

# The effect of cardiopulmonary bypass on Maresin-1 levels and implications for cardiac function

Bişar Amaç<sup>1</sup> , Mustafa Abanoz<sup>2</sup> , Mesut Engin<sup>3</sup> 

<sup>1</sup> Harran University, Faculty of Health Sciences, Department of Perfusion, Şanlıurfa, Türkiye

<sup>2</sup> University of Health Sciences, Şanlıurfa Mehmet Akif İnan Training and Research Hospital, Department of Cardiovascular Surgery, Şanlıurfa, Türkiye

<sup>3</sup> University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Cardiovascular Surgery, Bursa, Türkiye

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## Correspondence:

Dr. Bişar AMAÇ

Harran University, Faculty of Health Sciences, Department of Perfusion, Şanlıurfa, Türkiye.

E-mail: amacbisar@gmail.com



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## Abstract

**Aim:** Cardiopulmonary bypass (CPB) surgery causes changes in biomarkers associated with inflammatory responses and cardiac stress. Maresin-1 is a novel lipid mediator involved in inflammation resolution, and its role in cardiac function and its prognostic value postoperatively have not yet been sufficiently investigated. The aim of this study is to investigate the effect of CPB on Maresin-1 levels and to comparatively evaluate the prognostic value of Maresin-1 in the pathophysiology of coronary artery disease.

**Methods:** Eighty patients were included in this study. Maresin-1 levels were investigated in 40 patients before surgery (group 1) and after surgery (group 2). The other 40 individuals included in the study formed the healthy control group. Maresin-1 and NT-proBNP levels were measured in the preoperative and postoperative periods. The data were evaluated comparatively using the Wilcoxon test and ROC analysis.

**Results:** Preoperative Maresin-1 levels were significantly higher than those in the control group ( $p < 0.001$ ). Postoperative Maresin-1 levels decreased markedly ( $p < 0.001$ ); however, no significant difference was detected between postoperative Maresin-1 levels in the control group ( $p = 0.942$ ). ROC analysis demonstrated that Maresin-1 and NT-proBNP possess high discriminatory power in distinguishing patients with coronary artery disease from healthy controls (AUC: 0.918 and 0.923)

**Conclusion:** Maresin-1 levels significantly increase before CPB and decrease significantly in the early post-CPB period, reflecting pathophysiological changes in cardiac function. Maresin-1 can be considered a complementary biomarker with prognostic potential in patients undergoing CPB, compared with NT-proBNP.

**Keywords:** Cardiopulmonary bypass, Maresin-1, coronary artery disease, cardiac pathophysiology, prognostic biomarker

## Introduction

Cardiovascular disease is one of the leading causes of morbidity and mortality globally. The persistence of chronic inflammation and the inadequacy of resolution mechanisms play significant roles in the pathogenesis of these diseases (1). While acute inflammation contributes physiologically to tissue repair and the maintenance of homeostasis, prolonged inflammatory responses increase tissue damage and may lead to adverse clinical outcomes, such as atherosclerosis, myocardial infarction, and cardiac remodelling.

Coronary artery disease and its complications are a remarkable leading cause of death worldwide. Endothelial inflammatory activation and dysfunction are key events in the development and pathophysiology of atherosclerosis and are associated with an increased risk of cardiovascular events. There is considerable interest in better understanding the pathophysiological mechanisms underlying endothelial dysfunction and atherosclerotic progression, and in identifying new biomarkers and therapeutic strategies to prevent endothelial dysfunction and atherosclerosis and reduce the risk of developing coronary artery disease and its complications (2).

In recent years, it has been understood that the resolution process of inflammation is not a passive reversal but an actively regulated process mediated by endogenous chemical mediators. These specific lipid mediators are called specialized pro-resolving mediators and are derived from omega-3 fatty acids. This group includes resolvins, protectins, and maresins, with Maresin-1 in particular playing a critical role in resolving the inflammatory response, enhancing phagocytosis, and supporting tissue repair and organ protection (1,3,4).

