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ORIGINAL RESEARCH

Serum Periostin as a Novel Biomarker for Predicting 30-Day Major Adverse Cardiac Events After Off-Pump Coronary Artery Bypass Grafting

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Background: The identification of predictors for major adverse cardiovascular events (MACEs) is essential for reducing mortality associated with off-pump coronary artery bypass grafting (OPCAB). The objective of this study is to assess serum periostin levels as a novel predictor of MACEs in patients undergoing OPCAB.

Methods: This prospective study included 79 patients diagnosed with coronary artery disease (CAD) who underwent OPCAB between May 2022 and May 2023. The changes in periostin levels (ΔPOSTN) were calculated using the formula: postoperative POSTN levels minus preoperative POSTN levels. Based on the optimal cut-off value determined from the receiver operating characteristic (ROC) curve, patients were categorized into Low POSTN Change (LPC) and High POSTN Change (HPC) groups for subgroup analysis. The primary outcomes assessed were MACEs, including cardiac death, myocardial infarction (MI), heart failure, and stroke.

Results: Follow up for the patients was conducted for 30 days, with 71 patients ultimately being included in the final analysis. During this period, 13 MACEs were recorded, representing an incidence rate of 18.3%. The events included 2 cases of cardiac death (2.8%), 5 cases of MI (7.0%), 5 cases of heart failure (7.0%), and 1 case of stroke (1.4%). The risk of MACEs increased by 4% for each unit increase in the ΔPOSTN (Odds Ratio [OR]: 1.04, 95% Confidence Interval [CI]: 1.01–1.06; $p = 0.005$). The area under the ROC curve was 0.869 (95% CI: 0.768–0.938; $p < 0.001$). Based on the Youden index ($J = 0.683$), the optimal threshold for ΔPOSTN was determined to be 16.6 μg/L, with a sensitivity of 76.9% and a specificity of 91.4%.

Conclusion: Changes in serum periostin levels during the perioperative period may serve as an independent predictor of 30-day MACEs in patients undergoing OPCAB.

Trial Registration: Link of the registry: https://www.chictr.org.cn. Date of registration: 2022/05/22. Trial registration number: ChiCTR2200060220.

Keywords: MACE, myocardial infarction, OPCAB, serum periostin, ventricular remodeling

Introduction

Coronary artery disease (CAD) is a major global health issue, requiring effective treatments like medications, percutaneous interventions, and surgical procedures such as coronary artery bypass grafting (CABG).[1] Recently, off-pump CABG (OPCAB) has gained popularity for potentially better outcomes and fewer complications compared to traditional on-pump CABG. OPCAB involves performing bypass surgery on a beating heart without a heart-lung machine, aiming to maintain hemodynamic stability and reduce inflammation, thereby minimizing risks like stroke, renal failure, and extended recovery.[2] However, major adverse cardiovascular events (MACEs) are common and significant complications can take place after off-pump coronary artery bypass grafting (OPCAB), affecting approximately 4.4%-23.1% of patients.[3–5] Prior studies have indicated that OPCAB surgery induces inflammatory, hemostatic, and immune responses,

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which can lead to early postoperative complications.[6,7] Factors like myocardial ischemia due to aortic cross-clamping, reperfusion injury, plaque rupture, microembolization, and different types of anesthesia may contribute to CABG-related inflammation.[7] While several serum biomarkers, including cardiac troponin I (cTnI), brain natriuretic peptide (BNP), and myoglobin, have been used to predict MACEs post-CABG, their predictive accuracy is constrained by their specificity to particular cardiac conditions.[8,9] These biomarkers do not fully account for the multifaceted nature of MACEs, which result from a complex interplay of various independent factors. Consequently, there is a need for more effective prognostic indicators for OPCAB—particularly serum biomarkers—that are still lacking.

Serum periostin (POSTN), a protein with a molecular weight of approximately 90 kDa, is highly expressed in the extracellular matrix of activated fibroblasts.[10] In patients with coronary artery disease (CAD), particularly those experiencing pressure overload, myocardial infarction, and ischemic cardiomyopathy, there is a notable increase in periostin expression due to fibroblast activation.[11,12] Prior studies have demonstrated that serum periostin levels are significantly elevated in Chinese patients with CAD compared to healthy volunteers.[13]

However, the overexpression of periostin has been associated with a poor prognosis in patients with CAD, particularly when acute inflammation is present, and it is also linked to the extent of cardiac damage. Iekushi et al reported that the overexpression of the exogenous periostin gene in the rat heart could lead to cardiac dysfunction.[14] Ling et al found that preoperative periostin levels could serve as a significant predictor of mortality in patients with acute myocardial infarction (AMI).[15] Nguyen et al observed a significant increase in serum periostin levels on days 5–7 in patients with AMI, which was strongly correlated with AMI severity.[16] Additionally, animal studies have demonstrated that POSTN levels rise significantly following coronary artery ligation and are closely related to the severity of cardiac damage.[17,18] Thus, it is crucial to investigate the prognostic value of POSTN for predicting adverse cardiac events following OPCAB surgery.

However, as per the knowledge of the author, there have been no human studies addressing this issue. Consequently, a prospective observational study was conducted to assess POSTN levels during the perioperative period as a novel prognostic marker for MACEs in patients undergoing OPCAB surgery.

Methods

Study Design

The prospective cohort study was conducted involving patients with CAD who underwent first-time elective OPCAB surgery at Affiliated Hospital 2 of Nantong University, Nantong, China, between May 2022 and May 2023. The study received approval from the Ethical Committee of Affiliated Hospital 2 of Nantong University (Reference: 2020KT030) and is registered with the China Clinical Trial Registry (Reference: ChiCTR2200060220, accessible at https://www.chictr.org.cn). Informed written consent was obtained from all participants. Inclusion criteria for patients diagnosed with CAD were aligned with the latest diagnostic guidelines issued by the American College of Cardiology (ACC) and the American Heart Association (AHA) in 2023.[19]

The inclusion criteria for the study were as follows: patients with CAD who underwent first-time elective OPCAB and were aged 18 years or older. Both male and female patients were included. Exclusion criteria were: 1) severe hepatorenal insufficiency (chronic kidney disease stage 4 or higher or Child-Pugh class C); 2) a history of previous open heart surgery; 3) withdrawal from the study or refusal to cooperate with blood sample collection; 4) conversion of the surgery to extracorporeal circulation; 5) a history of anaphylactic disease or requirement for long-term hormone therapy, both preoperatively and perioperatively;[20,21] or 6) acute congestive heart failure prior to surgery, emergency surgery, or a combination of other surgical procedures.

Patients were monitored for 30 days through telephone interviews or outpatient follow-ups, during which any MACEs were documented. To examine the association between serum periostin levels and MACEs in patients undergoing OPCAB surgery, a total of 79 patients were included for subgroup analysis. The primary outcome was the incidence of MACEs, including cardiac death, MI, heart failure, or stroke.[22] For further details, refer to the supplementary material.

