

Relationship of Pentraxin-3 and Suppression of Tumourigenicity 2 with Myocardial Injury in Non-Cardiac Surgery

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ABSTRACT

Introduction: Myocardial injury after non-cardiac surgery (MINS) is a prevalent complication. It is caused by both cardiac and non-cardiac pathophysiological mechanisms. Previous studies have identified pentraxin-3 (PTX-3) and suppression of tumourigenicity 2 (ST2) as potential biomarkers associated with myocardial injury. This study is designed to evaluate the role of PTX-3 and ST2 in predicting early MINS.

Methods: This prospective observational cohort study involved patients who were deemed to be at moderate to high-risk of undergoing non-cardiac surgery. In patients with normal preoperative hs-cTnT levels, MINS was defined as a pattern of increase and/or decrease, in high-sensitivity cardiac troponin T (hs-cTnT) levels at 24 and 72 hours postoperatively. Patients without a significant change in hs-cTnT levels pre- and postoperatively were considered MINS-negative. Preoperative PTX-3 and ST2 biomarker levels were compared between MINS-positive and MINS-negative groups.

Results: The study population comprised 340 patients, of whom 79 (23.24%) were classified as MINS-positive and 261 (76.76%) as MINS-negative. PTX-3 levels were significantly higher in the MINS-positive group than in the MINS-negative group (0.24 ± 0.11 vs. 0.021 ± 0.06 , $p=0.007$). There was no significant difference in the level of ST2 between the two groups of patients.

Conclusion: Elevated PTX-3 levels in the MINS-positive group suggest that this biomarker may serve as a valuable predictor of myocardial injury.

Keywords: Myocardial injury, non-cardiac surgery, biomarkers

Introduction

Despite advancements in surgical techniques and close postoperative patient monitoring, the morbidity and mortality rates in patients undergoing non-cardiac surgery remain high worldwide. Cardiovascular complications are the most prevalent cause of morbidity and mortality, with myocardial infarction (MI) being the leading cause of mortality within the initial 30 days post-surgery (1). This has led to the introduction of the term “myocardial injury after non-cardiac surgery” (MINS). MINS is a condition characterized by myocardial injury caused by both cardiac and non-cardiac pathophysiological mechanisms (2). MINS is often sub-clinical (3), which underscores the importance of early diagnosis and investigation of the underlying causes of MINS to aid in its prevention.

Developing predictive markers for MINS in non-cardiac surgery could play a critical role in improving its management and outcomes.

Pentaxin-3 (PTX-3) is a multimeric acute-phase inflammatory glycoprotein that is synthesized in response to primary inflammatory signals; it has been implicated in the pathophysiology of atherosclerosis and other cardiovascular events (4). PTX-3 is expressed in endothelial cells under pro-inflammatory and pro-coagulant conditions (5). Similarly, suppression of tumourigenicity 2 (ST2), an interleukin-1 receptor family member, has emerged as a biomarker. There are two isoforms of ST2: a transmembrane receptor (ST2L) and a soluble receptor (sST2). The release of sST2 is triggered by heart failure, cardiac injury and stressful environments, making it relevant in cardiovascular assessment (6,7).



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This study aims to evaluate whether biomarkers PTX-3 and sST2 are associated with MINS in medium- and high-risk non-cardiac surgery patients.

Methods

Study Population

The calculation was made of the minimum number of patients required for an effect size of 0.2, in conjunction with a 90% power analysis. In this observational and prospective study, 340 patients who underwent non-cardiac surgery at medium and/or high-risk, and did not have postoperative symptoms of myocardial ischemia, were included. Ethical approval was obtained from the Ethics Committee for Non-Invasive Clinical Research, Faculty of Medicine, Zonguldak Bülent Ecevit University (approval number: 2021/14, date: 28.07.2021). Between October 1, 2021, and October 1, 2022, a total of 340 patients aged over 40 years who underwent medium- and/or high-risk non-cardiac surgery at Zonguldak Bülent Ecevit University Health Practice and Research Center were enrolled after providing informed consent. The classification of surgeries as medium- or high-risk was based on the European Society of Cardiology guidelines on “cardiovascular assessment and management in non-cardiac surgery” (8). The study flowchart, detailing the inclusion and exclusion criteria, is presented in Figure 1.