Maresin-1 is one of the prominent metabolites of eicosapentaenoic acid, which exhibits various potent anti-inflammatory effects in inflammatory diseases. Maresin-1 has been reported to play an important role as a protective biomarker in cardiovascular diseases. Moreover, Maresin-1 has been reported to increase cyclic adenosine monophosphate levels in vascular endothelial cells and vascular smooth muscle cells, suppressing nuclear factor kappa-B (NF- $\kappa$ B) activation, thereby reducing tumor necrosis factor-alpha (TNF- $\alpha$ )-induced monocyte adhesion and reactive oxygen species (ROS) formation. It has also been demonstrated that, through systemic administration, it prevents vascular re-occlusion by reducing neointima formation triggered by inflammation following vascular injury. Considering that chronic inflammation is a fundamental mechanism in atherosclerosis, Maresin-1 has been shown to limit atherosclerotic plaque progression by suppressing necrosis and macrophage accumulation and increasing the thickness of the fibrous cap in vascular smooth muscle cells. In addition, leucine-rich repeat-containing G protein-coupled receptor 6 regulates macrophage-apoptotic vascular smooth muscle cell interactions via

transforming growth factor-beta 2 (TGF- $\beta$ 2) signalling and suppresses aneurysm growth in abdominal aortic aneurysms. All these findings demonstrate that Maresin-1 plays an important function in the pathophysiology of cardiovascular diseases with both anti-inflammatory and vasculoprotective properties (5).

Experimental studies have demonstrated that Maresin-1 possesses a wide range of protective effects, from stabilizing atherosclerotic plaques and suppressing the progression of abdominal aortic aneurysms to promoting tissue repair after myocardial infarction and reducing cardiac damage associated with sepsis (6-9). However, the role of maresins as biomarkers at the clinical level has not yet been sufficiently elucidated.

Although cardiopulmonary bypass (CPB) is a frequently used intervention in cardiac surgery, it may result in systemic inflammatory response and disrupt of the immunometabolic balance. Understanding the changes in the resolution mediators of inflammation during this process is of great importance in predicting possible complications in the postoperative period (10). One of the most commonly used biomarkers in the assessment of cardiac function today is NT-proBNP. NT-proBNP is widely used in clinical practice as a reliable indicator of cardiac load and hemodynamic stress. However, in recent years, new lipid mediators involved in the resolution phase of inflammation have also been the subject of research. The potential effects of Maresin-1, a member of this class of mediators, on cardiac function remain to be fully understood. In this study, the relationship between Maresin-1 and the assessment of postoperative cardiac function was investigated, while NT-proBNP was also included in the analysis for comparison purposes. Thus, it was aimed to contribute to the literature by evaluating the diagnostic and prognostic power of Maresin-1, a new lipid mediator, together with NT-proBNP, which has proven clinical validity.

For that reason, this prospective study aimed to compare the effect of CPB on Maresin-1 levels in patients undergoing cardiac surgery with a healthy control group and to evaluate changes in Maresin-1 levels in order to understand the pathophysiology of coronary artery disease and assess the predictive role of Maresin-1 in coronary artery disease.

## Materials and Methods

### Ethical approval

This study has been approved by the institution where it was conducted and Harran University Clinical Research Ethics Committee (Date: 13 May 2024, Approval no: HRÜ/24.06.07). The study was conducted in accordance with the principles of the Declaration of Helsinki. Furthermore, informed consent was obtained from all participants in the study.

## Sample size calculation

Sample size was calculated using G\*Power software (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) based on the primary outcome, defined as the within-patient difference in Maresin-1 levels between the preoperative and postoperative periods. With a two-tailed alpha of 0.05, 80% statistical power, and an assumed effect size of  $d_z = 0.65$ , the required sample size was estimated at 21 paired patients. A total of 40 patients were therefore enrolled in the surgical group, and 40 healthy individuals were additionally included as controls, yielding an overall study population of 80 participants.