Experimental Development

Preoperative and Intraoperative Management

Patients received their standard preoperative medication, and their medication history was recorded. Additionally, routine preoperative assessments were conducted, including electrocardiography (ECG), chest computed tomography (CT), head CT, cardiac ultrasound, and coronary arteriography.

All surgical procedures were performed by a highly experienced surgical team specializing in OPCAB. A median sternotomy was conducted for all patients, followed by complete myocardial revascularization using either an arterial or a saphenous vein graft. During the primary OPCAB procedure, unfractionated heparin was administered, with the activated clotting time (ACT) maintained above 250 seconds. When the surgery was completed, the anticoagulant effects of heparin were reversed with protamine, and dexamethasone was routinely administered to prevent protamine-induced allergies. When the patients arrived in the operating room, they were monitored using pulse oximetry, ECG (lead II), noninvasive blood pressure measurements, radial artery catheter blood pressure measurements, bispectral index, and temperature monitoring. Anesthesia induction involved 0.05 mg/kg midazolam, 0.3 mg/kg etomidate, and 1 μg/kg sufentanil, with neuromuscular blockade achieved using 0.15 mg/kg cisatracurium. After endotracheal intubation, mechanical ventilation was provided with tidal volumes of 6–10 mL/kg of ideal body weight, and the respiratory rate was adjusted to maintain end-tidal carbon dioxide levels between 35–40 mmHg. Anesthesia was maintained with a continuous infusion of propofol (4–6 mg/kg/h), cisatracurium (0.1–0.2 mg/kg/h), remifentanil (0.2–0.3 mg/kg/h), and sevoflurane (0.5–1%). The goal of perioperative blood pressure control was to maintain a mean arterial pressure of ≥ 70 mmHg.[23] Vasoactive drugs like deoxyephedrine or norepinephrine, were used to sustain intraoperative coronary perfusion pressure, and inotropic agents, including dopamine or dobutamine, were administered in combination with vasoactive drugs for patients who were hemodynamically unstable during surgery. Surgeons, anesthesiologists, and nursing staff were blinded to group allocation.

Determination of Serum Periostin Levels

Preoperative peripheral blood samples were collected prior to anesthesia induction, and postoperative samples were obtained once the surgery was completed. After allowing the samples to stand for 1 hour, the supernatant was separated and stored in an EP tube. The supernatant was then frozen at −80 °C for 20 minutes. POSTN expression was quantified using an enzyme-linked immunosorbent assay (ELISA) (Wuhan Elierite Biological Technology Co., Ltd)., following the instructions provided by the manufacturer. Each measurement was repeated three times to ensure accuracy and reliability of the results. All blood samples were collected by a single researcher who was blinded to patient group assignments.

Measurement of the Deltas for POSTN

The change in serum periostin (ΔPOSTN) was defined as the arithmetic difference between preoperative and postoperative POSTN levels. ΔPOSTN was calculated using the formula: postoperative POSTN levels - preoperative POSTN levels. The optimal cutoff value for ΔPOSTN was determined through receiver operating characteristic (ROC) curve analysis. Based on this threshold, patients were classified into two groups: Low POSTN Change (LPC) and High POSTN Change (HPC). The categorization of patients and the documentation of clinical data were carried out by two investigators who were not involved in blood sample collection or follow-up procedures.

Follow-Up

Follow-ups for the patients were conducted for 30 days after surgery, during which any MACEs were recorded by a single researcher. During the hospitalization period, the researcher conducted ward visits and carefully reviewed each patient's discharge summary to document the occurrence of MACEs. After discharge, patients were monitored through telephone consultations and outpatient visits to assess their physical condition. Both patients and the researcher were blinded to group allocation.

Acquisition and Screening Disease Gene Targets

We utilized the R package to download datasets related to CAD from the GEO database, specifically GSE66360 and GSE42148.The specific information is shown in Supplementary Table 1. Among them, the chip platform of dataset

GSE66360 was GPL570 (CAD=49, control=50). The chip platform of dataset GSE42148 was GPL13607 (CAD=13, control=11). Finally, the R package limma was used to standardize the Combined GEO Datasets, annotate probes, and normalize them. To verify the effect of removing batch effect, Principal Component Analysis (PCA) is performed on the expression matrix after removing batch effect.

Gene Target Enrichment Analysis

We utilized the R package clusterProfiler (version 4.3.0; https://www.gsea-msigdb.org/gsea/index.jsp) to conduct Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of differentially expressed genes identified through differential analysis of high and low expression groups in CAD samples derived from integrated GEO Datasets (Combined Datasets). The entry screening criterion was an adjusted p-value (adj.p) < 0.05, with the p-value correction method implemented being Benjamini-Hochberg (BH). For Gene Set Enrichment Analysis (GSEA), we employed the GMT file containing All Canonical Pathways (3050). The screening criteria for GSEA included an adjusted p-value (adj.p) < 0.05 and a false discovery rate value (q value) < 0.25, both of which were deemed statistically significant. The p-value correction method applied was BH. To assess whether different pathways are enriched across distinct samples, we accessed the Molecular Signatures Database c2.cp.v2023.2.hs.symbols. The GMT gene set was utilized, and the R package Gene Set Variation Analysis (GSVA) (Version 1.50.0) was employed to integrate the GEO dataset. GSVA was performed on all genes from the CAD datasets to evaluate the differences in functional enrichment between the Low Expression group and the High Expression group of POSTN. The screening criterion for GSVA was a p-value < 0.05.

Upstream and Downstream Regulatory Relationships of POSTN in Cells

The transcription factors of target genes were predicted by established TF Regulatory Network through ChIPBase database (http://rna.sysu.edu.cn/chipbase/).

In order to analyze the relationship between the gene POSTN and microRNAs, through a starBase database (https://rnasysu.com/encori/) access to related to gene POSTN microRNAs.

Comparative Toxicogenomics Database (https://ctdbase.org/) was used to predict the direct and indirect drug targets of gene POSTN, and the interaction between gene POSTN and drugs was explored.

Sample Size Calculation

An acceptable margin of error of 6% was established between the sample MACE incidence and the expected incidence at the time of formal investigation. With a confidence level set at 95% and a significance level of 0.05, the required sample size was calculated using the "confidence intervals for one proportion" method, resulting in a sample size of 63. To account for a potential loss to follow-up of 25%, the study was designed to recruit 79 participants.

Statistical Analysis

The statistical analysts were not involved in blood sample collection, anesthesia, or postoperative follow-up. Statistical analysis was conducted using SPSS 24.0 and MedCalc. Data are presented as means ± standard deviations (SDs), medians (P25, P75), and frequencies (%). Comparisons between serum biomarkers in two groups were conducted using the Wilcoxon matched-pairs signed-rank test. For two-group comparisons, unpaired two-tailed Student's t-tests were used for normally distributed data, rank-sum tests for skewed data, and chi-squared tests or Fisher's exact tests for categorical data. Logistic regression was used to discover predictors of a composite endpoint of 30-day MACEs and 30-day mortality. Variables with *p*-values of < 0.05 in univariate analyses were included in the multivariable model. ROC and AUC curves were calculated and compared using the Hanley–McNeil test (AUC = 0.5: no prediction; AUC = 1.0: perfect prediction). Pairwise comparisons of ROC curves were conducted using the DeLong test. All statistical tests were two-tailed, with significance set at $P < 0.05$.

