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Association of Post-Operative Cardiac Enzyme Levels with Early Mortality Following Coronary Artery Bypass Grafting

Prashiddha Bikram Kadel,[1] Anil Bhattarai, [1] Ravi Kumar Baral,[1] Prabhat Khakural,[1] ,Krishnaprasad Bashyal,[2] Srijana Thapa[1]

[1]Department of Cardiothoracic and Vascular Surgery, Manmohan Cardiothoracic Vascular and Transplant Centre, Maharajgunj, Kathmandu, Nepal, [2]Kathmandu Medical College, Kathmandu, Nepal.

ABSTRACT

Background: Post-operative myocardial injury is an important determinant for mortality and morbidity following Coronary Artery Bypass Graft surgery. This study evaluated the role of serial post-operative cardiac biomarker and enzyme (CK-MB, Troponin I) measurement in predicting in-hospital mortality following CABG surgery.

Methods: This retrospective study included patients undergoing CABG procedure at Manmohan Cardiothoracic Centre from January 2020 to January 2021. Cardiac Biomarkers (CK-MB and Troponin I) were measured at 6,12 and 24 hours post-operatively. The Mann–Whitney U test was used for comparison of biomarkers between survivors (n=40) and non-survivors (n=3). Receiver Operating Characteristic (ROC) curve analysis with Youden Index was used to determine optimal cutoffs values.

Results: A total of 43 patients were enrolled in the study. In-hospital mortality was 7% (3/43) with 40 survivors and 3 non-survivors. No significant differences were observed in cardiac enzymes measured at 6 hours, between the survivors and non-survivors (Troponin I, p=0.206; CK-MB, p=0.391). However, biomarkers were significantly higher in non-survivors at 12 hours (Troponin I p=0.038; CK-MB p=0.004) and 24 hours (Troponin I p=0.007; CK-MB p=0.005). ROC demonstrated excellent predictive performance of CK-MB at 12 hours (AUC=1.00, cutoff at 146 IU/L, sensitivity 100%, specificity 100%), CK-MB at 24 hours (AUC =0.95, cutoff at 155 IU/L) and Troponin I at 24 hours (AUC=0.92, cutoff at 5.17ng/ml). However, these findings should be interpreted cautiously due to only three mortality events.

Conclusions: Post operative Cardiac biomarkers (Troponin I >5.17 ng/ml at 24 hours and CK-MB >146 IU/L at 12 hours and >155 IU/L at 24 hours) were associated with in-hospital mortality following CABG and warrants further evaluation as a post-operative risk stratification marker.

Keywords: Cardiac biomarkers; coronary artery bypass surgery; creatine kinase MB; myocardial injury; troponin I.

INTRODUCTION

Coronary artery bypass grafting (CABG) remains the durable surgical revascularization strategy for patients with multivessel coronary artery disease, particularly in those with diabetes mellitus, left main disease and patients with left ventricular systolic dysfunction.[1] Despite significant advances in myocardial protection, cardiopulmonary bypass techniques and perioperative care, post-operative morbidity and mortality remain important challenges after CABG.[2]

Various factors like preoperative cardiac function, completeness of revascularization, the perioperative ischemia- reperfusion injury, cardiopulmonary bypass duration and graft related complication determine the early outcome of CABG. Among these, perioperative myocardial injury has also been recognized as determinant of unfavourable outcomes including low cardiac output syndrome, arrhythmias and even mortality.[3]

Various biomarkers like Creatine Kinase-MB (CK-MB) and cardiac Troponin I have high myocardial tissue specificity and sensitivity.[4] Particularly Troponins play a role in determining perioperative myocardial infarction

Correspondence: Dr Prashiddha Bikram Kadel , Department of Cardiothoracic and Vascular Surgery, Manmohan Cardiothoracic Vascular and Transplant Centre, Maharajgunj, Kathmandu, Nepal. Email: prashiddhakadel@gmail.com, Phone: +9779841674980.

or myocardial injury. Biomarker elevation may denote surgical manipulation, global ischemia during cardiopulmonary bypass, reperfusion injury or failure of the graft.[2] Mild rise is expected following CABG however rising trend or persistent level of biomarkers may signify perioperative myocardial infarction leading to worse clinical outcomes.[5]

As these cardiac biomarkers are widely used, the optimal cutoff values and timing of measurement is still a topic of debate with wide variation in different studies and population.[6] Early identification of persistent elevation may facilitate closer hemodynamic surveillance, escalation of care, timely investigation for graft related complication. Due to lack of regional data and variation in surgical protocols in monitoring of cardiac biomarkers, this study aimed to evaluate the role of post-operative cardiac enzymes, as predictors of early mortality, defined as in-hospital mortality, following coronary artery bypass grafting. Two cardiac biomarkers (CK-MB and Troponin I) have been selected due to their availability at out institution.