High-sensitivity cardiac troponin T (hs-cTnT) levels were measured preoperatively and at 24 and 72 hours postoperatively. A 12-lead electrocardiogram (ECG) was performed in patients with a post-operative pattern of increase or decrease in hs-cTnT levels. Echocardiography was

performed to rule out wall motion abnormalities if the post-operative ECG showed changes from the preoperative ECG. Patients were classified as “MINS positive” if they had evidence of myocardial injury, but no ECG findings or symptoms of ischaemia. Conversely, patients with normal hs-cTnT levels at all time points (preoperatively and at 24 and 72 hours postoperatively) were classified as MINS-negative.

Sample Collection and Biomarker Analysis

Preoperative demographics, risk factors, comorbidities, medical history, medications, laboratory parameters, and perioperative data were recorded for all patients. Peripheral venous blood samples (5 mL) were collected on admission to hospital and placed in EDTA-coated vacuum tubes. The samples were immediately centrifuged at 3000 rpm for 15 minutes. The serum was separated and stored at -70 °C until analysis.

Serum levels of PTX-3 (SEK411Hu, Cloud-Clone Corp., Katy, Texas, USA) and sST2 (SED171Hu, Cloud-Clone Corp., Katy, Texas, USA) were measured using ELISA kits according to the manufacturer's protocol. The minimum detectable concentration for PTX-3 was 6000-9375 pg/mL, with intra- and inter-assay coefficients of variation of <10% and <12%, respectively. For sST2, the minimum detectable concentration was 0.156-10 ng/mL, with intra- and inter-assay coefficients of variation of <10% and <12%, respectively.

Myocardial injury was defined as an increase in hs-cTnT above the 99th percentile upper reference limit (URL) within 24 hours of surgery. Non-ischemic causes of elevated hs-cTnT such as atrial fibrillation (AF), pulmonary embolism, sepsis, or chronically high baseline values were excluded.

Definition of MINS

MINS is primarily ischemic in nature. However, the classic symptoms associated with MI, such as chest pain or shortness of breath, can often be obscured during the perioperative period due to the effects of sedation and analgesia. As a result, typical signs of myocardial ischemia might not manifest clearly on an ECG. MINS is defined as an elevation in the levels of hs-cTnI above the 99th percentile URL, accompanied by a dynamic pattern of rise and/or fall. While most cases occur within the first 72 hours after non-cardiac surgery, MINS can develop up to 30 days postoperatively. It is essential to distinguish MINS from other non-ischemic causes of myocardial injury, such as pulmonary thromboembolism, sepsis, AF, acute decompensated congestive heart failure, renal failure, and cardioversion. These causes are excluded from its definition.

Statistical Analysis

All statistical analyses were performed using SPSS software version 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Normality of data distribution was assessed using both visual and analytical methods. Descriptive statistics are presented as means $\pm$ standard deviations for normally distributed variables and as medians with interquartile ranges for variables that are not normally distributed. Categorical variables are expressed numerically as either whole numbers or percentages. A series of comparisons between groups was conducted, with the unpaired Student's t-test utilized for normally distributed continuous variables, the

