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Journal of Diabetes, Metabolic Disorders & Control

Mini Review

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Does diabetes mellitus increase the mortality risk in coronary artery disease patients undergoing coronary artery bypass grafting surgery at the National Heart Institute of Kuala Lumpur?

Abstract

Background: Multiple studies had shown that coronary artery disease (CAD) has been the principal cause of mortality in patients with diabetes mellitus (DM). Furthermore, DM has always been a major risk predictor for unfavorable outcomes in patients undergoing cardiac revascularization either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery.

Objective: To investigate whether the presence of DM increase mortality risk in patients undergoing CABG.

Methods: A retrospective single-center study was performed. A special database was created to include all EuroSCORE II variables, EuroSCORE II predicted mortality and actual mortality of 1718 patients undergoing Coronary Artery Bypass (CABG) surgery in Malaysia from 1st January 2016 till 31st December 2016. Univariate and multivariate logistic regressions were done to identify significant predictors of in-hospital mortality among this group of patients.

Results: More than half of the patients undergoing CABG surgery are diabetic (56.3%) while 20.3% are on long-term insulin. In terms of mortality, a significantly higher proportion of in-hospital mortality was observed among patients with DM (5.7%) compared to those without DM (3.4%). On univariate logistic regression analysis, both non-insulin dependent DM (OR:1.737, 95% CI 1.072-2.815, p=0.025) and insulin-dependent DM (OR: 1.960, 95% CI: 1.209–3.179, p=0.006) are significant predictors of in-hospital mortality in this group of patients undergoing CABG surgery. However, in multivariate logistic regression, which took into consideration of other related variables in the EuroSCORE II, only female gender, age more than or equal to 65 years old, serum creatinine more than 120 mol/litre and longer ICU stays are significant predictors of in-hospital post-CABG mortality.

Conclusion: In conclusion, a significant proportion of patients undergoing CABG surgery in IJN are actually diabetics while a higher in-hospital mortality risk post-CABG was observed in patients with DM. However, insulin-dependent diabetes mellitus was not a significant risk factor for in-hospital mortality in this group of patients.

Keywords: coronary artery disease (CAD), diabetes mellitus (DM), EUROScore II, mortality

Volume 5 Issue 4 - 2018

Ahmad Farouk Musa,[1] Xian Pei Cheong,[1] Christina Gertrude Yap,[1] Jeswant Dillon,[2] Rusli Bin Nordin,[1]

[1]Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, Malaysia

[2]Department of Cardiothoracic Surgery, National Heart Institute, Kuala Lumpur, Malaysia

Correspondence: Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, Malaysia, Email farouk@monash.edu

Received: April 27, 2018 | **Published:** August 16, 2018

Introduction

Globally, the number of patients with diabetes mellitus (DM) has increased to almost 451 million in 2017 and has become a worldwide epidemic. Even more worrisome is that 49.7% of them remain undiagnosed.[1] Studies have shown that coronary artery disease (CAD) is the principal cause of mortality in DM patients and linked with significantly higher cardiovascular mortality due to myocardial infarction and stroke.[2,3] DM has always been a major risk predictor for unfavourable outcomes in patients undergoing cardiac revascularization either percutaneous coronary intervention (PCI)[4] or coronary artery bypass grafting (CABG),[5,6] surgery.

Methods

We performed a single-centre retrospective study on the validation of EuroSCORE II among 1718 patients undergoing CABG surgery at the National Heart Institute (IJN) of Kuala Lumpur from 1st January to 31st December 2016. EuroSCORE II is a risk evaluation tool that included ten patient-related factors, five cardiac-related factors, and three operation-related factors with the aim of determining in-hospital mortality after cardiac surgery. Patient-related factors include age (year), gender (male /female), renal impairment (creatinine clearance), extra cardiac arteriopathy, poor mobility, previous cardiac surgery, chronic lung disease, active endocarditic, critical preoperative state and diabetes on insulin. Cardiac-related factors include the New York Heart Association (NYHA) stages, Canadian Cardiovascular Society (CCS) class 4 angina, Left Ventricular (LV) function (ejection fraction >50%, 31-50%, 21-30%, <20%), recent myocardial infarction (MI) (within 90 days) and pulmonary hypertension (31-55mm Hg / >55mm Hg). Operation-related factors include urgency (elective, urgent, emergency, salvage), weight of the intervention (isolated CABG, isolated single non-CABG, 2-procedures, and 3-procedures)

and surgery on thoracic aorta.[7] Details regarding EuroSCORE II calculation are available from the EuroSCORE site.

Ethics approval and data source

Approval for data usage was obtained from the IJN Research Ethics Committee (IJNREC/238/2018). Additionally, it was also approved by the Monash University Human Research Ethics Committee (MUHREC/12981). All patients-related demographic and clinical information was retrieved from a comprehensive electronic in-house database of the National Heart Institute of Malaysia.