## Study population

The study included patients who underwent coronary artery bypass graft replacement with CPB and healthy individuals who voluntarily agreed to participate in the study.

## Study groups

A total of 80 individuals were included in the study. Forty of these were in the control group, consisting of healthy volunteers, and the other 40 were in the patient group, consisting of patients undergoing cardiac surgery with CPB. Within the patient group, samples collected before and after CPB were evaluated separately, forming two subgroups:

- **Group 1 (Preoperative Maresin):** Blood samples taken prior to surgery from patients scheduled for coronary artery bypass grafting with CPB.
- **Group 2 (Postoperative Maresin):** Blood samples were taken on the third day after CPB from the same patients in Group 1.
- **Group 3 (Control):** Healthy volunteers with no known medical conditions.

The descriptive data of the groups, including age, gender, height, weight, and body surface area (BSA) data, were evaluated in this study.

## Inclusion and exclusion criteria

Patients undergoing emergency cardiac surgery, patients scheduled for additional cardiac surgery such as aortic aneurysm or dissection, patients undergoing repeat cardiac surgery, patients with known systemic inflammatory disease, patients with chronic liver disease, and patients with chronic kidney disease or on haemodialysis were excluded from the study.

After applying the exclusion criteria, coronary artery disease patients who voluntarily agreed to participate in the study and healthy adults aged 18 to 85 years were included in the study.

## Perfusion method

Standard coronary surgical techniques were applied to all patients. In patients who underwent coronary heart surgery, arterial cannulation was performed from the ascending aorta after median sternotomy, while venous cannulation was performed from the right atrium using a single venous cannula in a two-stage procedure (two-stage venous cannula). The left mammary artery graft was used in all cases. The saphenous vein graft was used for other coronary grafts. Complete revascularization was performed in all patients. Standard extracorporeal circulation systems (heart-lung machine & perfusion techniques) were also used.

## Measurement of biomarkers

Serum Maresin-1 and NT-proBNP levels were measured in the patients. Maresin-1 levels were examined to evaluate their relationship with postoperative cardiac function, whereas NT-proBNP was included in the analysis as a comparison parameter due to its widespread use in clinical practice as a biomarker of cardiac dysfunction and hemodynamic stress.

## Determination of the blood Maresin-1 levels

Blood samples taken from healthy individuals and patients diagnosed with coronary artery disease scheduled for open heart surgery (preoperative and postoperative) for routine procedures were transferred to anticoagulated sterile biochemistry tubes. The samples were centrifuged at 4,000 rpm for 10 minutes. The plasma fraction was transferred to Eppendorf tubes and stored at  $-80^{\circ}\text{C}$  until the day of analysis. On the day of analysis, all Eppendorf tubes containing blood samples were removed from  $-80^{\circ}\text{C}$  and thawed at room temperature.

A ready-to-use ELISA kit (Cat. no: EA0190Hu; BT Lab Systems, St. Louis, MO, USA) was used to determine the blood Maresin-1 level. All ELISA protocols were performed according to the manufacturer's instructions. Results for maresin-1 levels are shown in pg/ml and were considered statistically significant.

## Assessment of postoperative cardiac function

NT-proBNP levels have been used as a biochemical marker to assess postoperative cardiac function. NT-proBNP pg/mL is a sensitive indicator reflecting ventricular wall stress and the risk of cardiac insufficiency (11-13). An increase in NT-proBNP levels during the postoperative period is associated with cardiac overload and ventricular dysfunction.

## Statistical analysis

Patient data collected within the scope of the study were analysed using the IBM Statistical Package for the Social Sciences software (Version 25; IBM Corp., Armonk, NY, USA). The mean and standard deviation were calculated for continuous data. The Kolmogorov-Smirnov test was used to assess the normality of distribution (as the number of participants in each group was greater than 30). To compare the same parameters between the preoperative and postoperative data, the Compare means (Paired-samples t-test) and Nonparametric test (2-related samples> Wilcoxon) were used to evaluate normally and non-normally distributed data, respectively. When comparing the data of the patient group (preoperative and postoperative) with the control group, the independent samples t-test (Student's t-test) was used for variables with normal distribution, while the 2 independent samples test (Mann-Whitney U test) was used for variables without normal distribution. Frequency and percentage analyses were performed for nominal data. A p-value less than 0.05 was considered statistically significant.