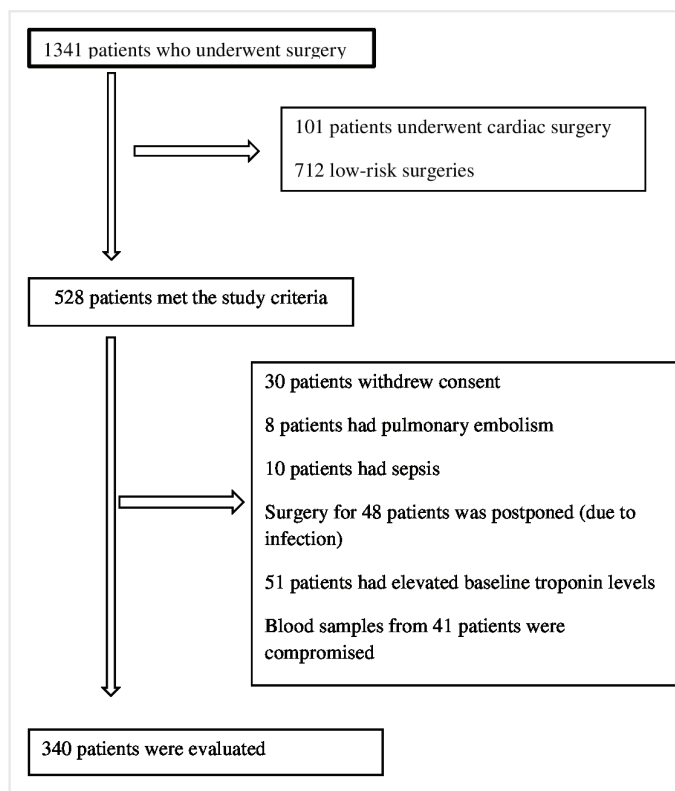


Figure 1. Inclusion criteria for the study population

Mann-Whitney U test employed for non-normally distributed variables, and the chi-squared test applied to categorical variables. Independent predictors of myocardial injury were determined using univariate and multivariate logistic regression analyses, and 95% confidence intervals (CI) and odds ratios (OR) were shown. As the cut-off values for PTX-3 and C-reactive protein (CRP) vary in the literature due to different methods and kits, the values obtained from the receiver operating characteristics (ROC) analysis were used to stratify the study population into four groups using a 2 x 2 approach. The ability of these groups to predict myocardial injury was analyzed using the low CRP/low PTX-3 group as the reference category. p-values of <0.05 were considered statistically significant.

Results

Baseline Characteristics

All study participants were classified, of whom 79 (23.24%) were as MINS (+) and 261 (76.76%) as MINS (-). There were no statistically significant differences between the two groups in terms of sex, age, BMI, comorbidities (e.g., hypertension, diabetes mellitus) or medication use ($p > 0.05$ for all, Table 1).

Laboratory Findings

Postoperative laboratory analysis revealed significantly higher PTX-3 levels in the MINS (+) group compared to the MINS (-) group (0.24 ± 0.11 vs. 0.021 ± 0.06 , $p = 0.007$). Similarly, CRP levels were elevated in the MINS (+) group (23.5 ± 39.1 vs. 15.8 ± 26.5 , $p = 0.047$). However, no significant differences were observed for other biomarkers, such as sST2 ($p = 0.202$, Table 2).

Perioperative Characteristics

Perioperative data demonstrated a higher prevalence of emergency surgery in the MINS (+) group (19% vs. 9.2%, $p = 0.017$), a higher prevalence of use of general anesthesia (91.1% vs. 79.7%, $p = 0.019$), and higher ASA scores (12.7% vs. 8.0%, $p = 0.038$). A revised cardiac risk index (RCRI) > 3 was also significantly more common in the MINS (+) group (15.2% vs. 5.7%, $p < 0.001$).

Perioperative complications including hypotension (46.8% vs. 33.3%, $p = 0.029$), bradycardia (25.3% vs. 13%, $p = 0.009$), hypoxia (10.1% vs. 2.7%, $p = 0.005$) and vasopressor requirement (5.1% vs. 1.1%, $p = 0.032$) were significantly more common in the MINS (+) group. In addition, the duration of surgery was longer in the MINS (+) group than in the MINS (-) group (186 ± 95 vs. 159 ± 77 minutes, $p = 0.020$, Table 3).

Predictors of Myocardial Injury

Logistic regression analysis identified CRP ($p = 0.012$), use of general anesthesia ($p = 0.030$), bradycardia ($p = 0.005$), intraoperative hypoxia ($p = 0.016$), and a RCRI score greater than 3 ($p = 0.025$) as independent predictors of myocardial injury. Additionally, PTX-3 levels were found to be an independent predictor of MINS (OR: 1.043; 95% CI: 1.011-1.075; $p = 0.008$) (Table 4).

