

# Prognostic Value of Cardiac Biomarkers in Patients Undergoing On-Pump Coronary Artery Bypass Grafting: A Cohort Study in An Iranian Population

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## ARTICLE INFO

**Received** July 15, 2024

**Revised** December 20, 2024

**Accepted** December 22, 2024

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See Commentary page 107.

**Background:** The predictive value of creatine kinase-myocardial band (CK-MB) and high-sensitivity troponin T (hs-TnT) for adverse outcomes in coronary artery bypass grafting (CABG) has been well established in previous studies. However, most of these investigations have focused on perioperative complications. The present study assessed the preoperative and postoperative prognostic value of hs-TnT and CK-MB in individuals undergoing on-pump CABG.

**Methods:** This cohort study included patients who underwent isolated on-pump CABG at a tertiary hospital, Tehran Heart Center, between November 2018 and March 2021. We evaluated the associations of preoperative and postoperative hs-TnT and CK-MB levels with the incidence of major adverse cardiovascular events (MACE) within 1 year after surgery.

**Results:** Of the 3,188 participants, 231 (7.2%) experienced MACE. Factors associated with a higher incidence of MACE included older age, diabetes mellitus, history of peripheral vascular disease, lower left ventricular ejection fraction, and the occurrence of acute kidney injury after surgery. The adjusted hazard ratios (HRs) for the association between hs-TnT levels and 1-year MACE were 1.17 (95% confidence interval [CI], 1.07–1.29;  $p < 0.001$ ) for preoperative levels, 1.22 (95% CI, 1.02–1.47;  $p = 0.044$ ) at 8 hours post-surgery, and 1.38 (95% CI, 1.17–1.62;  $p < 0.001$ ) at 24 hours post-surgery. CK-MB levels at 8 hours (HR, 1.05; 95% CI, 1.01–1.10;  $p = 0.023$ ) and 24 hours (HR, 1.07; 95% CI, 1.04–1.10;  $p < 0.001$ ) after surgery were also associated with adverse events.

**Conclusion:** Preoperative and postoperative serum levels of hs-TnT and CK-MB may be considered significant predictors of MACE within 1 year after on-pump CABG.

**Keywords:** Troponin, Myocardial creatine kinase, Coronary artery bypass surgery, Major adverse cardiac event

## Introduction

Coronary artery disease (CAD) is a prevalent non-communicable disease and the leading cause of mortality and morbidity worldwide. Coronary artery bypass grafting (CABG) is a well-established revascularization technique for patients with multivessel CAD [1-3].

On-pump CABG utilizes cardiopulmonary bypass to maintain a bloodless operative field. It is not uncommon to observe some degree of myocardial injury in patients undergoing on-pump cardiac surgery. Myocardial damage during

CABG can result from several factors, including direct injury from surgical interventions, myocardial ischemia, coronary artery thrombosis, and acute graft failure [4-6].

Elevated levels of biochemical markers indicative of myocardial damage, such as creatine kinase-myocardial band (CK-MB) and troponins, are commonly observed following CABG. Nevertheless, uncertainty remains about the interpretation of changes in troponin levels during the postoperative period and whether elevated troponin concentrations can predict in-hospital and long-term adverse events after CABG. Previous studies exploring the rela-

tionship between troponin levels and patient prognosis have had notable limitations, including relatively small sample sizes and the absence of troponin measurements within the first 24 hours after surgery [7,8].

This study aimed to assess the predictive value of preoperative and postoperative serum concentrations of high-sensitivity troponin T (hs-TnT) and CK-MB regarding 1-year outcomes after on-pump CABG.

## Methods

### Study design and population

This cross-sectional cohort study included patients who underwent isolated on-pump CABG at Tehran Heart Center between November 2018 and March 2021. We excluded patients who had undergone other cardiac procedures, such as valve replacement, valve repair, or atrial and ventricular wall repair, or who had other concomitant cardiovascular diseases requiring additional surgical intervention. Of 3,905 patients considered for CABG, 633 underwent off-pump CABG. Surgery was canceled for 23 cases, and 7 patients withdrew their consent for the procedure, leading to their exclusion from the study. Of the remaining 3,242 patients who underwent on-pump CABG, there were 43 in-hospital deaths, and 11 patients did not participate in follow-up. Ultimately, 3,188 patients met the study criteria and were included in the analysis (Fig. 1). We conducted this study in compliance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Research Ethics Committee of Tehran Heart Center (reference number: IR.TUMS.MEDICINE.REC.1397.137), and written informed consent was obtained

from all participants.