## Results

When the demographic data for the patient and control groups participating in the study were examined, the mean age was found to be  $61.0 \pm 8.2$  years in the patient group and  $58.0 \pm 10.0$  years in the control group. No significant difference was found between the groups in terms of height, weight, and BSA values. The gender distribution was similar in both groups; the proportion of women was 40% in the patient group and 45% in the control group. These results indicate that the patient and control groups were comparable in terms of basic demographic characteristics (Table 1).

**Table 1.** Demographic characteristics of the study population.

| Variable              | Patient group<br>(Group 1 & 2) (n=40) | Control group<br>(n=40) |
|-----------------------|---------------------------------------|-------------------------|
| Age (years)           | $61.0 \pm 8.2$                        | $58.0 \pm 10.0$         |
| Height (cm)           | $163.0 \pm 8.0$                       | $169.0 \pm 9.0$         |
| Weight (kg)           | $80.0 \pm 13.0$                       | $81.0 \pm 14.0$         |
| BSA (m <sup>2</sup> ) | $1.80 \pm 0.19$                       | $1.85 \pm 0.18$         |
| Female, n (%)         | 16 (40.0%)                            | 18 (45.0%)              |
| Male, n (%)           | 24 (60.0%)                            | 22 (55.0%)              |

BSA: Body surface area, n: number

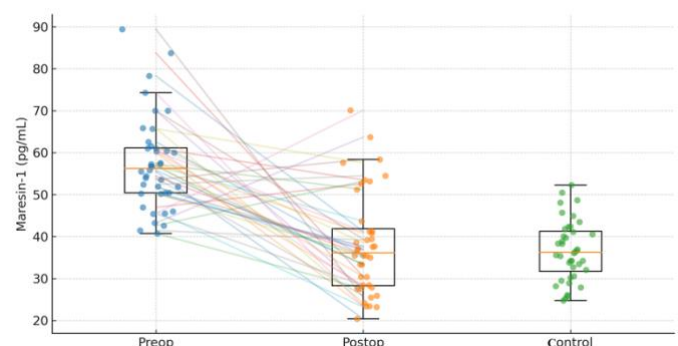
Table 2 presents the descriptive statistics of Maresin-1 and NT-proBNP levels in the preoperative, postoperative, and control groups. Preoperative Maresin-

1 levels (mean  $57.31 \pm 11.09$  pg/mL) were higher than those in the postoperative ( $38.07 \pm 12.23$  pg/mL) and control groups ( $36.65 \pm 7.12$  pg/mL) (Fig. 1). NT-proBNP levels were also highest in the preoperative period ( $160.83 \pm 58.41$  pg/mL), decreased significantly in the postoperative period ( $72.26 \pm 71.37$  pg/mL), and were found to be lowest in the control group ( $23.21 \pm 27.33$  pg/mL). These findings reveal that both Maresin-1 and NT-proBNP levels increased during the preoperative period and then decreased significantly after surgery, approaching levels observed in the control group.

**Table 2.** Maresin-1 and NT-proBNP levels in the preoperative, postoperative, and control groups (n=40).

| Descriptive statistics  |         |         |          |          |
|-------------------------|---------|---------|----------|----------|
|                         | Minimum | Maximum | Mean     | SD       |
| Preop Maresin-1 pg/mL   | 40.80   | 89.40   | 57.3125  | 11.08705 |
| Postop Maresin-1 pg/mL  | 20.40   | 70.10   | 38.0675  | 12.22537 |
| Control Maresin-1 pg/mL | 24.80   | 52.30   | 36.6550  | 7.12446  |
| Preop NT-proBNP pg/mL   | 63.04   | 323.73  | 160.8387 | 58.41081 |
| Postop NT-proBNP pg/mL  | 1.23    | 342.31  | 72.2555  | 71.36681 |
| Control NT-proBNP pg/mL | 0.31    | 98.43   | 23.2110  | 27.32747 |