ROC Analysis for PTX-3 and CRP

ROC curve analysis revealed a cut-off value of 0.21 pg/mL for PTX-3 in predicting myocardial injury, with an area under the curve of 0.734 (95% CI: 0.612-0.856, $p = 0.004$). This cut-off showed a sensitivity of 69.2% and a specificity of 61.7% (Figure 2).

Table 1. Baseline clinical characteristics of patients

	Post-op MINS (-) (n=261; 76.76%)	Post-op MINS (+) (n=79; 23.24%)	p-value
Age (years)	65.95 $\pm$ 11.2	67.58 $\pm$ 11.48	0.295
Male n (%)	123 (47.1)	40 (50.6)	0.585
BMI (kg/m ²)	29.56 $\pm$ 6.44	29.49 $\pm$ 6.24	0.938
Baseline SKB (mmHg)	127.6 $\pm$ 63.3	125.9 $\pm$ 17.1	0.440
Baseline DKB (mmHg)	74.3 $\pm$ 11.1	72.9 $\pm$ 10.2	0.218
Baseline HR (beats/min)	79.7 $\pm$ 11.8	80.1 $\pm$ 12.8	0.794
Smoking, n (%)	48 (18.4)	15 (19.0)	0.905
HT, n (%)	178 (68.2)	49 (62.0)	0.307
DM, n (%)	95 (36.4)	31 (39.2)	0.647
HL, n (%)	54 (20.7)	18 (22.8)	0.690
COPD, n (%)	49 (18.8)	16 (20.3)	0.770
Medical treatment			
OAC, n (%)	24 (9.2)	6 (7.6)	0.660
Antiplatelet agent, n (%)	68 (26.1)	26 (32.9)	0.232
Beta blocker, n (%)	67 (25.7)	17 (21.5)	0.454
ACEi/ARB, n (%)	53 (20.3)	16 (20.3)	0.992

MINS: Myocardial injury after non-cardiac surgery, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, COPD: Chronic obstructive pulmonary disease, ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blockers

Table 2. Laboratory variables of patients

	Post-op MINS (-) (n=261; 76.76%)	Post-op MINS (+) (n=79; 23.24%)	p-value
Creatinine (mg/dL)	0.88 $\pm$ 0.36	0.85 $\pm$ 0.28	0.517
LDL (mg/dL)	101.2 $\pm$ 34.7	105.6 $\pm$ 36.7	0.328
HDL (mg/dL)	43.1 $\pm$ 12.5	43.5 $\pm$ 13.7	0.940
Triglycerides (mg/dL)	150.6 $\pm$ 80.2	153.0 $\pm$ 106.3	0.742
Total cholesterol (mg/dL)	174.6 $\pm$ 42.2	179.9 $\pm$ 42.2	0.433
Glucose (mg/dL)	119.7 $\pm$ 40.5	127.7 $\pm$ 38.9	0.135
WBC (10 ³ /μL)	8.37 $\pm$ 2.55	8.92 $\pm$ 2.47	0.091
Hgb (g/dL)	11.86 $\pm$ 1.88	11.97 $\pm$ 1.74	0.633
Plt (10 ³ /μL)	263.1 $\pm$ 102.9	245.7 $\pm$ 84.3	0.173
N/L ratio	5.23 $\pm$ 4.47	6.45 $\pm$ 8.2	0.090
MPV (fL)	8.86 $\pm$ 1.04	8.78 $\pm$ 0.97	0.218
ALT	19.2 $\pm$ 16.7	23.7 $\pm$ 61.1	0.290
PTX-3 (pg/mL)	0.021 $\pm$ 0.06	0.24 $\pm$ 0.11	0.007
CRP (mg/dL)	15.8 $\pm$ 26.5	23.5 $\pm$ 39.1	0.047
sST2 (ng/mL)	3.45 $\pm$ 1.67	3.72 $\pm$ 1.62	0.202

MINS: Myocardial injury after non-cardiac surgery, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, Hgb: Hemoglobin, N/L: Neutrophil/lymphocyte ratio, MPV: Mean platelet volume, ALT: Alanine aminotransferase, PTX-3: Pentraxin-3, CRP: C-reactive protein, sST2: Soluble ST2

Patients were further stratified according to PTX-3 and CRP levels. Compared to the reference group (low CRP/low PTX-3), the low CRP/high PTX-3 group was associated with an increased risk of myocardial injury (OR: 2.68, 95% CI: 1.30-5.49, $p=0.007$), while the combination of high

CRP and high PTX-3 levels showed the strongest predictive ability (OR: 4.22, 95% CI: 1.99-8.96, $p<0.001$). The high CRP/low PTX-3 group did not reach statistical significance (OR: 2.28, 95% CI: 0.98-4.93, $p=0.054$) (Figure 3).