Results

Patient Demographic and Clinical Characteristics

Among the 79 patients included, surgeries for 2 were canceled, and 6 required cardiopulmonary bypass, which led to totally 71 patients being analyzed. At the 30-day follow-up, 13 cases of MACEs were recorded (18.3%), while 58 cases were classified as non-MACEs (81.7%), as depicted in Figure 1.

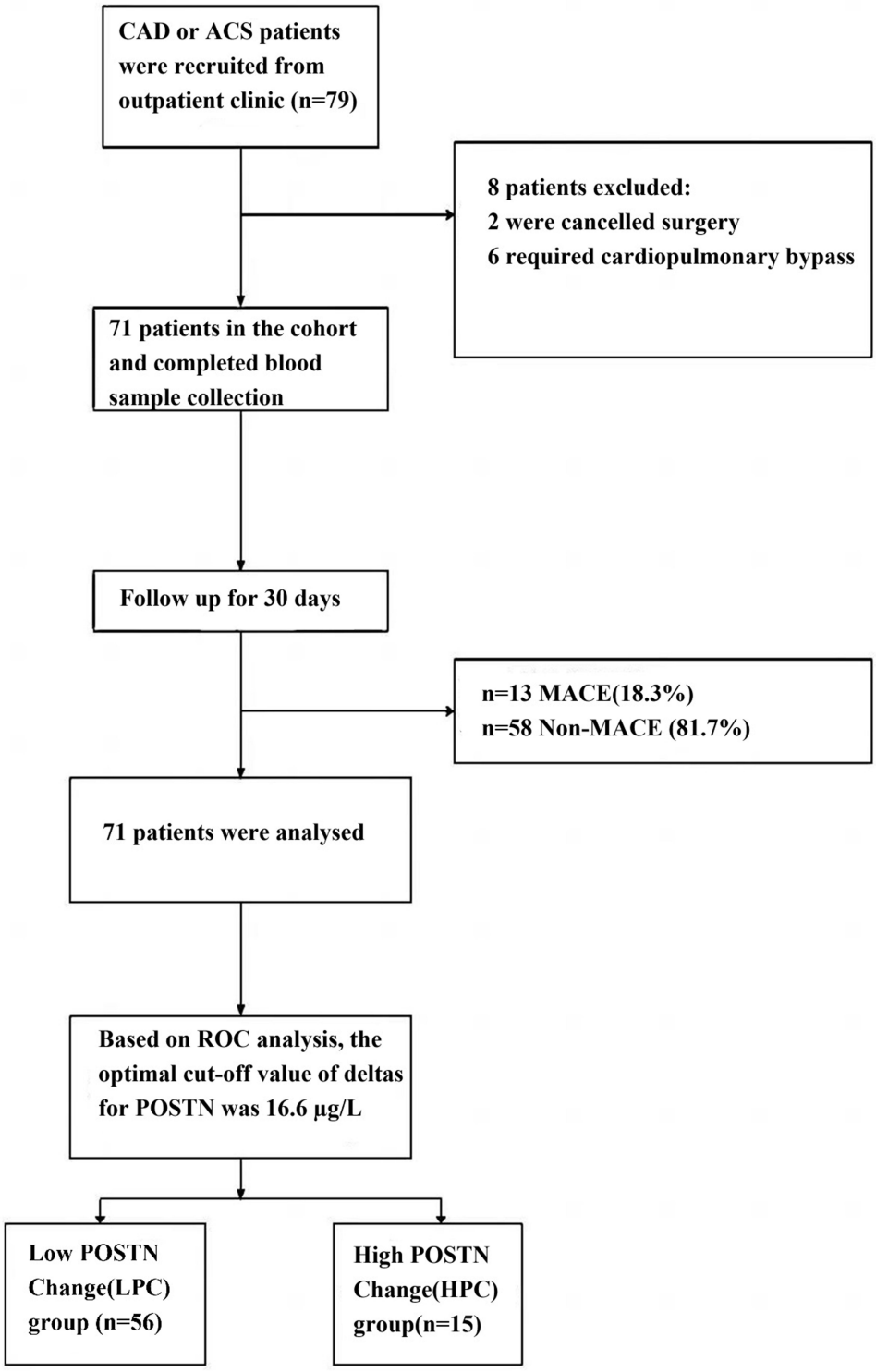

Figure 1 Participant enrollment flow chart.

The baseline characteristics are detailed in Table 1. Overall, no statistically significant differences were observed between the two groups concerning sex, weight, body mass index, duration of surgery, history of hypertension or diabetes, and the number of diseased or bypassed vessels (Table 1; $p > 0.05$).

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Table 1 Baseline Characteristics of Patients with or Without MACEs