METHODS

This study was approved by institutional review committee with waiver of informed consent in view of retrospective de-identified design. In this study, a total of 43 patients who underwent CABG in the Department of Cardiothoracic and Vascular Surgery at Manmohan Cardiothoracic Vascular and Transplant Center, Maharajgunj between January 2020 to January 2021 were enrolled. Patients who underwent isolated CABG were enrolled in the study whereas those patients who underwent concomitant procedure other than CABG, redo CABG, emergency CABG, off-pump CABG, recent acute myocardial infarction with elevated Troponin, patients on renal replacement therapy or any concomitant procedures were excluded from the study to reduce potential confounding. Preoperative variables included -age, sex, comorbidities, presentation, preoperative ejection fraction (EF). Intraoperative variables included number of vessel grafted, cardiopulmonary bypass time and aortic cross-clamp time. Post-operatively Troponin I and CK-MB were measured at 6, 12 and 24 hours ,serum CK-MB and cardiac Troponin I levels were measured using the Vitros 5600 Integrated System (Ortho Clinical Diagnostics, Raritan, NJ, USA). CK-MB was estimated by the dry chemistry method, while cardiac Troponin I was measured using a chemiluminescent immunoassay (CLIA). The laboratory reference range for CK-MB was 0–25 U/L and a Troponin I value of <12 ng/L was considered normal. The primary outcome was early mortality defined as in-hospital death occurring during the index hospitalization following CABG surgery and cause of death was recorded. Since all the eligible patients in the given timeframe were included in the study, no formal sample size calculation was done. Continuous variables were summarized as mean ± standard deviation or median (interquartile range), as appropriate. Owing to the small sample size and non-normal distribution of biomarker levels, comparison of biomarkers between the survivors and non-survivors was done using Mann–Whitney U test. Receiver Operating Characteristic (ROC) curve analysis was used to predict the performance of cardiac biomarkers for in-hospital mortality, optimal cutoffs were determined using the Youden Index (sensitivity + specificity- 1). The area under the curve (AUC) was calculated to assess discrimination ability. The diagnostic performance was interpreted as follows: AUC 0.5 (no discrimination), 0.7–0.8 (acceptable), 0.8–0.9 (good), and >0.9 (excellent)

RESULTS

A total of 43 patients were enrolled in the study. There were 40 survivors and 3 in-hospital deaths corresponding to mortality rate of 7%, two patients died due to low cardiac output syndrome with intractable ventricular arrythmia on Post-operative day zero and Post-operative day one and one from multiorgan failure (n=1) on Post-operative day 20. Non-survivors were older (66.7±8.1) than survivors 56.9 ± 9.3 years (p=0.12). Baseline and preoperative characteristic of survivors and non-survivors are summarized in the table 1.

Table 1. Baseline and perioperative chararcteristics of Survivors and Non-survivors
Note- Due to small number of events in the non-survivor group, some comparison were limited.

Variable	Survivors (n=40)	Non-Survivors (n=3)	p-value*
Age (years), mean ± SD	55.1 ± 8.8	66.7 ± 8.1	0.12
Male, n (%)	36 (90.0%)	3 (100%)	-
Hypertension (HTN), n (%)	26 (65.0%)	3 (100%)	-
Diabetes Mellitus (DM), n (%)	10 (25.0%)	2 (66.7%)	-
Dyslipidemia, n (%)	6 (15.0%)	0 (0%)	-
Pre-operative EF (%), mean ± SD	55.4 ± 10.0	46.7 ± 15.3	0.25
3-vessel disease, n (%)	34 (85.0%)	3 (100%)	-
Previous PCI, n (%)	6 (15.0%)	0 (0%)	-
Cardiopulmonary bypass time (min), mean ± SD	111.8 ± 14.4	102.3 ± 13.7	0.28
Aortic cross-clamp time (min), mean ± SD	72.0 ± 11.1	59.3 ± 6.1	0.08