SD: Standard Deviation



**Figure 1.** Maresin-1: Preoperative - Postoperative matched and Control comparison.

In pairwise comparisons between groups, preoperative maresin levels were found to be significantly higher than those in the control group. No significant difference was found between postoperative maresin levels and the control group. However, postoperative levels were significantly lower compared to preoperative values. This indicates that CPB causes a marked decrease in maresin levels (Table 3).

**Table 3.** Maresin-1 Mann-Whitney U test and Wilcoxon Signed Ranks test.

| Ranks              |                   | N               | Mean rank | Sum of ranks |
|--------------------|-------------------|-----------------|-----------|--------------|
|                    |                   |                 |           |              |
| Maresin-1          | Preop Maresin-1   |                 | 58.95     | 2358.00      |
|                    | Control Maresin-1 |                 | 22.05     | 882.00       |
| Maresin-1          | Preop Maresin-1   |                 | 40.31     | 1612.50      |
|                    | Control Maresin-1 |                 | 40.69     | 1627.50      |
| Postop Maresin-1 - | Negative ranks    | 34 <sup>a</sup> | 22.26     | 757.00       |
|                    | Positive ranks    | 6 <sup>b</sup>  | 10.50     | 63.00        |
| Preop Maresin-1    | Ties              | 0 <sup>c</sup>  |           |              |
|                    | Total             | 40              |           |              |

a: Postop Maresin-1 < Preop Maresin-1; b: Postop Maresin-1 > Preop Maresin-1; c: Postop Maresin-1 = Preop Maresin-1

According to test statistics, a statistically significant difference was found between the preoperative maresin

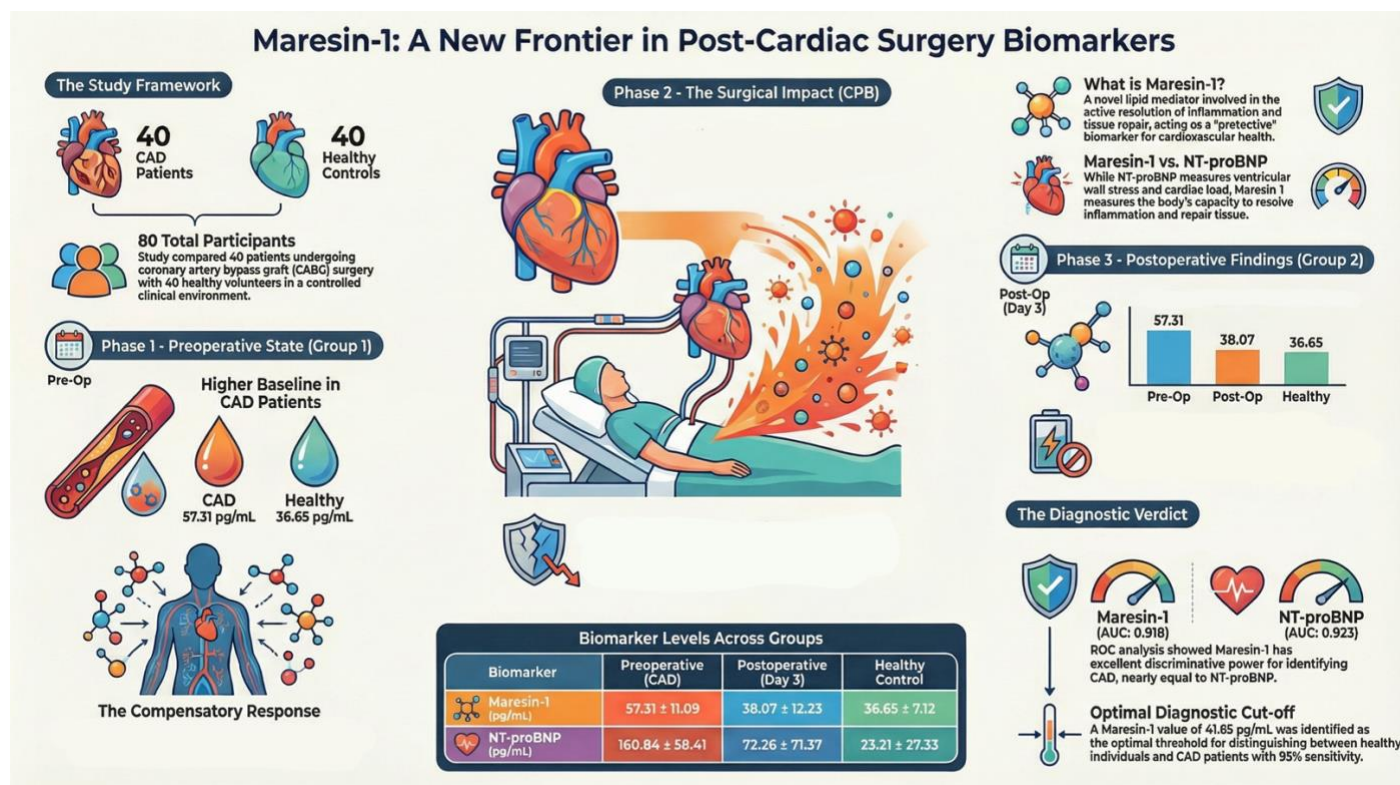
levels and the control group at the  $p < 0.001$  level. No statistically significant difference was found between the postoperative maresin levels and those of the control group ( $p = 0.942$ ). On the other hand, postoperative maresin levels were found to be significantly lower than preoperative values ( $p < 0.001$ ). These findings indicate that maresin levels are markedly suppressed in the early postoperative period (Table 4).