Sample size calculation

The prevalence of diabetes mellitus among patients with coronary artery disease is about 50% as shown by previous studies.[8] In the sample size calculation of our present study, we use a prevalence of diabetes of 50%, level of significance of 5% and precision of ±5%. The formula used is n = (z/Δ)2 p (1-p), where p is the prevalence of diabetes, 0.5, and absolute precision (Δ) is ±5%. This gives us a sample size of (1.96/0.05)2 0.5(1-0.5) = 384 subjects.

Inclusion and exclusion criteria

Inclusion criteria:

All patients who had coronary artery disease

All patients who underwent CABG surgery

Exclusion criteria:

Patients with unknown diabetes status

Possible bias

Being a single centre study, we acknowledge that our results might not be representative of the entire population of Malaysia. However, we attempted to tackle this by including patients with a fair share of race distribution (Malay: 53.8%, Chinese: 21.7%, Indian: 19.4% and Other races: 5.1%) that is similar to our country. Moreover, due to its retrospectivity, the study might be bound to information bias, in which there is a certain amount of missing data. Therefore, we have included significantly more patients than our calculated sample size in this study so that it can account for patients with missing data.

Statistical analysis

All demographic and clinical data was recorded using the Microsoft Excel 2016 and analysed using the Statistical Package for Social Sciences (SPSS) version 23.0. Important variables including insulin-dependent diabetes and non-insulin dependent diabetes were presented as percentage and cross-tab analysis was done with regards to discharge status (alive / death). Chi-square test was performed to identify differences between groups. Both univariate and multivariate logistic regression analysis were undertaken to determine significant predictors of in-hospital mortality.

Results

Many international studies have examined the validity of EuroSCORE II in predicting in-hospital mortality post-CABG. Most of the validation studies in Europe including Spain, Italy, Greece, Serbia and Hungary have an area under the receiver operating characteristic (ROC) curve (AUC) of more than 0.7, indicating good discriminatory power and calibration.[9–13] However, there was a collaborative study between two centres in the Netherlands and United Kingdom, which showed that EuroSCORE II was not good in predicting mortality in patients undergoing cardiac operation. It showed an unsatisfactory AUC of 0.67, indicating poor discriminatory power.[14] among our own population of CABG patients in IJN, we observed an AUC of 0.7, which is deemed to be satisfactory in predicting in-hospital mortality.

In this review, we aim to use the data collected based on the EuroSCORE II variables to investigate whether the presence of DM increase the mortality risk in patients undergoing CABG.

Our results showed that more than half of the patients undergoing CABG surgery are diabetic (56.3%) while 20.3% were on long-term insulin. This once again proved the known correlation between CAD and DM, in which patients with DM will definitely have a greater burden of atherogenic risks as compared to patients without DM.[15–17]

Table 1 shows the relationship between DM status and in-hospital post-CABG mortality. A significantly higher (p=0.011) proportion of in-hospital mortality is observed among patients with insulin dependent DM (7.4%), followed by non-insulin dependent DM (4.7%) and patients with no DM (3.3%).

Table 1 Relationship between diabetic patients and post-CABG mortality

Diabetes Mellitus	Discharge status		Total
	Alive	Dead	
Insulin Dependent DM	323 (92.6%)	26 (7.4%)	349
Non-Insulin Dependent DM	590 (95.3%)	29 (4.7%)	619
No DM	725 (96.7%)	25 (3.3%)	750
Total	1638 (95.3%)	80 (4.7%)	1718

Pearson Chi-Square test, X2: 9.092, df: 2, p=0.011

On univariate binary logistic regression analysis, non-insulin dependent DM (OR: 1.425, 95% CI 0.826-2.460, *p*=0.203) was not found to be significant in predicting in-hospital mortality. However, insulin-dependent DM (OR: 2.334, 95% CI: 1.327–4.105, *p*=0.003) is a significant predictor of mortality in this group of patients undergoing CABG surgery. On multivariate binary logistic regression, which took into consideration other related variables in the EuroSCORE II, only age ≥65 years, female gender, serum creatinine 120 µmol/litre, longer ICU stays and poor mobility are significant predictors of in-hospital post-CABG mortality (Table 2).

Table 2 Multiple logistic regression between independent variables and in-hospital post-CABG mortality

Variable	p value	Adjusted Odds Ratio	95% CI	
		OR)	Lower	Upper
Age ≥65 years	0.004	2.27	1.303	3.954
Female gender	<0.001	3.118	1.701	5.718
Serum Creatinine ≥120mmol/L	<0.001	3.54	2.024	6.19
ICU stays (days)	<0.001	1.093	1.061	1.127
Poor Mobility	<0.001	5.896	2.297	15.135

Cox and Snell R square=0.078; Nagelkerke's R square=0.24; ICU, Intensive Care Unit

On a side note, in our EuroSCORE II study, analysis of the discriminatory power was done on specific subgroups. It showed that the AUC was 0.672 in diabetic patients (95% CI 0.602–0.741,

Citation: Musa AF, Cheong XP, Yap CG, et al. Does diabetes mellitus increase the mortality risk in coronary artery disease patients undergoing coronary artery bypass grafting surgery at the National Heart Institute of Kuala Lumpur? *J Diabetes Metab Disord Control.* 2018;5(4):141–144.
DOI: 10.15406/jdmdc.2018.05.00153

p<0.001) and 0.728 in patients without DM (95% CI 0.614–0.841, p<0.001). Therefore, the EuroSCORE II has a better discriminatory power in patients without DM.