Table 3. Perioperative characteristics of patients

	Post-op MINS (-) (n=261; 76.76%)	Post-op MINS (+) (n=79; 23.24%)	p-value
Emergency surgery, n (%)	24 (9.2)	15 (19.0)	0.017
Type of anesthesia			0.019
General, n (%)	208 (79.7)	72 (91.1)	
Epidural, n (%)	53 (20.3)	7 (8.9)	
ASA Score, n (%)			0.038
1	14 (5.4)	3 (3.8)	
2	91 (34.9)	15 (19.0)	
3	135 (51.7)	51 (64.6)	
4	21 (8.0)	10 (12.7)	
Func. Mets, n (%)			0.087
<1	29 (11.1)	14 (17.7)	
1-4	75 (28.7)	28 (35.4)	
4-10	157 (60.2)	37 (46.8)	
Revised cardiac risk index, n (%)			<0.001
0-1	205 (78.6)	46 (58.2)	
2	41 (15.7)	21 (26.6)	
>3	15 (5.7)	12 (15.2)	
CAD, n (%)	53 (20.3)	31 (39.2)	0.001
CHF, n (%)	37 (14.2)	19 (24.1)	0.038
CVD, n (%)	31 (11.9)	14 (17.7)	0.179
Receiving insulin therapy, n (%)	66 (25.3)	24 (30.4)	0.369
Creatinine >2 mg/dL, n (%)	23 (8.8)	11 (13.9)	0.185
Type of surgery, n (%)			0.135
Thoracic	5 (1.9)	1 (1.3)	
Orthopedic/neurosurgery	166 (63.6)	45 (57.0)	
Gastrointestinal	25 (9.6)	5 (6.3)	
ENT	12 (4.6)	2 (2.5)	
Gynecology/urology	18 (6.9)	13 (16.5)	
Hepatobiliary	35 (13.4)	13 (16.5)	
Perioperative complications, n (%)			
Hypotension	87 (33.3)	37 (46.8)	0.029
Hypertension	129 (49.4)	40 (50.6)	0.851
Bradycardia	34 (13.0)	20 (25.3)	0.009
Tachycardia	23 (8.8)	13 (16.5)	0.053
Hypoxia	7 (2.7)	8 (10.1)	0.005
Blood loss (mL)	137±231	245±473	0.052
Total transfusion (mL)	2166±1003	2489±1382	0.057
Surgery duration (minutes)	159±77	186±95	0.02
Intraoperative vasopressor use, n (%)	3 (1.1)	4 (5.1)	0.032

MINS: Myocardial injury after non-cardiac surgery, ASA: American Society of Anesthesiologists, Func. Mets: Functional metabolic equivalent (functional capacity), CAD: Coronary artery disease, CHF: Congestive heart failure, CVD: Cerebrovascular disease, ENT: Ear, nose, and throat

Table 4. Predictors of perioperative myocardial injury

Variables	Univariate analysis Odds ratio (CI 95%)	p-value	Multivariate analysis Odds ratio (CI 95%)	p-value
CRP (per 1 mg/dL)	1.006 (1.002-1.022)	0.018	1.011 (1.002-1.019)	0.012
General anesthesia	2.9 (1.105-7.153)	0.019	2.70 (1.10-6.63)	0.030
Bradycardia	2.82 (1.046-4.048)	0.004	2.69 (1.35-5.33)	0.005
Hypoxia	4.11 (1.23-9.35)	0.009	3.99 (1.29-12.34)	0.016
Revised cardiac risk index >3	2.05 (1.006-7.1159)	0.029	2.76 (1.13-6.74)	0.025
Pentraxin-3 x100	1.033 (1.007-2.262)	0.012	1.043 (1.011-1.075)	0.008
DM	1.525 (1.001-3.128)	0.047	1.323 (0.852-3.332)	0.116
CAD	1.496 (0.244-1.728)	0.272		
Emergency surgery	1.946 (0.601-2.504)	0.118		
HT	1.467 (0.840-2.971)	0.056		