	Non-MACE (n=58)	MACE (n=13)	P value
Characteristics			
Age (y)	67.0(59.0, 71.0)	70.0(65.5, 75.5)	0.083[a]
Sex (male/female, n)	44/14	10/3	1.000[b]
Body mass index (kg/m2)	24.9±2.8	25.1±4.1	0.889[c]
NYHA (n, %)			
I–II	18(31.0)	3(23.1)	0.459[b]
III–IV	40(69.0)	10(76.9)	
No. of diseased vessels (n, %)			
1–3	38(65.5)	10(76.9)	0.526[b]
>4	20(34.5)	3(23.1)	
No. of bypass vessels (n, %)			
1–3	25(43.1)	6(46.2)	0.841[d]
>4	33(56.9)	7(53.8)	
Diagnosis at the time of surgery			
CAD (n, %)	38(65.5)	9(69.2)	1.000[b]
ACS (n, %)	20 (34.5)	4 (30.8)	
Risk factors			
Previous MI (n, %)	7 (12.1)	3 (23.1)	0.376[b]
Hypertension (n, %)	35(60.3)	8(61.5)	0.937[d]
Diabetes (n, %)	25(43.1)	5(38.5)	0.759[d]
Preoperative LVEF (%)	62.6±6.7	61.3±8.2	0.560[c]
Duration of surgery (min)	268.4±58.8	267.3±58.3	0.954[c]
Preoperative medications			
Inotropic agents (n, %)	6(10.3)	1(7.7)	1.000[b]
Vasopressors (n, %)	5(8.6)	2(15.4)	0.604[b]
Perioperative medications			
Inotropic agents (n, %)	25(43.1)	2(15.4)	0.112[b]
Vasopressors (n, %)	10(17.2)	7(53.8)	**0.005[d]**
Dexamethasone(mg)	10(10, 20)	10(10, 20)	0.627[a]
Anesthetics			
Sufentanil consumption (μg)	70.0(43.8, 100.0)	45.0(40.0, 80.0)	0.151[a]
Propofol consumption (mg)	960.0(800.0, 1100.0)	1000.0(787.5, 1000.0)	0.828[a]
Biomarkers			
Presurgical POSTN (μg/L)	187.1(154.0, 218.8)	159.3(112.6, 248.7)	0.174[a]
Presurgical myoglobin (μg/L)	32.3(21.1, 45.6)	30.5(23.1, 42.8)	0.789[a]
Presurgical TnI (μg/L)	0.03(0, 0.28)	0.06(0, 0.72)	0.568[a]
Presurgical proBNP (pg/L)	457.7(105.3, 1162.3)	1037.0(281.3, 1720.0)	0.128[a]
Postsurgical POSTN (μg/L)	166.8(131.1, 223.9)	195.5(164.5, 261.8)	**0.069[a]**
Postsurgical myoglobin (μg/L)	128.8(102.0, 231.7)	288.4(164.4, 458.4)	0.008[a]
Postsurgical TnI (μg/L)	0.54(0.19, 0.97)	1.13(0.34, 11.75)	0.107[a]
Postsurgical proBNP (pg/L)	861.3(352.0, 1305.8)	1235.0(728.9, 2421.0)	**0.042[a]**
Changes in biomarkers			
Deltas for POSTN (μg/L)	−15.7(−33.0, 4.05)	65.6(16.7, 89.9)	**<0.001[a]**
Deltas for myoglobin (μg/L)	98.5(63.4, 190.9)	234.6(130.1, 431.3)	**0.013[a]**
Deltas for TnI (μg/L)	0.36(0.08, 0.76)	0.34(−0.16, 11.75)	0.677[a]
Deltas for BNP (pg/L)	195.0(−28.0, 665.2)	541.3(−530.5, 953.0)	0.466[a]
Inflammatory markers			
Presurgical CRP (mg/mL)	3.04(1.20, 10.31)	3.16(0.08, 15.6)	0.835[a]

Notes: The results are presented as the means±SDs, medians (p25, p75) and numbers (%). [a]Mann–Whitney *U*-test; [b]Fisher's test; [c]unpaired Student's test; [d]Pearson chi-square test. Bold numbers indicate P <0.05.

Abbreviations: MACEs, major adverse cardiovascular events; NYHA, New York Heart Association; POSTN, serum periostin; TnI, troponin I; BNP, brain natriuretic peptide; MI, myocardial infarction; LVEF, Left ventricular ejection fractions; CRP, C-reactive protein.

In the MACE group, the mean age, percentage of patients with a history of previous MI, New York Heart Association (NYHA) heart function classification, consumption of propofol, and presurgical CRP levels were higher compared to the non-MACE group; however, these differences did not reach statistical significance (Table 1; $p > 0.05$).

Conversely, in the MACE group, the use of perioperative vasopressors, postsurgical myoglobin levels, postsurgical proBNP levels, changes in periostin (ΔPOSTN), and changes in myoglobin (Δmyoglobin) were significantly higher compared to the non-MACE group (Table 1; $p < 0.05$).

Multivariate Logistic Regression Results

Logistic regression analysis was conducted to discover risk factors associated with variations in serum biomarkers following OPCAB in patients with CAD.

Table 2 summarizes the results of the logistic univariate analysis, which assessed variables including sex, age, BMI, NYHA classification, number of diseased vessels, preoperative and perioperative medications, anesthetics, and serum biomarkers. The analysis indicated that changes in ΔPOSTN were a significant risk factor for MACEs following OPCAB. Specifically, each 1-unit increase in ΔPOSTN was associated with an approximately 4% increase in the risk of MACEs (Table 2). Furthermore, the logistic multivariate analysis confirmed that ΔPOSTN independently served as a prognostic factor for MACEs in patients diagnosed with CAD undergoing OPCAB.

Table 2 Logistic Regression Analysis Results

Characteristics	N(%) Or Median (P25, P75)	OR [95% CI] Univariate	P value	OR [95% CI] Multivariate	P value
Age (y)					
<60	26(23.6)	Reference		–	–
≥60	45(63.4)	4.19[0.50, 34.98]	0.186	–	–
Sex					
Female	17(23.9)	Reference		–	–
Male	54(76.1)	1.06[0.26, 4.40]	0.935	–	–
Body mass index (kg/m2)	25.0±3.1	1.01[0.83, 1.24]	0.887		
NYHA				–	–
I–II	21(29.6)	Reference		–	–
III–IV	50(70.4)	1.50[0.37, 6.11]	0.572	–	–
No. of diseased vessels					
1–2	48(67.6)	Reference		–	–
≥3	23(32.4)	1.65[0.19, 14.68]	0.655	–	–
No. of bypass vessels					
1–2	31(43.7)	Reference		–	–
≥3	40(56.3)	1.05[0.44, 2.51]	0.920	–	–
Diagnosis at the time of surgery					
CAD (n, %)	47(66.2)	Reference		–	–
ACS (n, %)	24(33.8)	0.84[0.23, 3.09]	0.798	–	–
Risk factors					
Previous MI (n, %)	10(14.1)	2.19[0.48, 9.92]	0.311	–	–
Hypertension (n, %)	43(60.6)	1.05[0.31, 3.62]	0.937	–	–
Diabetes (n, %)	30(42.3)	0.83[0.24, 2.83]	0.760	–	–
Preoperative LVEF				–	–
≥50%	67(94.4)	Reference		–	–
<50%	4(5.6)	5.09[0.65, 40.10]	0.122	–	–
Duration of surgery (min)	268.17±58.3	1.00[0.99, 1.01]	0.953	–	–

(*Continued*)

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Table 2 (Continued).