Post-operative cardiac biomarkers (Troponin I in ng/ml and CK-MB in IU/L) is presented with statistical analysis in table 2.Statistical analysis of cardiac enzymes done at 6 hours did not show statistical significance between the survivors and non-survivors (Troponin I, p=0.206; CK-MB, p=0.391).However both Troponin I and CK-MB were significantly higher in non-survivors group at 12 and 24 hours after CABG surgery. Specifically, non-survivors group CK-MB at 12 hours (p=0.004) and both Troponin I (p=0.007) and CK-MB (p=0.005) at 24 hours were significantly associated with in- hospital mortality. ROC curve analysis demonstrated excellent discriminatory ability within this cohort -Troponin I at 24 hours (AUC = 0.92) with optimal cutoff at 5.17ng/ml yielding 100 percent sensitivity and 92.5% specificity. CK-MB measured at 24 hours demonstrated excellent predictive accuracy (AUC = 0.95), with an optimal cutoff of 155 IU/L providing 100% sensitivity and 97.5% specificity as demonstrated by table 2. Among all, CK-MB at 12 hours achieved excellent predictive ability (AUC = 1.0) between survivors and non-survivors with a cutoff value of 146 IU/L resulting in 100% sensitivity and 100% specificity.

Table 2. Post-operative cardiac biomarker levels and predictive performance.

Biomarker	Survivors (n=40)	Non-Survivors (n=3)	p-value	AUC (95% CI)	Optimal Cutoff (Youden)	Sensitivity (%)	Specificity (%)
Troponin I (6h)	3.11 ± 2.8	27.60 ± 45.1	0.206	0.48 (0.10-1.00)	4.92 ng/mL	66.7	87.5
CK-MB (6h)	67.97 ± 27.5	288.67 ± 378.5	0.391	0.63 (0.18-1.00)	83.0 IU/L	66.7	72.5
Troponin I (12h)	4.25 ± 3.9	51.81 ± 42.3	**0.038**	0.86 (0.55-1.00)	71.0 ng/mL	66.7	100.0
CK-MB (12h)	59.25 ± 25.8	466.33 ± 366.5	**0.004**	**1.00 (1.00-1.00)**	**146.0 IU/L**	**100.0**	**100.0**
Troponin I (24h)	3.60 ± 5.1	54.47 ± 43.9	**0.007**	0.92 (0.72-1.00)	**5.17 ng/mL**	**100.0**	92.5
CK-MB (24h)	52.27 ± 32.4	2888.33 ± 3790	**0.005**	0.95 (0.82-1.00)	**155.0 IU/L**	**100.0**	97.5

DISCUSSION

The present study evaluated the prognostic utility of serial cardiac biomarkers monitoring in predicting mortality following CABG. Early mortality was defined as in-hospital mortality occurring during the index hospitalization after CABG. Although non-survivors in our study had higher age as compared to survivors, it failed

to reach any statistical significance (p>0.05), this may be due to small sample size with even smaller mortality event. Nevertheless, advanced age is also considered an independent risk factor for adverse outcome following CABG and is incorporated into various validated cardiac surgical risk prediction models as EuroSCORE II.[7] Likewise, other baseline and perioperative variables like comorbidities, preoperative ejection fraction, vessels involved, cardiopulmonary bypass time and aortic cross clamp time were comparable between the two study groups.

Our study demonstrated that cardiac biomarkers both CK-MB and Troponin I at 12 hours and 24 hours were significantly higher in non-survivor group and showed excellent predictive performance of in-hospital mortality on ROC analysis. However cardiac biomarkers at 6 hours failed to show a meaningful association. Early post-operative biomarker elevation probably reflects expected myocardial injury related to surgical manipulation of myocardium, ischemic time during cardiopulmonary bypass or reperfusion injury rather than irreversible myocardial necrosis.[8] However persistent elevation of biomarkers may suggest worsening or ongoing myocardial injury and an increased risk of adverse outcomes.[9] According to Fourth universal definition of Myocardial Infarction (MI) , isolated elevated post-operative cardiac biomarkers is insufficient to diagnose perioperative MI (type 5 MI). The diagnosis requires substantial elevated cardiac Troponin together with supportive clinical , electrocardiographic, angiographic or imaging of evidence of new myocardial ischemia.[4] Nevertheless, persistent elevation of cardiac enzymes even in absence of confirmed type 5 MI has consistently been associated with adverse clinical outcomes.[10]

The biological kinetics of these cardiac enzyme also support this observation as both CK-MB and Troponin I usually peak within 12-24 hours of CABG with persistent elevation denoting ongoing myocardial damage.[11,12] The observation is consistent with the previous studies, demonstrating that elevation of myocardial biomarkers is associated with adverse outcome. Domanski et al demonstrated a graded association between elevation in the level of cardiac biomarkers and mortality with progressively higher level independently associated with increased risk of death following CABG.[3]