CI: Confidence interval, CRP: C-reactive protein, DM: Diabetes mellitus, CAD: Coronary artery disease, HT: Hypertension

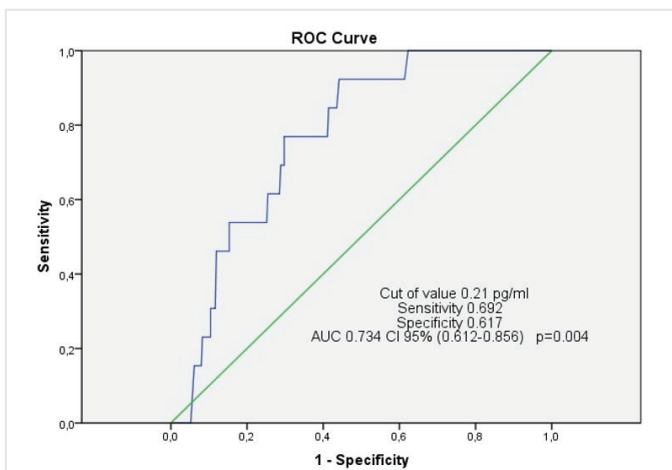


Figure 2. ROC curve demonstrating the discriminative ability of pentraxin-3 levels for myocardial injury
AUC: Area under the ROC curve, CI: Confidence interval, ROC: Receiver operating characteristics

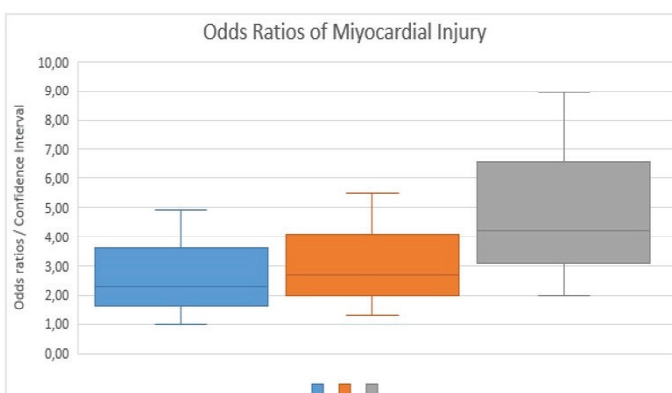


Figure 3. Predictive value of perioperative PTX-3 and CRP levels for myocardial injury
Blue bar: High CRP/Low PTX-3 group, Orange bar: Low CRP/High PTX-3 group, Gray bar: High CRP/High PTX-3 group
CRP: C-reactive protein, PTX-3: Pentraxin-3

Discussion

This observational study investigates the association between MINS and the biomarkers PTX-3 and sT2 in patients undergoing non-cardiac surgery at a medium to high-risk. The results demonstrated that there was a significant increase in PTX-3 levels in patients diagnosed with MINS, suggesting its potential role as a predictive biomarker of perioperative myocardial injury. In contrast, sT2 levels were not significantly different between groups.

MINS is a frequently overlooked postoperative complication associated with significant adverse outcomes, yet it remains largely underdiagnosed due to its asymptomatic nature and the absence of routine screening protocols. Most cases are only detected through elevated hs-cTnT levels. The VISION study provided a critical insight into the burden of MINS, reporting that 17.9% of patients aged 45 years and older who underwent non-cardiac surgery developed MINS, with 93.1% of cases asymptomatic (9). Furthermore, elevated perioperative hs-cTnT levels were strongly associated with increased 30-day mortality, highlighting the importance of systematic postoperative troponin monitoring in high-risk patients (9). These findings have been further validated by large cohort studies, which consistently highlight the prognostic significance of perioperative troponin elevation (3,10).