Trained research personnel collected detailed demographic and clinical data on the patients, including age, sex, weight, height, presence of diabetes mellitus (DM), history of peripheral vascular disease (PVD), history of stroke, previous CABG, number of culprit vessels, pulmonary diseases, left ventricular ejection fraction (LVEF), and readmission. These data were extracted from the patients' health records, medical histories, nursing notes, echocardiograms, angiograms, and surgical reports. Additionally, comprehensive follow-up was conducted to ensure the accuracy and reliability of the information gathered.

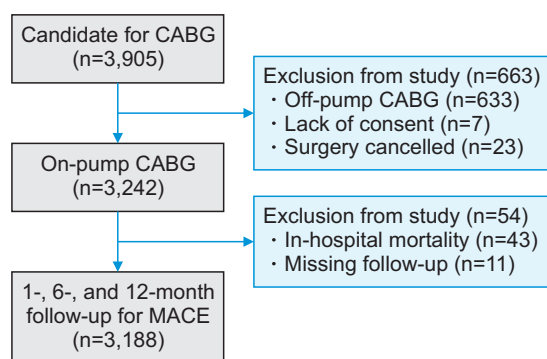
The attending clinicians had full autonomy in managing all facets of perioperative and intensive care. This included the choice of surgical techniques, the selection and dosing of catecholamines for weaning from cardiopulmonary bypass, the establishment of blood transfusion triggers, coagulation management, and decisions regarding the duration of stay in the intensive care unit.

Complete coronary revascularization was performed in all patients, defined as surgical revascularization of any territory supplied by a suitable coronary artery with at least 50% stenosis. Left internal mammary artery (LIMA), right internal mammary artery (RIMA), and saphenous vein grafts (SVG) were utilized for revascularization. Among the 3,188 patients, 3,178 received both LIMA and SVG, 5 received only LIMA, 3 received only SVG, and 2 received both LIMA and RIMA grafts.

### Clinical endpoints

The clinical endpoints evaluated were major adverse cardiovascular events (MACE), comprising cardiovascular death, non-fatal acute coronary syndrome, cerebrovascular accident (CVA), decompensated heart failure necessitating hospitalization, and cardiac reoperation within the 12 months following surgery.

Cardiovascular death was defined as mortality resulting from myocardial infarction (MI), sudden cardiac arrest, stroke, heart failure, or other conditions related to the cardiovascular system. Non-fatal acute coronary syndrome, including MI and unstable angina, is characterized by reduced blood flow to the heart without resulting in death. CVA, or stroke, involves the sudden loss of neurological function due to an interruption in the brain's blood supply. In this study, postoperative CVA was diagnosed through a combination of imaging studies and clinical assessments. Decompensated heart failure referred to the acute exacerbation of heart failure symptoms, such as fluid overload,



**Fig. 1.** Sampling flowchart of the study evaluating the prognostic value of cardiac biomarkers in patients undergoing on-pump coronary artery bypass grafting (CABG). MACE, major adverse cardiac events.

dyspnea, and fatigue, necessitating hospital admission. Cardiac reoperation denoted any subsequent surgical intervention on the heart or great vessels within 12 months of the initial operation.

## Follow-up

Postoperative follow-up was conducted through scheduled visits at 1, 6, and 12 months after the surgical procedure. Patients were required to provide their medical documents and discharge summaries for documentation purposes. For those unable to attend their scheduled visits, attempts were made to maintain contact with them or their close relatives via telephone. Trained research nurses, who were unaware of the patients' personal information, conducted the interviews.