ROC analysis in the present study demonstrated strong predictive performance particularly for CK-MB at 12 hours (AUC-1.00) with optimal cutoff at 146 IU/L yielding 100% sensitivity and 100% specificity. The perfect AUC discrimination observed likely represents the very small number of mortality events rather than true diagnostic performance. Similarly, CK-MB at 24 hours (AUC = 0.95, optimal cutoff 155 IU/L, 100% sensitivity and 97.5% specificity and Troponin I measured at 24 hours (AUC = 0.92, optimal cutoff at 5.17ng/ml ,100 percent sensitivity and 92.5% specificity) showed excellent discriminatory capacity however these values should be interpreted cautiously due to small number of mortality events and may have resulted in optimistic estimates of diagnostic performance. External validation with larger cohort group is required.

Our findings are consistent with previous investigations implying the value of post-operative cardiac biomarkers. Croal et al. highlighted that post-operative elevation of Troponin I is independently associated with short and long term mortality after cardiac surgery.[13] Similarly, Lurati Buse et al. reported that post-operative elevation of troponin I correlated with an increased risk of cardiac events and mortality.[14] Comparable findings have also been reported for CK-MB, with intermediate and high post-operative CK-MB independently predicted 1-year mortality after cardiac surgery.[15] These observations further suggest that the level of cardiac enzyme is an objective measure of post operative cardiac damage. The excellent predictive performance at 12 and 24 hours in our study further supports the value of serial biomarker evaluation for improved post-operative risk stratification.

The optimal biomarker threshold identified in the present study differed from those reported previously, probably reflecting difference in assay characteristics, patient characteristics, timing of biomarker measurement, perioperative management and study design. Croal et al reported that elevated Cardiac Troponin I exceeding 13ng/ml concentration experienced significantly increased mortality following cardiac surgery .[13] In contrast, our study identified a lower threshold of 5.17ng/ml at 24 hours, suggesting that clinically relevant risk stratification could be obtained at lower biomarker concentration in our patient population. Likewise, Domanski et al. demonstrated a graded increase in mortality with rise in post-operative CK-MB level, notably the elevation of CK-MB exceeding 10 times the normal level exhibited significantly poorer prognosis although no single universal threshold was identified.[3] Our ROC analysis identified CK-MB concentration of 150 IU/L (146 IU/L and 155 IU/L at 24 hours) as the optimal cut-off values following CABG. These values exceed more than 10 times the normal level threshold of CK-MB and may represent a useful threshold for identifying

high risk patients. However, these values should be considered preliminary until validated in larger multicentric studies.

From a clinical perspective, serial cardiac monitoring at 12 and 24 hours is important to prognosticate and identify ongoing myocardial injury which may alert clinician for close monitoring and early intervention. Incorporating serial cardiac biomarkers in post-operative care may therefore improve risk stratification and certainly benefit patients particularly in resource limited settings where advanced imaging or invasive investigations are not readily available. Consequently, post-operative serial cardiac biomarkers monitoring represents an easily available, inexpensive, simple and widely accessible strategy for identification of patients at increased risk of adverse outcome following CABG.

This is a retrospective single institution study with small sample size, with even smaller event rate which limits the statistical power and increases the risk of overfitting particularly with perfect AUC in our study. The very small number of mortality events (n=3), precluded Multivariate logistic regression to determine the independent predictive value of biomarkers after adjusting for potential confounders. We did not systematically assess perioperative Myocardial Infarction (MI) according to the fourth universal definition of Myocardial infarction thus the findings in our study reflect the prognostic significance of cardiac biomarkers rather than occurrence of confirmed perioperative MI. according to fourth Universal definition. Potential selection bias may be present in the study. As follow-up was limited early mortality denoted only in-hospital mortality. Therefore, deaths occurring after discharge were not captured. The findings require validation in larger, multicentric cohorts before widespread clinical application.

CONCLUSIONS

Post operative Cardiac biomarker particularly Troponin I (>5.17 ng/ml at 24 hours) and CK-MB (>146 IU/L at 12 hours and >155 IU/L at 24 hours) were associated with in-hospital mortality following CABG in this cohort. Serial monitoring of cardiac biomarkers may serve as an important tool in post-operative risk stratification and early identification of high-risk patient requiring close monitoring and intervention. Larger prospective studies are needed to validate these cutoffs and confirm their independent predictive value.

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CONFLICT OF INTEREST

Author declares no conflict of interest.

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