**Table 4.** Intergroup comparison of Maresin-1 levels.

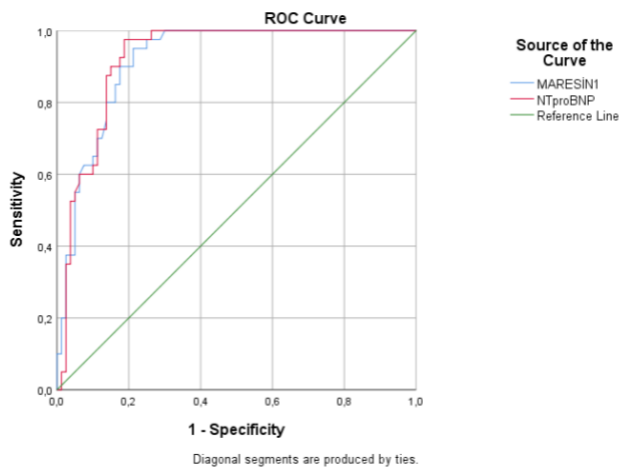
|                 | Preop Maresin-1 - Control Maresin-1 | Postop Maresin-1 - Control Maresin-1 | Postop Maresin-1 - Preop Maresin-1 |
|-----------------|-------------------------------------|--------------------------------------|------------------------------------|
| Test statistics | -7.102                              | -0.072                               | -4.664                             |
| p*              | 0.000 <sup>a</sup>                  | 0.942 <sup>a</sup>                   | 0.000 <sup>b</sup>                 |

<sup>a</sup>: Mann-Whitney U Test, <sup>b</sup>: Wilcoxon Signed Ranks Test.

A graphical illustration of the study is shown in Figure 2. It was enhanced with the assistance of Google NotebookLM Pro (Google, San Francisco, CA, USA).