Discussion

As shown in our results, a higher mortality is observed among both patients with insulin dependent DM and non-insulin dependent DM as compared to those who do not have DM. Compared with a previous study of about 1800 patients who underwent CABG, in-hospital mortality rate was about 5% in patients with DM while it was only 0.36% in non-diabetics.[18] Multiple other studies have also verified that the mortality risk was higher in diabetic patients.[19–21]

In our original study,[22] we have determined both the calibration and discriminatory power of the EuroSCORE II in our local population of Kuala Lumpur, Malaysia, undergoing CABG surgery at the National Heart Institute, KL. We noted in that study that there was no significant difference in the the Hosmer-Lemeshow goodness of fit test between the expected and observed mortality in accordance to the EUROScore II model (Chi square = 13.758, p=0.089). This indicates good calibration of the model in our population. We also noticed a good discriminatory power where the Area Under the ROC curve (AUC) for EUROScore II was 0.7 (95% CI 0.640-0.759). This result is consistent with the validation studies performed in Europe which has an AUC of more than 0.7 that was also indicative of good discriminatory power and calibration.

Our previous study also showed that the significant predic- tors of in-hospital mortality in patients who underwent CABG were age of 65 years and above, female gender, serum creatinine of more than 120 micromole/litre, longer ICU stay and poor mobility. These were based on the logistic regression test that we performed. In this particular case as well, we selected the independent variables according to the principle of parsimony in order for the analysis to be more consistent and to limit the number of variables to as few as possible in our prediction model.

Few studies have identified the fact that EuroSCORE and EuroSCORE II risk model might not be as precise and accurate on older patients' populations. This is particularly important as a significant portion of the patients undergoing CABG are from the older age group. A study in France has shown that the EuroSCORE II performance was poorer on patients more than 80 years old, showing overestimation.[23] At the same time, another study in the United Kingdom has shown that both the original EuroSCORE and the EuroSCORE II has a ROC c-statistic value below 0.7 for patients more than or equal to 70 years of age, which indicates a potential issue with accuracy and validity of the risk prediction model.[24] Lastly, among our own population in Malaysia, we have also identified that the AUC was 0.7 in those aged below 60 years while it was 0.673 in those aged 60 years and above.

In the risk prediction model of EuroSCORE II, insulin-dependent diabetes was known as one of the many dichotomous variables (yes/no) in predicting mortality after cardiac surgery. According to the EuroSCORE database, diabetics on insulin recorded 1.43 times higher risk of in-hospital mortality after surgery.[7] Wang et al.[25]

specifically looked into the significance of diabetes on post-operative outcomes. It was shown that preoperative HbA1c was actually the only diabetic variable that managed to independently predict mortality post-CABG. This indicated that HbA1c value, rather than the presence of diabetes on insulin, might stand as a relatively better endpoint in predicting mortality, which also explained the non-significance of insulin-dependent variable in predicting mortality among our population.

Limitations

First of all, as mentioned in the discussion, our study lacked Hba1C values which was proven in previous studies to serve as a better predictor of surgical mortality as compared to the presence of diabetes mellitus as a dichotomous variable. Secondly, this study was also limited due to its retrospectivity, which led to an unavoidable amount of missing data and values that in turn led to a relatively smaller sample size. Lastly, IJN is a regional cardiac centre with surgeons with varying level of clinical experience. This might directly or indirectly affect the in-hospital mortality rate.

Future Directions

In the time to come, we aim to undertake a prospective large scale study to look at the relationship between Hba1c and mortality risk among patients with severe coronary artery disease requiring CABG surgery. Should it be proven to be significant, we would like to consider the incorporation of Hba1c values into a risk assessment model so that prediction accuracy can be further refined. In terms of surgeons' experience, we hope to include years of experience as a variable so that subgroup analysis can be performed based on surgical experience in our future study.

Conclusion

In conclusion, a significant proportion of patients undergoing CABG surgery in IJN are diabetics which confers a higher in-hospital mortality rate post-CABG. However, insulin-dependent diabetes mellitus was not a significant risk factor for in-hospital mortality in this group of patients.

Data Availability

Dataset 1. Raw patient data[26]

Dataset 2. Statistical analysis output file[27]

Grant Information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgement

We would like to acknowledge the Research Department of the National Heart Institute, Kuala Lumpur, for their assistance in providing the EUROScore II data.

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DOI: 10.15406/jdmdc.2018.05.00153