Characteristics	N(%) Or Median (P25, P75)	OR [95% CI] Univariate	P value	OR [95% CI] Multivariate	P value
Preoperative drugs					
Inotropes (n, %)	7(9.9)	0.72[0.08, 6.57]	0.773	–	–
Vasopressors (n, %)	7(9.9)	1.93[0.33, 11.24]	0.466	–	–
Anesthetics					
Sufentanil consumption (μg)	65.0[40.0, 100.0]	0.99[0.97, 1.01]	0.179	–	–
Propofol consumption (mg)	1000[800, 1100]	1.00[1.00, 1.00]	0.855	–	–
Perioperative medications					
Inotropic agents (n, %)	27(38.0)	0.24[0.05, 1.181]	0.079	–	–
Vasopressors (n, %)	17(23.9)	5.60[1.55, 20.26]	0.009a	5.20[0.71, 38.15]	0.105
Dexamethasone(mg)	10 [10, 20]	0.97[0.88, 1.07]	0.546	–	
Serum biomarkers				–	–
Presurgical CRP (mg/mL)	3.04[1.20, 10.63]	1.02[0.98, 1.05]	0.411	–	–
Presurgical POSTN (μg/L)	180.2[152.4, 221.2]	1.00[0.99, 1.01]	0.375	–	–
Presurgical myoglobin (μg/L)	31.2[21.6, 45.5]	1.00[0.99, 1.01]	0.860	–	–
Presurgical TnI (μg/L)	0.03[0, 0.33]	1.01[0.89, 1.13]	0.940	–	–
Presurgical BNP (pg/L)	500[129.9, 1205.0]	1.00[1.00, 1.00]	0.090	–	–
Postsurgical POSTN (μg/L)	169.3[135.3, 228.6]	1.01[1.00, 1.01]	0.080	–	–
Postsurgical myoglobin (μg/L)	143.9[106.8, 265.7]	1.00[1.00, 1.01]	0.014[a]	1.00[0.97, 1.03]	0.817
Postsurgical TnI (μg/L)	0.56[0.23, 1.13]	1.13[1.01, 1.27]	0.036[a]	1.21[0.92, 1.59]	0.167
Postsurgical BNP (pg/L)	883.3[399.5, 1383.0]	1.00[1.00, 1.00]	0.026[a]	1.00[1.00, 1.00]	0.454
Changes in biomarkers					
Deltas for POSTN	−10.0[−31.8, 13.8]	1.04[1.02, 1.06]	<0.001[a]	1.04[1.01, 1.06]	0.005[b]
Deltas for myoglobin	116.6[70.4, 226.1]	1.00[1.00, 1.01]	0.016[a]	1.00[0.98, 1.03]	0.767
Deltas for TnI	0.35[0.08, 0.94]	1.09[1.00, 1.19]	0.056	–	–
Deltas for BNP	263.8[−34.1, 716.0]	1.00[1.00, 1.00]	0.416	–	–

Notes: The results are presented as the means±SDs, medians (p25, p75) and numbers (%). OR: odds ratio; CI: confidence interval; Univariate predictors with P values<0.05 were included in the multivariable model. [a]Univariate analysis revealed that the history of perioperative vasopressors, postmyoglobin, postTnI, postBNP, deltas for POSTN, and deltas for myoglobin were significantly correlated with MACEs. (P <0.05). [b]Multivariate analysis revealed that only the change in the serum periostin concentration was independently correlated with MACEs (P <0.05). Bold numbers indicate P <0.05.

Abbreviations: NYHA, New York Heart Association class; CAD, coronary artery disease; ACS, acute coronary syndrome; MI, myocardial infarction; LVEF, Left ventricular ejection fractions; CI, confidence interval; OR, odds ratio; CRP, C-reactive protein; POSTN, periostin; TnI, troponin I; BNP, brain natriuretic peptide.

ROC Analysis for Predicting MACEs

Accurate prediction and assessment of MACEs in patients with CAD undergoing OPCAB surgery are essential for implementing appropriate therapeutic interventions. The ROC analysis discovered four reliable predictor factors for MACE occurrence: post-myoglobin, post-BNP, changes in periostin (ΔPOSTN), and changes in myoglobin (Δmyoglobin), as depicted in Table 3. Among these, ΔPOSTN demonstrated the highest predictive performance, with an area under the ROC curve (AUC) of 0.869 [95% CI: 0.768, 0.938; $P < 0.001$]. The ROC analysis, using the Youden index (= 0.683), established an optimal cutoff value of 16.6 μg/L for ΔPOSTN, with sensitivity of 76.9% and specificity of 91.4%, as depicted in Table 3. The potential of a combined predictive model, incorporating multiple variables, was also analyzed. This model used logistic regression with post-myoglobin, post-BNP, changes in ΔPOSTN, and changes in Δmyoglobin as independent variables and MACEs as the binary dependent variable (Table 3). The combined model demonstrated superior performance compared to individual predictors, achieving an AUC of 0.881 [95% CI: 0.782, 0.946; $P < 0.001$], as depicted in Figure 2.

Additionally, ROC analysis was conducted for traditional predictor factors of MACE occurrence, including NYHA classification, preoperative LVEF, and the number of diseased vessels, as depicted in Figure 3. ΔPOSTN again exhibited the highest predictive performance. Furthermore, a second combined predictive model (combined variable 2) was established using logistic regression with NYHA classification, preoperative LVEF, the number of diseased vessels, and ΔPOSTN as independent variables, and MACEs as the binary dependent variable. This combined model

Table 3 ROC analysis for Serum Biomarkers

	AUC	95% CI	Standard Error	P value	Optimal Cut-off	Youden index J	Sensitivity (%)	Specificity (%)
Variable(s)								
Post-myoglobin	0.736	[0.618, 0.834]	0.091	**0.010**	236.6	0.485	69.2	79.3
Post-TnI	0.644	[0.521, 0.754]	0.095	0.129	-	0.349	-	-
Post-BNP	0.682	[0.560, 0.787]	0.082	**0.026**	1080	0.322	61.5	70.7
Deltas for POSTN	0.869	[0.768, 0.938]	0.076	**<0.001**	16.6	0.683	76.9	91.4
Deltas for myoglobin	0.721	[0.602, 0.821]	0.091	**0.016**	173.3	0.511	76.9	74.1
NYHA	0.560	[0.437, 0.677]	0.083	0.470	-	-	-	-
No. Of diseased vessels	0.540	[0.417, 0.659]	0.072	0.578	-	-	-	-
Preoperative LVEF	0.518	[0.396, 0.638]	0.101	0.518	-	-	-	-
Combine Variables								
Post-myoglobin+Post-BNP+ Deltas for POSTN+Deltas for myoglobin	**0.881**	[0.782, 0.946]	0.066	**<0.001**	0.26	0.718	76.9	94.8
NYHA+No. Of diseased vessels +preoperative LVEF+Deltas for POSTN	0.879	[0.780, 0.956]	0.075	**<0.001**	0.23	0.760	84.6	91.38
Pairwise comparison								
Post-myoglobin vs Deltas for POSTN	-	[−0.097, 0.363]	0.117	0.256[a]	-	-	-	-
Post-proBNP vs Deltas for POSTN	-	[0.023, 0.352]	0.084	0.026[b]	-	-	-	-
Post-TnI vs Deltas for POSTN	-	[0.017, 0.434]	0.106	0.034[c]	-	-	-	-

Notes: Pairwise comparison of ROC curves were conducted using DeLong test. [a]There was no statistically significant difference between post-myoglobin and deltas for POSTN in ROC curves. [b]There was a statistically significant difference between post-proBNP and deltas for POSTN in ROC curves (P<0.05). [c]There was a statistically significant difference between post-TnI and deltas for POSTN in ROC curves.(P<0.05). Bold numbers indicate P <0.05.