## Cardiac biomarkers

Venous blood samples were collected on the day of admission, as well as 8 and 24 hours after surgery. Serum levels of CK-MB and hs-TnT, both using assays from Roche Diagnostics in Penzberg, Germany, were analyzed by the central laboratory at Tehran Heart Center Hospital. The reference limits for CK-MB levels were set at less than 6.73 ng/mL for men and less than 3.77 ng/mL for women. Elevated hs-TnT was defined as a level above 14 ng/L, which corresponds to the 99th percentile of the normal population reference range. At this threshold, the assay demonstrated a coefficient of variation of less than 10%.

## Statistical analysis

The data are presented as the mean±standard deviation for continuous variables with a normal distribution, as the median with the lower and upper quartiles for variables with a non-normal distribution, and as proportions for categorical variables. The adjusted and unadjusted associations of CK-MB and hs-TnT with MACE were assessed using the Cox proportional hazards model. Variables identified as known confounders in the literature, along with those that significantly affected MACE in this study, were considered potential confounders. The results were reported as hazard ratios with 95% confidence intervals (CIs).

## Results

A total of 3,188 patients who underwent isolated on-pump CABG at our institution were included in this study. The

mean age of the participants was 61.4±9.4 years, and 73.5% were male. The baseline and clinical characteristics of the patients are presented in Table 1. The strengths of this study lie in its large population size, high follow-up rate of 98.9%, and minimal missing biomarker data (less than 2%). These factors increased the reliability and robustness of the findings. Notably, factors such as older age, history of DM, PVD, reduced LVEF, and postoperative acute kidney injury (AKI) were associated with a higher incidence of MACE during the follow-up period (Table 1).

Throughout the study period, 231 patients (7.2%) experienced MACE. Specifically, cardiovascular death was reported in 2.7% of all participants, 2.6% developed acute coronary syndrome, 0.7% experienced CVA, 0.3% were hospitalized for decompensated heart failure, and 0.9% required cardiac reoperation (Table 2).

As indicated by the box plot of CK-MB levels, the median CK-MB concentrations peaked at 8 hours after on-pump CABG across all patients, as well as in the groups with and without MACE. Additionally, this figure reveals a negatively skewed distribution among all participants, a positively skewed distribution in the non-event group, and a normal distribution among the patients who experienced MACE. Similarly, median hs-TnT levels also peaked at 8 hours postoperatively. The distribution of postoperative hs-TnT levels was normal for the entire patient cohort and for both the MACE and non-event groups (Fig. 2).

The findings indicated that age, DM, history of PVD, LVEF, and AKI following on-pump CABG were significantly associated with an increased risk of MACE at 1 year, even after adjusting for other clinical factors. The univariate Cox proportional hazards model revealed a significant association between postoperative CK-MB levels and the occurrence of 1-year MACE in the study population. Furthermore, a significant correlation was found between preoperative and postoperative serum levels of hs-TnT and the risk of MACE within 1 year.

The associations between cardiac enzyme levels and the incidence of 1-year MACE remained statistically significant even after adjusting for various potential confounders, including age, body mass index, LVEF, history of PVD, extent of CAD, and New York Heart Association classification. This suggests that preoperative and postoperative hs-TnT levels, as well as postoperative CK-MB serum levels, are independent predictors of 1-year MACE following on-pump CABG (Table 3). Given the consistency between the adjusted and unadjusted analyses, the marginal confounding effect of the potential factors was apparent. A 100-unit increase in hs-TnT levels was associated with a significant-