**Figure 2.** Graphical illustration of the study (Enhanced with the assistance of Google NotebookLM Pro).

ROC analysis was performed to evaluate the diagnostic performance of Maresin-1 and NT-proBNP in distinguishing patients with coronary artery disease from healthy controls. The AUC value for Maresin-1 was 0.918 (95% CI: 0.871-0.966,  $p < 0.001$ ), while that for NT-proBNP was 0.923 (95% CI: 0.875-0.970,  $p < 0.001$ ), indicating excellent discriminative ability for both biomarkers. At the optimal cut-off value of 41.65, Maresin-1 demonstrated high sensitivity (95%) with adequate specificity, whereas NT-proBNP showed perfect sensitivity (100%) with moderate specificity at a cut-off value of 12.05 (Fig. 3).



**Figure 3.** Evaluation and comparison of the diagnostic discrimination of Maresin-1 and NT-proBNP using ROC analysis.

## Discussion

In this study, Maresin-1 levels were examined in coronary artery bypass graft patients undergoing CPB and compared with a healthy control group. According to our findings, patients' maresin levels were significantly higher than those of the control group in the preoperative period. This suggests that chronic inflammatory processes and resolution responses play an active role in the pathophysiology of coronary artery disease. The literature reports that maresins are key mediators in inflammation resolution and tissue repair. The increase in preoperative levels may indicate that the organism has developed a compensatory response to chronic inflammation. However, a significant decrease in maresin levels was observed in the postoperative period. The systemic inflammatory response triggered by CPB, oxidative stress, and reperfusion injury may have suppressed maresin production. The absence of a significant difference in postoperative maresin levels between our study and the control group indicates that patients' anti-inflammatory reserves are weakened in the early postoperative period. This finding supports the adverse effects of CPB on immunometabolic balance. Similarly, some previous studies have indicated that CPB suppresses resolution mediators of inflammation and

may be associated with postoperative complications (14). Statistical analyses also confirm these observations. Wilcoxon tests showed that preoperative maresin levels were higher than in the control group, but this advantage was lost in the postoperative period, and levels fell significantly compared to preoperative values. These results suggest that maresin levels may be a sensitive biomarker for CPB and play an important role, particularly in the assessment of the perioperative inflammatory response. The most significant contribution of our study is the comparative demonstration of dynamic changes in maresin levels before and after CPB. In this context, maresins can be evaluated not only as mediators of inflammation resolution but also as biochemical indicators of the postoperative recovery process. Investigating the relationship between the decline in the postoperative period and clinical outcomes may reveal the prognostic value of maresins. A similar study in the literature also demonstrates that CPB causes significant changes in inflammatory mediators. Hanbeyoglu et al. (15) reported that Maresin-1 levels were significantly higher in healthy controls than in CPB patients and decreased progressively, especially in the early stages of the surgical process (T1-T3). Similarly, in our study, Maresin-1 levels were higher in the preoperative period than in healthy controls, but a significant decrease was observed on the third day after CPB. When the results of both studies are considered together, it can be said that CABG suppresses Maresin-1 production, which may be related to the systemic inflammatory response. However, the Maresin-1 levels detected in our study, which were higher than those in the control group in the preoperative period, may reflect a compensatory response to the resolution of chronic inflammation in coronary artery disease. From this perspective, the results of these two studies, conducted with different patient populations and timing, support the notion that Maresin-1 may be a sensitive biomarker in both coronary artery disease and inflammatory processes associated with CPB (15). The immunological changes that occur during CPB develop as a result of complex mechanisms triggered by surgical trauma, ischemia-reperfusion injury, and extracorporeal circulation. The literature reports that CPB causes transient immunodeficiency by affecting both innate and acquired immune components, particularly in relation to T lymphocyte dysfunction and decreased T cell receptor expression. It has been suggested that during this process, myeloid suppressor cells increase arginase-1 (Arg-1) activity, thereby accelerating L-arginine (L-Arg) consumption, which leads to decreased CD3ζ chain expression in T lymphocytes, suppression of proliferative responses, and ultimately a weakened immune response. In our study, we also found that Maresin-1, one of the inflammation resolution mediators, was significantly reduced in the postoperative period in patients undergoing CPB. When these findings are considered together, it is thought that CPB may predispose to postoperative complications by suppressing both immune cell function and the inflammation resolution process, and that the decrease