Abbreviations: ROC, receiver operating characteristic; TnI, troponin I; BNP, brain natriuretic peptide; POSTN, periostin; NYHA, New York Heart Association class; AUC, Area under the receiver operating characteristic curve; LVEF, Left ventricular ejection fractions.

demonstrated enhanced performance compared to individual predictors, with an AUC of 0.879 [95% CI: 0.780, 0.945; $P < 0.001$], as depicted in Figure 3.

Subgroup Analysis Among the LPC Group and HPC Group

Based on the optimal cutoff value of 16.6 μg/L, the study population was categorized into two subgroups for further analysis: 56 patients were classified into the LPC group, and 15 patients were classified into the HPC group, as depicted in Table 4.

Table 4 depicts the incidence of 30-day MACEs within these subgroups. The recorded events included 2 cases of cardiac death (2.8%), 5 cases of MI (7.0%), 5 cases of heart failure (7.0%), and 1 case of stroke (1.4%). The incidence of MACEs in the HPC group was significantly higher compared to that in the LPC group (66.7% vs 5.4%; $P < 0.001$). Additionally, the incidence of MI was notably greater in the HPC group (33.3% vs 0%; $P < 0.01$). However, no significant differences were observed between the groups concerning the incidence of cardiac death, heart failure, or stroke.

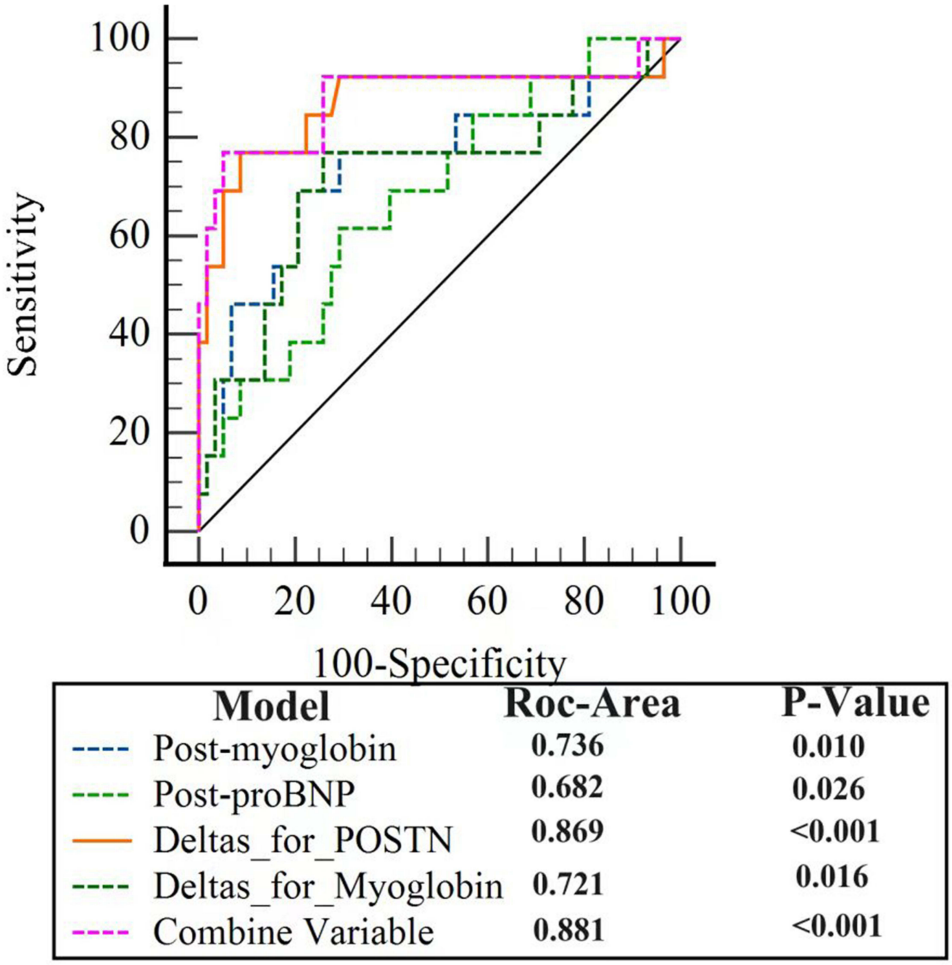

Figure 2 Receiver operating characteristic (ROC) curve analyses for predicting major adverse cardiovascular events (MACEs): Model A (blue): includes post-myoglobin levels. Model B (green): includes post-proBNP levels. Model C (Orange): includes deltas for POSTN. Model D (green): includes deltas for myoglobin. Model E (pink): includes the most predictive variables, comprising post-myoglobin, post-proBNP, deltas for POSTN, and deltas for myoglobin.

A Cox regression model was used to indicate prognostic factors, as depicted in Table 5. After adjusting for demographic characteristics like age, sex, and BMI, a significant increase in the risk of MACEs following OPCAB surgery was observed in patients with high changes in serum periostin (HPC) compared to those who were unexposed to such changes (HR: 10.37, 95% CI: 2.78–38.62; $P < 0.001$). When accounting for risk factors, including previous MI, hypertension, diabetes, and preoperative LVEF, the risk of MACEs remained significantly elevated in the HPC group (HR: 9.89, 95% CI: 2.54–38.57; $P < 0.001$). Further adjustments for clinical characteristics like NYHA classification, the number of diseased vessels, and the number of bypassed vessels also indicated a significantly increased risk (HR: 11.87, 95% CI: 3.10–45.54; $P < 0.001$). After controlling for the history of clinical medications, including the use of vasopressors and inotropes, both preoperatively and perioperatively, the risk of MACEs in the HPC group remained significantly higher (HR: 8.31, 95% CI: 2.00–34.61; $P < 0.001$). Finally, when adjusting for inflammation-related factors like preoperative CRP levels and perioperative dexamethasone use, the increased risk persisted (HR: 11.08, 95% CI: 2.83–43.31; $P < 0.001$). These findings propose that an elevation in serum periostin levels exceeding 16.6 μg/L during the perioperative period is associated with a substantial increase in the likelihood of MACEs in the postoperative period.