**Table 1.** Baseline and clinical characteristics of patients undergoing isolated on-pump CABG

Characteristic	All patients (n=3,188)	MACE (n=231)	Non-event (n=2,957)	p-value
Age (yr)	61.4±9.4	63.1±10.4	61.3±9.4	<0.001
Sex				0.674
Male	2,342 (73.5)	164 (71.0)	2,178 (73.7)	
Female	846 (26.5)	67 (29.0)	779 (26.3)	
Body mass index (kg/m <sup>2</sup> )	26.46±4.24	26.92±4.34	45.1±9.0	0.383
Diabetes mellitus	1,320 (41.4)	106 (45.9)	1,214 (41.1)	0.019
History of TIA/CVA	363 (11.4)	33 (14.3)	330 (11.2)	0.455
History of PVD	61 (1.9)	9 (3.9)	52 (1.8)	0.013
Previous CABG	8 (0.2)	0	8 (0.3)	0.624
History of COPD	89 (2.8)	6 (2.6)	83 (2.8)	0.117
LVEF (%) at discharge	44.9±9.1	41.9±9.9	45.1±9.0	0.006
Patient diagnoses				0.689
Stable angina	183 (5.8)	7 (3.0)	176 (6.0)	
Unstable angina/NSTEMI	2,567 (80.5)	194 (84.0)	2,373 (80.2)	
STEMI	438 (13.7)	30 (13.0)	408 (13.8)	
Extent of CAD				0.841
Left main (solely)	2 (0.06)	0	2 (0.07)	
One-vessel	122 (3.8)	9 (3.9)	113 (3.8)	
Two-vessel	661 (20.7)	33 (14.3)	628 (21.2)	
Three-vessel	2,403 (75.4)	189 (81.8)	2,214 (74.9)	
NYHA classification at discharge				0.561
I	1,628 (51.1)	106 (45.9)	1,522 (51.5)	
II	1,183 (37.1)	85 (36.8)	1,098 (37.1)	
III	361 (11.3)	39 (16.9)	322 (10.9)	
IV	16 (0.5)	1 (0.4)	15 (0.5)	
AKI after CABG	74 (2.3)	19 (8.2)	55 (1.9)	<0.001
hs-TnT serum levels				
Preoperative	33.92 (2.07–54.02)	42.04 (30.7–90.6)	43.46 (37.87–61.03)	<0.0001
8 hr after CABG	369.35 (247.05–569.5)	422.1 (277.9–652.3)	324.4 (205.2–521.9)	0.004
24 hr after CABG	235.8 (151.5–401.6)	312.6 (165.7–601)	232 (149.5–390.3)	<0.0001
CK-MB serum levels				
Preoperative	3.62 (3.17–4.37)	5.85 (4.38–6.7)	3.6 (3.16–4.33)	0.83
8 hr after CABG	34.37 (29.05–43.75)	20.21 (14.91–31.54)	33.32 (27.98–42.31)	0.048
24 hr after CABG	21.20 (17.32–28.92)	12.59 (7.45–22.08)	21.08 (17.30–28.57)	<0.0001

Values are presented as mean±standard deviation, number (%), or median (lower quartile–upper quartile).

CABG, coronary artery bypass grafting; MACE, major adverse cardiovascular events; TIA, transient ischemic attack; CVA, cerebral vascular accident; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricle ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; CAD, coronary artery disease; NYHA, New York Heart Association; AKI, acute kidney injury; hs-TnT, high-sensitivity troponin T; CK-MB, creatine kinase-myocardial band.