in Maresin-1 levels may be related to these immunological mechanisms (16). In our study, Maresin-1 levels were found to be  $57.3 \pm 11.0$  pg/mL on average in the preoperative period, decreasing significantly to  $38.0 \pm 12.2$  pg/mL in the postoperative period. These values are noteworthy when compared to the average of  $36.7 \pm 7.1$  pg/mL in the healthy control group. The higher Maresin-1 levels observed in patients compared to the control group, particularly in the preoperative period, may reflect a compensatory response to the resolution of the inflammatory burden associated with chronic coronary artery disease. In contrast, the decrease in these levels to levels similar to those in the control group in the postoperative period indicates that CPB suppresses the capacity for inflammation resolution, leading to a decrease in anti-inflammatory mediators. This finding is consistent with previous reports suggesting that CPB may increase the inflammatory response by disrupting immunological balance and suppressing resolution mediators. Biochemical markers play a clinically significant role in assessing postoperative cardiac function. NT-proBNP levels reflect ventricular wall stress and the risk of cardiac insufficiency. An increase in NT-proBNP is generally associated with cardiac overload and ventricular dysfunction (17). The findings obtained in this study revealed that Maresin-1 levels were significantly suppressed in the postoperative period. NT-proBNP levels, as indicated in the literature, were consistent with the changes predicted as a reliable biomarker of cardiac dysfunction and haemodynamic stress. The primary reason for including NT-proBNP in the study was to comparatively evaluate Maresin-1, a novel lipid mediator, with a clinically validated biomarker. This allowed the diagnostic and prognostic potential of Maresin-1 to be tested against current clinical standards. Our findings suggest that Maresin-1 has the capacity to reflect changes in cardiac function in a manner similar to NT-proBNP but may exert its effects through different biological mechanisms. From this perspective, it is concluded that Maresin-1 could contribute to clinical practice as a complementary biomarker to NT-proBNP in the assessment of cardiac function.

## Limitations

This study has several limitations. A major limitation of this study is that it was conducted at a single center. Multicenter studies with larger sample sizes are needed to validate the findings of this study, and the inclusion of additional data would provide more comprehensive results.

## Conclusion

This study revealed changes in Maresin-1 levels in patients undergoing CPB. According to our findings, Maresin-1 levels in patients were higher than those in healthy controls during the preoperative period;

however, these levels decreased significantly after surgery, falling to levels similar to those in the control group. This suggests the presence of a compensatory response aimed at resolving chronic inflammation associated with coronary artery disease, but that CPB suppresses this response by triggering systemic inflammatory processes. Consequently, it was concluded that changes in Maresin-1 levels may have clinical value as a potential biomarker for both understanding the pathophysiology of coronary artery disease and evaluating the inflammatory response associated with CPB.

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## Disclosures

**Ethical Approval:** This study has been approved by the institution where the study was conducted and the local ethics committee (Harran University Clinical Research Ethics Committee). The study was conducted in accordance with the principles of the Declaration of Helsinki. Furthermore, informed consent was obtained from all participants in the study (Date: 13 May 2024, Approval no: HRÜ/24.06.07).

**Use of AI-Assisted Technologies in Visualization:** During the preparation of this manuscript, the author(s) utilized Google NotebookLM Pro to enhance Figure 2, the graphical representation of the study. The underlying data, context, and prompts input into the tool were solely provided by the authors and derived from the original research. The author(s) have rigorously reviewed and verified the enhanced visual for scientific accuracy and take full responsibility for the integrity of the final published figure.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - B.A., M.A., M.E.; Design - B.A., M.A., M.E.; Supervision - B.A., M.A., M.E.; Materials - B.A., M.A., M.E.; Data collection &/or processing - B.A., M.A., M.E.; Analysis and/or interpretation - B.A., M.A., M.E.; Literature search - B.A., M.A., M.E.; Writing - B.A.; Critical review - B.A., M.A., M.E.

**Conflict of Interest:** The authors declare that they have no competing interests.

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