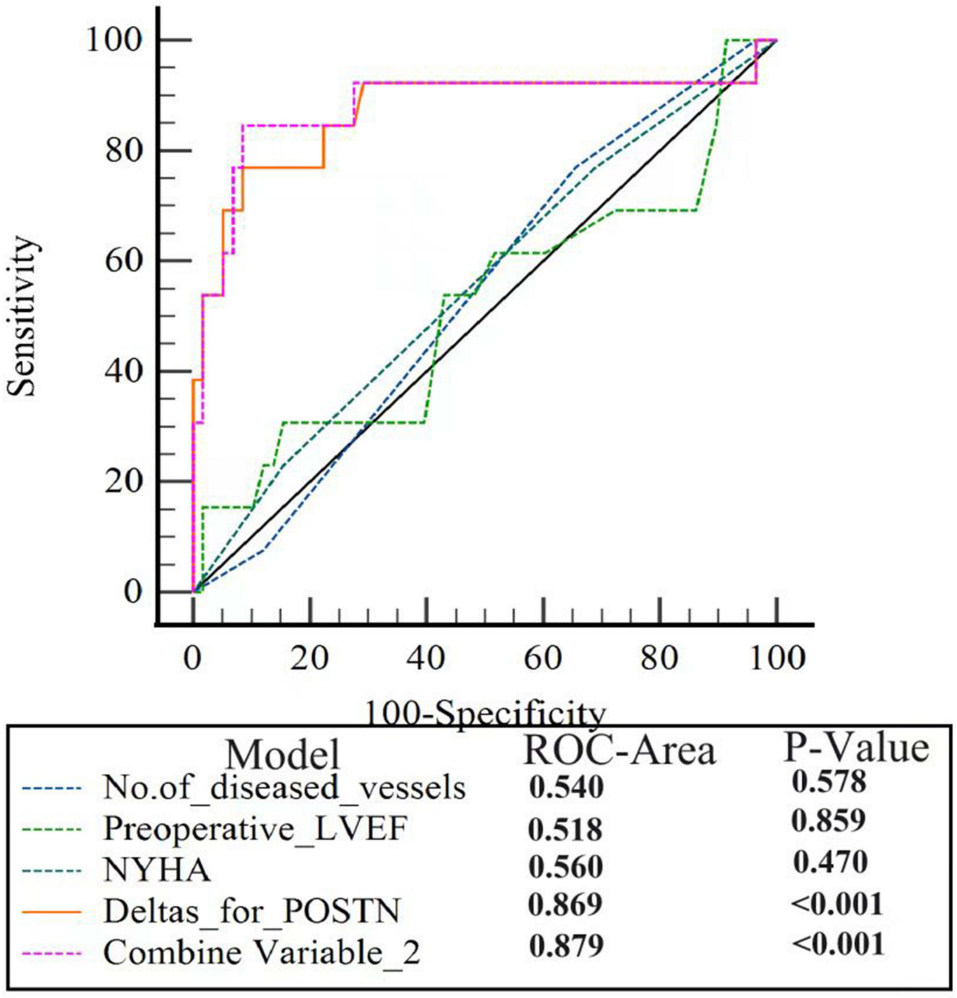

Figure 3 Receiver operating characteristic curve (ROC) analyses for the prediction of Major adverse cardiovascular events (MACEs).

The Expression of POSTN in CAD Samples

We download two datasets from the GEO database, including GSE66360 and GSE42148. The Combined Datasets included 62 CAD samples and 61 Control samples (Supplementary Table 1). The Expression of POSTN in CAD samples was higher than that in control samples (as shown in Supplementary Figure 1).

Table 4 Incidence of MACEs Among the Subgroups

Variables	Total (n = 71)	LPC group (n = 56)	HPC group (n = 15)	Statistic	P value
MACEs, n(%)	13(18.3)	3(5.4)	10(66.7)	–	<0.001[a]
Heart failure, n(%)	5 (7.0)	2 (3.6)	3 (20.00)	χ^2=2.69	0.101
Stroke, n(%)	1 (1.4)	0 (0.00)	1 (6.7)	–	0.211
Myocardial infarction, n(%)	5 (7.0)	0 (0.00)	5 (33.3)	χ^2=15.31	<0.001[a]
Cardiac death, n(%)	2 (2.8)	1 (1.8)	1 (6.7)	–	0.380
30 day mortality, n(%)	2 (2.8)	1 (1.8)	1 (6.7)	–	0.380

Notes: Results are presented as number (%) [95% confidence interval for %]. [a]Two-group comparisons were conducted via Fisher's Test. Bold numbers indicate P <0.05.
Abbreviations: MACEs, major adverse cardiovascular events; LPC, Low POSTN Change; HPC, High POSTN Change.

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Table 5 Multivariable COX Regression About POSTN Subgroups and MACEs

Category	Models	HR[95% CI]	P value
MACEs	Crude model	10.37[2.78, 38.62]	**<0.001**
	Model 1[a]	9.89[2.54, 38.57]	**<0.001**
	Model 2[b]	11.87[3.10, 45.54]	**<0.001**
	Model 3[c]	10.39[2.73, 39.51]	**<0.001**
	Model 4[d]	8.31[2.00, 34.61]	**0.004**
	Model 5[e]	11.08 [2.83, 43.31]	**<0.001**

Notes: Crude model: unadjusted model; Exposure variable: POSTN subgroups (LPC group and HPC group). [a]Model 1 was adjusted for demographic features, including age, gender and Body mass index. [b]Model 2 was adjusted for risk factors, including previous myocardial infarction, hypertension, diabetes and preoperative Left ventricular ejection fractions. [c]Model 3 was adjusted for clinical characteristics, including New York Heart Association class, the number of diseased vessels, and the number of bypassed vessels. [d]Model 4 was adjusted for the history of clinical medications, including vasopressors and inotropes, both preoperative and perioperative. [e]Model 5 was adjusted for Inflammation-related factors: preoperative C-reactive protein levels and perioperative dexamethasone use. Bold numbers indicate P <0.05.

Abbreviations: COX, proportional hazards model; POSTN, periostin; HR, hazard ratio; MACEs, major adverse cardiovascular events; LPC, Low POSTN Change; HPC, High POSTN Change.

Gene Set Enrichment Analysis (GSEA) for Coronary Heart Disease

The results showed that all genes in the combined datasets were significantly enriched in the apoptosis-related network and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) Signaling pathways (Supplementary Table 2). These data suggested that POSTN deficiency resulted in the activation of apoptosis-related network and NF-κB signaling pathways.

The results of GSVA showed that epithelial mesenchymal transition was statistically significant in the Low Expression group and the High Expression group ($p < 0.001$, Supplementary Table 3). Signatures representative of epithelial mesenchymal were enriched in High Expression group ($p < 0.001$, Supplementary Figure 2). Furthermore, glycolysis, angiogenesis and TGF beta signaling were statistically significant in Low Expression group and High Expression group ($p < 0.05$).

Discussion

In this study, the incidence of MACEs within 30 days following OPCAB surgery was 18.3%, which is higher than the rates reported in recent studies within the same field.[24,25] Several factors may account for this discrepancy. Notably, this study included a higher proportion of patients with NYHA heart function classification III–IV (72.3% vs 16–33.8%) compared to other studies, and these patients are known to have an elevated risk of MACEs.[26] Additionally, the duration of surgery in this study was longer than in other OPCAB studies.[24,25] Prolonged surgical time is associated with extended myocardial tissue ischemia and increased systemic inflammation, both of which are recognized as having potentially adverse effects on patient outcomes.[7]

In a previous in vitro study, it was demonstrated that POSTN may be upregulated, contributing to the exacerbation of NLRP3 inflammasome-mediated pyroptosis in myocardial ischemia and reperfusion injury. Knockdown of the POSTN gene effectively inhibited NLRP3 inflammasome activation.[16] However, in the current study, the administration of dexamethasone during surgery in all selected patients may have inhibited the anticipated increase in POSTN levels. This inhibition is likely due to the known role of dexamethasone in modulating inflammation by reducing the expression of inflammatory factors like IL-1, IL-6, and IL-13.[27–29] Future research should consider randomized controlled trials that include both dexamethasone and non-dexamethasone groups to strengthen the conclusions drawn from this study.

