVD.

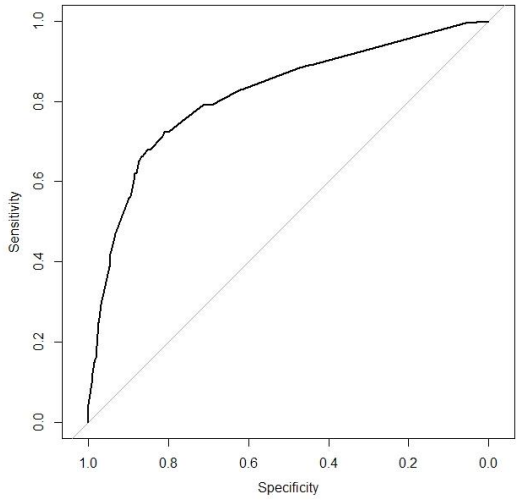

Fig. 1: ROC curve for the Bayesian model

Variables such as diabetes mellitus, family history of CVD, chronic lung disease, renal disease, Killip class and age group were found to be significant risk factors in mortality of CVD male patients in Malaysia. In this study, male patients with diabetes mellitus had higher risks of dying compared to those without it. Similar result was reported in other study of the CVD male patients admitted in a hospital in Malaysia (19). Also, diabetes mellitus was classified as one of the significant and the most prevalence mortality risk factor in CVD among males in Saudi Arabia(2) , India and few countries worldwide (2,20,21).

In this study, family history of CVD is one of the risk factors. Framingham' Study stated that having CVD in at least one parent has doubled the 8-yr risk of CVD mortality among men (22). Moreover, previous studies have estimated the OR of 1.10 to 2.63 for an individual with a single first-degree relative with a history of a cardiovascular event (23,24). However, in this study, the OR shown that this is not always the case. There is indicative evidence that an awareness of one's family history of CVD increases the person's perceived CVD risk. This perceived risk has some effect on a person's health-related behaviour towards positive lifestyle modification (25).

As for chronic lung disease, it has been associated with deteriorated pulmonary function among Japanese males (26). In line with the previous study, we found that chronic lung disease is a significant risk factor for mortality among Malaysian CVD male patients. Also, chronic lung disease was more prevalent in males especially in developing countries, at once contributed to the higher mortality rate of CVD (27).

Other risk factor is renal disease whereby in Malaysia, male patients with CVD have higher prevalence of renal failure than male patients in western counterparts (28). Renal disease is common and strongly associated with short-term and long-term outcomes in male patients with heart failure (29,30).

Malaysia is well known as a multi-ethnic nation (31), however, ethnicity was not a significant mortality risk factors of CVD patients. This could be explained by the similar eating habits of most Malaysian even though they have come from various cultural background (10). Besides, patients' characteristics in Malaysian CVD patients were generally different from other developed countries. For instance, the mean age reported in the Malaysian NCVD-ACS report was 55.9 to 59.1 whereas the mean age of CVD patients in most developed countries was 63.2 to 68 yr (32). Malaysian males had higher mortality risk of CVD at an older age (13) which was consistent with the findings of this study. Thus, age has become a significant mortality risk factor of CVD.

As for clinical presentation in this study, patients with higher Killip class IV were more likely to die than patients in Killip class I. Consistent results were found in other studies where the Killip II-IV patients were more likely to have a higher prevalence of previous myocardial infarction, diabetes mellitus and chronic kidney disease on admission and at once contributes to higher in-hospital mortality rate than the Killip I patients (33,34).

Bayesian MCMC approach has the benefits of being able to make direct probability assessments of the results and provides parameters estimates of the posterior distribution which have natural, clinical interpretations, which are not available from the frequentist model (35,36). The probability of parameter values can be obtained by calculating the area of the posterior distribution to the right of that value, which is simply equal to the proportion of values in the posterior sample of the parameter which are greater than that value (37). This information is used to report the results of Bayesian analyses as means with the 95% credible intervals for parameter estimates. Also, the results can be updated, add observations and calculate probabilities for complex functions.

As mentioned earlier, non-informative prior was used in this study. This type of prior is applied to allow the data to speak for themselves (18,38). Our results were in accordance with this assertion where the used of non-informative prior in the Bayesian approach was able to provide good results. For the iteration, typical choice in the literature are 10,000 iterations, 1000 burn in and 10 or 20 thinning (39). At least 1000 and up to a million iterations were used for estimation respectively (10,40). As in this study, 10,000 iterations in the univariate level and 100,000 iterations in the multivariate level are generally sufficed. Through all these, the proposed model has shown best overall fit with high discrimination and calibration power. Implication of the study is that it provides a better understanding on the risk factors associated with mortality among CVD male patients in Malaysia. This information may be a useful guide for clinicians when making prognosis of CVD patients. A limitation of this study is that it used retrospective registry data with inter-hospital variation.

Conclusion

Bayesian approach modelling provides a prognostic method in identifying the risk factors associated with mortality for CVD male patients in Malaysia. A set of six variables were identified to be the significant risk factors in the final Bayesian model namely diabetes mellitus, family history of CVD, Killip class, chronic lung disease, renal disease and age. Among the highest were Killip class (OR=18.0), renal disease (OR=2.46) and age group (OR=2.43). The final Bayesian model had good discrimination and calibration in predicting

mortality risk in the Malaysian NCVD-ACS registry dataset.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

The authors wish to thank all medical staffs and non-medical staffs who participated in the Malaysian NCVD-ACS registry.

Conflict of interest

The authors declare that there is no conflict of interest.

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