Despite its high prevalence and prognostic implications, MINS is often unrecognized by traditional clinical assessment and risk scores. While the incidence of acute coronary syndrome requiring revascularization after non-cardiac surgery is less than 0.2% (11), the silent nature of MINS highlights the need for more effective pre- and post-operative risk stratification (2,3,12,13). The current study contributes to this understanding by identifying PTX-3 as a potential biomarker for MINS, providing an additional tool for early detection in patients undergoing moderate- or high-risk surgery.

As an inflammatory biomarker, elevated PTX-3 levels are commonly detected in atherosclerotic lesions, underscoring its potential as a marker of vascular damage (14). Released from endothelial cells during localized vascular inflammation, PTX-3 has emerged as a promising diagnostic tool for acute cardiovascular events. Studies by Matsuura

et al. (15) and Turkmen et al. (16) have shown that PTX-3 levels are significantly higher in atherosclerotic patients and in patients with AMIs, and have linked PTX-3 to systemic inflammation and endothelial dysfunction, key mechanisms in coronary artery disease (CAD) (17). A meta-analysis has also confirmed that elevated levels of PTX-3 are independently associated with an increase in all-cause mortality and cardiac mortality in patients with CAD (18). Similarly, Peri et al. (19) reported significantly higher PTX-3 and CRP levels in AMI patients compared to healthy controls, reinforcing the utility of PTX-3 as a biomarker for cardiovascular risk stratification.

In our study, PTX-3 emerged as an important independent predictor of MINS. Furthermore, high preoperative PTX-3 and CRP levels were strongly associated with myocardial damage, reinforcing their role as valuable biomarkers for identifying high-risk patients. Patients with a history of CAD or heart failure were more likely to develop MINS, which highlights the importance of considering such pre-existing cardiovascular conditions in perioperative risk assessment.

A thorough preoperative cardiovascular risk evaluation may facilitate the identification of patients with an elevated probability of developing MINS. Perioperative risk assessments and PTX-3/CRP values can guide perioperative management and prevent MINS from being underestimated. Patients considered to be at high-risk of MINS may require modifications to their intraoperative care, including the initiation of secondary prophylactic interventions, invasive arterial pressure monitoring, strategies to prevent hypotension, and systematic preoperative and postoperative cTn monitoring. It is hypothesised that improvements in the diagnosis and understanding of MINS will ultimately result in enhanced postoperative outcomes following non-cardiac surgery.

Study Limitations

The present study is subject to several limitations. Because this was conducted as a single-centre study, the results may have limited generalizability, despite the homogeneity of the sample and the use of a standardised surgical protocol. Comparability with other studies is further challenged by variations in the ELISA kits used for biomarker measurements. In addition, PTX-3 levels were measured only once preoperatively, with no follow-up samples to assess postoperative changes that might influence outcomes. Finally, the initial sample size was not fully maintained, and thus the results should be interpreted as preliminary. Larger, multicenter studies with serial measurements of PTX-3 before and after surgery are needed to better elucidate its clinical significance and impact.

Conclusion

The present study's findings suggest that PTX-3 may serve as a valuable biomarker for predicting MINS in patients undergoing non-cardiac surgery. The strong association between elevated preoperative PTX-3 and CRP levels and myocardial injury highlights their potential role in identifying high-risk patients. These results support the need for further studies to evaluate the clinical utility of PTX-3.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee for Non-invasive Clinical Research, Faculty of Medicine, Zonguldak Bülent Ecevit University (approval number: 2021/14, date: 28.07.2021).

Informed Consent: All participants provided informed consent.

Footnotes

Authorship Contributions: Surgical and Medical Practices - F.P.T., B.G.K.; Concept - N.E.G., M.U.S.; Design - N.E.G., M.U.S., B.G.K., M.C.; Data Collection or Processing - F.P.T., B.G.K., M.C., U.K.; Analysis or Interpretation - U.K., İ.E.; Literature Search - F.P.T., N.E.G., M.U.S., B.G.K., U.K., İ.E., M.C.; Writing - F.P.T., N.E.G., M.U.S., İ.E.

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