In the current study, univariate analysis discovered six variables as significant predictors of MACEs: history of perioperative vasopressor use, post-operative myoglobin, post-TnI, post-BNP, myoglobin deltas, and POSTN deltas. Notably, when these factors were further assessed through multivariate analysis, the predictive performance of POSTN

deltas remained unaffected by other serum biomarkers, underscoring its potential as an independent predictor of MACEs in patients with CAD. These results indicate that serum POSTN levels may serve as valuable biomarkers for forecasting the risk of MACEs, consistent with findings from prior studies.[13,18] In this research, POSTN deltas exhibited superior predictive capability for composite MACE events following OPCAB surgery when compared to other traditional serum biomarkers.

We compared periostin deltas with other risk prediction factors for MACEs. These traditional factors demonstrated AUC values ranging from 0.682–0.736; however, their limited specificity reduces their clinical use. In contrast, POSTN is primarily quantified using the ELISA, a method that is straightforward, efficient, and offers rapid detection. This makes it particularly suitable for early post-operative detection following OPCAB surgery, enabling the timely identification of patients at high risk for developing MACEs. Furthermore, our study indicated that a combined model incorporating post-operative myoglobin, post-operative BNP, periostin deltas, and myoglobin deltas as independent variables demonstrated superior specificity compared to the individual predictive contributions of each variable. Additionally, a combined model including NYHA classification, the number of diseased vessels, preoperative LVEF, and periostin deltas revealed enhanced sensitivity over the individual variables.[15,16] Previous studies has suggested that it would also be useful to monitor anti-thrombotic therapy in the peri-operative period.[30,31] These findings indicate that for more accurate clinical predictions of MACE, changes in serum periostin should be assessed along with traditional predictors and other serum biomarkers. Several factors contribute to the increased predictive value of periostin concentration changes for MACEs. First, in the chronic phase of CAD, the upregulation of THBS1, TGFB2, and HGF gene expression leads to the overexpression of periostin, modulating the GSK3β and cyclin D1 signaling pathways, which ultimately promote myocardial fibrosis and left ventricular remodeling.[32] Additionally, improper surgical techniques or perioperative events can cause excessive stretching of cardiomyocytes and activation of the angiotensin II system, further increasing periostin expression in cardiac myocytes and fibroblasts.[33] Moreover, POSTN levels are significantly increased following coronary artery ligation, a process mediated by IL-13 signaling.[18]

The mechanisms underlying the elevation of serum POSTN levels may potentially counteract the dexamethasone-induced inhibition of IL-6 signaling, thereby contributing to the onset of cardiac interstitial fibrosis.[34] This fibrosis has been linked to adverse postoperative outcomes, including cardiomyocyte death, cardiac dysfunction, and heart failure, as indicated by numerous studies.[35–37] Our findings align with this perspective, as patients within the HPC group presented with a greater number of diseased vessels, a higher incidence of previous MI, and more frequent use of vasoactive drugs during surgery. These observations could be attributed to the more severe preoperative myocardial injury and compromised cardiac function observed in this group.

The GSEA further corroborated these findings by showing significant enrichment in apoptosis-related networks and NF-kB survival signaling pathways, which are crucial in the inflammatory response and cell survival mechanisms in CAD.[38] Previous studies have focused on the role of monocytes and macrophages in the progression of CAD, and this study further supplements the potential role of NK cells in the inflammatory microenvironment of CAD.[39,40] This conclusion differs from previous literature, which did not find this relationship.[41]

This study possesses two key strengths. First, it achieved a notably low patient dropout rate (0%) during the follow-up period, coupled with strict inclusion criteria that ensured a homogeneous study population. Second, the potential for testing changes in POSTN levels through blood samples presents a convenient and advantageous approach for clinical application and further advancement.However, this study is not without limitations. First, there was no dynamic monitoring of inflammatory markers or cardiac function post-OPCAB surgery, which could have provided a more comprehensive understanding of patient outcomes. Cardiac function assessment after surgery is not included in the statistics due to a significant amount of missing data, which may introduce substantial bias. Therefore, it was excluded from the analysis. Our study is both prospective and retrospective, and future studies should incorporate cardiac function assessment as an important diagnostic indicator. Second, the administration of dexamethasone to 66 participants (93%) as a prophylactic measure against protamine allergy may have confounded the observation of significant increases in POSTN expression, despite the lack of a substantial impact on the overall results. Third, the single-center nature of this study, coupled with the relatively small patient group, limited the ability to assess individual MACE complications in detail, though it was adequate

for assessing cumulative MACE outcomes. Future research should involve larger, randomized, controlled studies to address these limitations.

Conclusion

In conclusion, changes in serum periostin levels serve as an independent predictor of major cardiovascular outcomes within 30 days following OPCAB surgery, providing valuable prognostic insights into left ventricular performance. These results enhance the understanding of the role of periostin in AMI complications. However, given the limitations and relatively small sample size of this single-center study, caution is warranted in interpreting these findings. To substantiate these results, future research should include multicenter, randomized controlled trials with larger groups. Additionally, incorporating postoperative LVEF into future studies will provide a more comprehensive assessment of the relationship between periostin levels and cardiac function restoration.

Abbreviations

MACEs, major adverse cardiovascular events; POSTN, periostin; HPC, High POSTN Change; LPC, Low POSTN Change; OPCAB, off-pump coronary artery bypass grafting surgery; cTnI, cardiac troponin I; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting surgery; CAD, coronary artery disease; ACS, acute coronary syndrome; ELISA, enzyme-linked immunosorbent assay; AMI, acute myocardial infarction; MI, myocardial infarction; ACC, American College of Cardiology; AHA, American Heart Association; ROC, receiver operating characteristic; AUC, Area under the receiver operating characteristic curve; ECG, electrocardiogram; chest CT, computed tomography of the chest; NYHA, New York Heart Association class; LVEF, Left ventricular ejection fractions; Pre-, preoperative; Post-, postoperative; NLRP3, Nucleotide- binding oligomerization domain, leucine- rich repeat and pyrin domain- containing 3; THBS1, thrombospondin 1; TGFB2, transforming growth factor, β 2; HGF, hepatocyte growth factor; GSK3β, glycogen synthase kinase-3β; IL-13, Interleukin-13; IL-6, Interleukin-6; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval; BMI, Body mass index.

Data Sharing Statement

Data are available on request to the corresponding authors.

Ethics Approval and Consent to Participate

The original study was approved by the Ethical Committee of Affiliated Hospital 2 of Nantong University (Reference: 2020KT030). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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