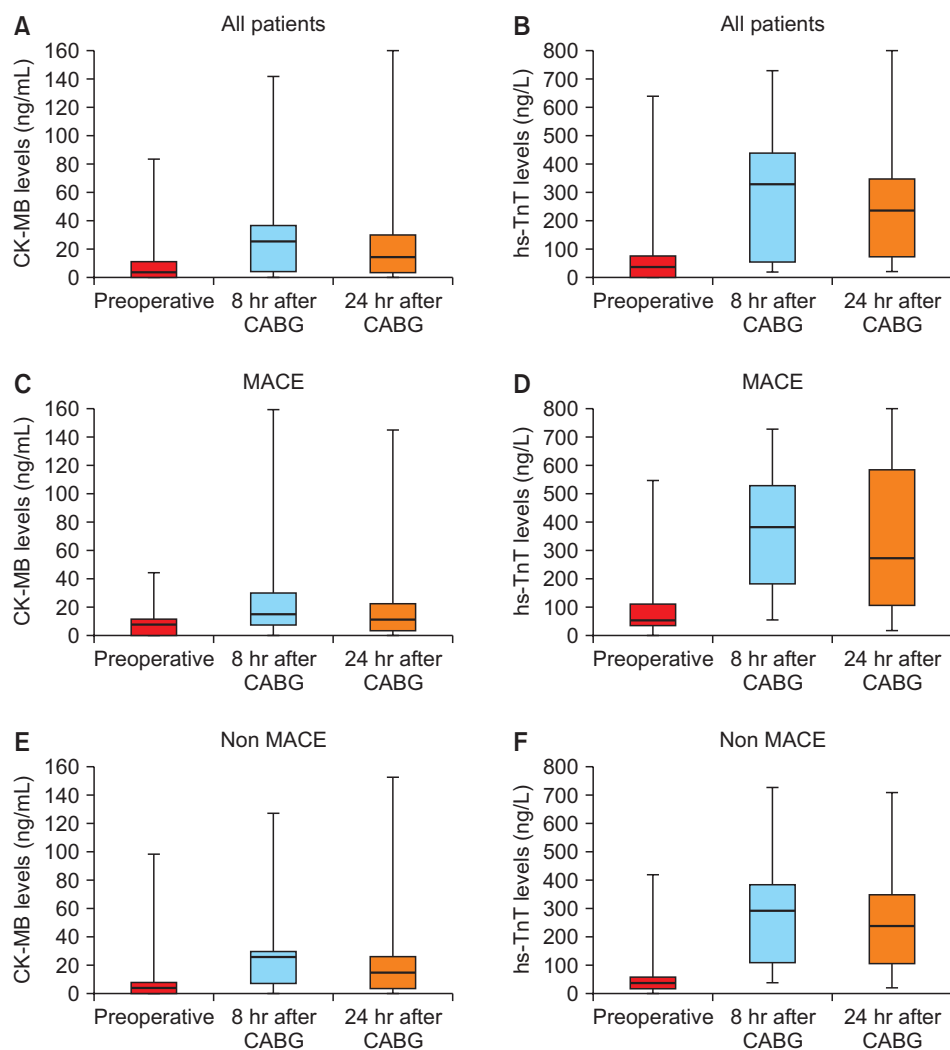
**Table 2.** Incidence of MACE among study participants (n=231)

MACE	No. (%)
Cardiovascular death	85 (2.7)
Acute coronary syndrome	83 (2.6)
Cerebrovascular accident	23 (0.7)
Hospitalized due to decompensated heart failure	10 (0.3)
Cardiac reoperation	30 (0.9)

MACE, major adverse cardiovascular events.

ly elevated risk of 1-year MACE. Specifically, a 100-unit increase in hs-TnT levels preoperatively, 8 hours postoperatively, and 24 hours postoperatively was linked to a 17%, 22%, and 38% increase in the likelihood of MACE, respectively. Additionally, a 5-unit rise in CK-MB levels at 8 hours and 24 hours post-surgery corresponded to a 5% and 7% increase in the risk of 1-year MACE, respectively.

We compared the cumulative incidence of MACE based on 6 levels of hs-TnT concentrations measured 24 hours postoperatively, categorized relative to the upper limit of normal (ULN). Higher hs-TnT levels measured 24 hours



**Fig. 2.** Box plots of the distribution of creatine kinase-myocardial band (CK-MB) and high-sensitivity troponin T (hs-TnT) among all participants (A, B), patients who experienced major adverse cardiac events (MACE) (C, D), and patients without MACE events (E, F). CABG, coronary artery bypass grafting.

after surgery, relative to the ULN, were associated with an increased rate of 1-year MACE. At this time point, 1,204 patients (37.8%) presented with hs-TnT levels between 2 and 5 times the ULN, while 932 patients (29.2%) had levels ranging from 1 to 2 times the ULN. The incidence of MACE was notably higher among patients with hs-TnT levels exceeding 10 times the ULN (Fig. 3).

## Discussion

This cohort study revealed that high serum levels of hs-TnT before and after surgery, as well as elevated postoperative levels of CK-MB, were predictive of 1-year MACE following isolated on-pump CABG, even after adjusting for potential preoperative and postoperative confounders. The findings suggest that preoperative and postoperative hs-TnT levels, along with postoperative CK-MB levels, can

serve as valuable biomarkers for reevaluating the risk of MACE after isolated on-pump CABG. These biomarkers are easily quantifiable through blood tests and provide a noninvasive method for identifying patients at elevated risk of MACE in the months after surgery.

Troponin is not typically detected in the bloodstream of individuals who have not undergone heart surgery or recently experienced a heart attack [9-11]. However, patients undergoing cardiac surgery frequently encounter atriotomy, surgical manipulation, inadequate cardioprotection, aortic cross-clamping, defibrillation, and reperfusion injury [12]. A certain degree of troponin release is expected during these surgical procedures, resulting in elevated troponin levels in patients after cardiac surgery. Higher troponin concentrations suggest more extensive myocardial damage and are associated with adverse clinical outcomes [4,13].

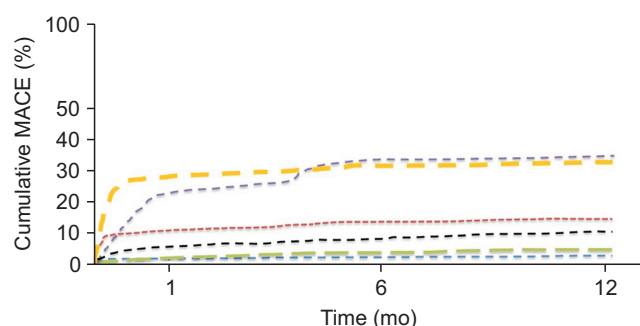


**Table 3.** Adjusted and unadjusted effects of CK-MB and hs-TnT levels, along with other clinical characteristics, on 1-year MACE in patients undergoing isolated on-pump CABG

Variable	Uni. HR (95% CI)	p-value	Multi. HR (95% CI)	p-value
Age (yr)	1.23 (1.08–1.47)	<0.001	1.18 (1.07–1.39)	<0.001
Sex (male)	0.94 (0.79–0.99)	0.674	0.93 (0.79–0.96)	0.723
Body mass index (kg/m <sup>2</sup> )	0.81 (0.73–0.94)	0.383	0.86 (0.76–0.99)	0.123
Diabetes mellitus	1.19 (1.07–1.38)	0.019	1.24 (1.08–1.34)	<0.001
History of TIA/CVA	0.88 (0.76–0.95)	0.455	0.9 (0.78–0.94)	0.388
History of PVD	1.39 (1.22–1.63)	0.013	1.06 (1.02–1.13)	0.047
Previous CABG	0.79 (0.67–0.88)	0.624	0.91 (0.83–0.98)	0.173
History of COPD	0.83 (0.76–0.89)	0.117	0.74 (0.63–0.81)	0.457
LVEF (%) at discharge	1.56 (1.37–1.83)	0.006	1.51 (1.36–1.8)	0.011
NYHA classification at discharge	0.68 (0.61–0.76)	0.561	0.7 (0.63–0.77)	0.544
AKI after CABG	1.46 (1.30–1.73)	<0.001	1.16 (1.06–1.28)	0.029
CK-MB serum level				
Preoperative	0.99 (0.98–1.02)	0.83	0.99 (0.97–1.02)	0.634
8 hr after CABG	1.04 (1.00–1.01)	0.048	1.05 (1.01–1.10)	0.023
24 hr after CABG	1.06 (1.04–1.01)	<0.0001	1.07 (1.04–1.10)	<0.001
hs-TnT serum level				
Preoperative	1.26 (1.16–1.36)	<0.0001	1.17 (1.07–1.29)	<0.001
8 hr after CABG	1.31 (1.08–1.58)	0.004	1.22 (1.02–1.47)	0.044
24 hr after CABG	1.48 (1.27–1.73)	<0.0001	1.38 (1.17–1.62)	<0.001

CK-MB, creatine kinase-myocardial band; hs-TnT, high-sensitivity troponin T; MACE, major adverse cardiovascular events; CABG, coronary artery bypass grafting; HR, hazard ratio; uni., univariate; multi., multivariate; CI, confidence interval; TIA, transient ischemic attack; CVA, cerebral vascular accident; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; AKI, acute kidney injury.

hs-TnT level (×ULN)	<×1	×1–2	×2–5	×5–10	×10–50	>×50
Total no. of patients	512	932	1,204	35	139	6
No. of cumulative MACE (%)	10 (2)	29 (3)	97 (8)	44 (11)	49 (35)	2 (33)

**Fig. 3.** Total number and cumulative incidence of major adverse cardiac events (MACE) based on high-sensitivity troponin T (hs-TnT) level at 24 hours postoperatively as a multiple of the upper limit of normal (ULN).

Several studies have explored the predictive value of troponin levels for short- to mid-term outcomes following CABG. However, these studies were limited by small sample sizes, low event frequencies, and a prevalent lack of ac-

counting for postoperative complications in risk assessments [14,15]. Additionally, many studies have examined the relationship between either preoperative or postoperative troponin levels and CABG outcomes [7,16–20]. Similarly, existing research has primarily focused on either troponin or CK-MB levels, without a thorough comparison of both biomarkers. In this study, we evaluated the association of preoperative and postoperative serum levels of troponin T (using the fifth-generation assay) and CK-MB with the occurrence of MACE within 1 year after CABG in a large patient cohort.

Beller et al. [7] examined the correlation between preoperative cardiac troponin I levels and long-term mortality in patients undergoing CABG. Their findings indicated that the peak troponin level did not impact outcomes following CABG and was an inadequate predictor of events when using the Society of Thoracic Surgeons (STS) predictive models [7]. While the study provided valuable insights, its scope was limited to patients undergoing urgent or emergent CABG, and it did not evaluate the prognostic value of the fifth-generation assay for troponin T. Furthermore, unlike our study, their model incorporated STS predictors. Petäjä et al. [16] investigated 648 patients who had undergone CABG or other cardiac procedures, assessing the prognostic role of preoperative and postoperative hs-TnT levels in

predicting short- and long-term outcomes. Their findings indicated that elevated postoperative hs-TnT levels, when combined with high preoperative hs-TnT concentrations, were predictive of mortality [16]. Thus, the combination of preoperative and postoperative hs-TnT measurements could serve as a valuable predictor of patient outcomes following cardiac surgery.

In other investigations, elevated levels of cardiac troponin T and I after cardiac surgery have been identified as independent predictors of adverse short-term outcomes [17,19]. A study by Søråas et al. [20] demonstrated that serum levels of CK-MB and cardiac troponin T could serve as prognostic markers for mortality after CABG, aligning with our findings. Their data indicated that, compared to CK-MB levels, elevated serum levels of cardiac troponin T had a stronger predictive value for long-term mortality following CABG [20]. Previous research has suggested that troponin and CK-MB levels are independent predictors of short- and mid-term mortality and morbidity in patients after CABG [11]. Overall, our results align with prior research that has evaluated various risk factors in addition to these 2 biomarkers.

We examined serum levels of hs-TnT (via the fifth-generation assay) and CK-MB in a direct comparison, adjusting for both preoperative and postoperative factors that influence outcomes at 12 months following CABG. The results highlight the value of incorporating hs-TnT measurements into predictive models for these patients.

Several limitations of our study should be noted. First, to ensure a homogeneous study population and to address the risks associated with patients undergoing concomitant CABG and other cardiac procedures, such as valve replacement, we excluded those individuals. Consequently, our findings are specifically applicable to patients undergoing isolated on-pump CABG and may not be generalizable to other cardiac procedures. Second, the time interval between the initial biomarker measurements (taken on the day of admission) and the day of surgery varied widely, potentially affecting the reliability of preoperative hs-TnT and CK-MB tests in predicting the short- and mid-term outcomes of CABG. Furthermore, although we excluded 43 cases of in-hospital mortality to preserve the integrity of our analysis, this exclusion could introduce selection bias, as these cases are associated with MACE.

In conclusion, preoperative and postoperative elevation of hs-TnT serum levels, as well as postoperative elevation of CK-MB, were associated with MACE occurring within 1 year after on-pump isolated CABG. The present findings highlight the importance of monitoring these biomarkers

in clinical practice to identify patients at high risk of adverse cardiovascular outcomes. Further research is required to explore potential interventions that could be informed by these predictive markers.

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Conceptualization: RE, YZ, HK. Study design: RE, YZ, HK. Data interpretation: MP, VAP, HK. Formal analysis: RE, HK. Writing—original draft: HK, VAP, MP. Critical revision of the manuscript for important intellectual content: YZ, HK, VAP, RE. Final approval of the manuscript: all authors.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

### Funding

This work was supported by a research grant from the Tehran University of Medical Sciences (reference number: IR.TUMS.MEDICINE.REC.1397.137).

### Acknowledgments

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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