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# The Role of Serum Resolvin D1 Levels in Determining the Presence and Prognosis of ST-Segment Elevation Myocardial Infarction

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**Highlights of the Study**

- Serum resolvin D1 levels are lower in patients with ST-segment elevation myocardial infarction compared to individuals with normal coronary arteries.
- Serum resolvin D1 levels are significantly associated with poor angiographic and echocardiographic parameters such as Thrombolysis in Myocardial Infarction thrombus grade and left ventricular ejection fraction.
- Serum resolvin D1 levels are negatively correlated with hs-CRP, pro-BNP, and peak troponin I level.

**Keywords**
Resolvin D1 · ST-segment elevation myocardial infarction · Inflammation · Thrombus grade

**Abstract**

***Background:*** Resolvin D1 (RvD1) can play a determining role in inflammatory cell migration and reduce the expression of inflammatory cytokines to enhance cardioprotection. The aim of this study was to compare serum RvD1 levels in patients with ST-segment elevation myocardial infarction (STEMI) and individuals with normal coronary arteries (NCAs) and to evaluate the association between serum RvD1 levels and prognostic markers of STEMI. ***Methods:*** 140 subjects (88 patients diagnosed with the indication of STEMI and 52 healthy individuals with NCA) were studied. ***Results:*** Regression analysis revealed that RvD1 levels were independently associated with STEMI. While RvD1 levels were negatively correlated with high-sensitivity C-reactive protein, pro-brain natriuretic peptide, peak troponin, and Thrombolysis in Myocardial Infarction thrombus grade, they were positively correlated with left ventricular ejection fraction. An RvD1 cut-off value of 5.07 (ng/mL) was effective in predicting STEMI with a sensitivity of 79.5% and specificity of 96.2%. ***Conclusion:*** Serum RvD1 levels were found to be lower in the group with STEMI compared to the control group. Levels of RvD1 at admission were associated with poor prognostic markers of STEMI.



## Introduction

Acute myocardial infarction (MI) is one of the leading factors that cause morbidity and mortality all around the world [1]. Inflammation is known to be an initiative process in the development of atherosclerosis, in addition to playing an inducing role in atherosclerosis plaque destabilization [2, 3]. ST-segment elevation myocardial infarction (STEMI) is triggered by the formation of an intracoronary thrombus, which results from the rupture or erosion of the atherosclerotic coronary plaque and by the

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incorporation of thrombogenic core and matrix materials, exposing the plaque content to the circulation. Inflammation and thrombosis interact significantly with each other during this pathophysiological process. Moreover, as indicated by numerous clinical studies, high intracoronary thrombus burden occurring in the peri-procedural period may result in major complications, including stent thrombosis, MI, and even mortality [4–6].

The D-series resolvins, with pro-resolution anti-inflammatory effects, are biosynthesized endogenously from the omega-3 polyunsaturated fatty acid (PUFA) and docosahexaenoic acid (DHA) as a response to injury or infection [7]. DHA is converted to D-series resolvin both by acetylated cyclooxygenase-2 (COX-2) and by 5-lipoxygenase (5-LOX) or by using cytochrome P-450 microbial and 15-lipoxygenase through a COX-independent pathway [8]. Resolvin D1 (RvD1) stimulates intracellular signaling by using receptors coupled with protein G (GPR32 and ALX receptors), which are expressed on endothelial cells and monocytes [9]. In vivo and in vitro studies have demonstrated that signaling through these receptors may result in atheroprotection and plaque stability [10, 11]. Resolvins of D and E series were shown to have pro-resolution characteristics, via the inhibition of migration of neutrophils and dendritic cells, observed especially in tissues experiencing hypoxia and inflammation. Apart from enhancing the purge of phagocytosis and apoptotic cells, the resolvins serve as substances that help fight inflammation by downregulating pro-inflammatory cytokines [9, 12]. The pro-resolving role of RvD1 has been studied in many systems including metabolic diseases and infections [13–15].

Inflammation is a prominent factor causing acute coronary syndrome, and pro-resolving lipid mediators such as RvD1 have been used to induce cardioprotection by limiting inflammation in animal models; however, this association has not been reported in patients diagnosed with acute coronary syndrome. In this context, our study aimed to investigate serum RvD1 levels in patients with STEMI and individuals with normal coronary arteries (NCAs) and to evaluate the association between serum RvD1 and prognostic markers of STEMI.

## Materials and Methods

This cross-sectional, single-center study was conducted between December 2021 and March 2022 at Yozgat City Hospital, Yozgat, Turkey. After the approval of the study protocol by the Bozok University Ethics Committee, Yozgat, Turkey, we obtained written informed consent from each patient.

*Study Population*

We included consecutive patients who were diagnosed with STEMI and treated with primary percutaneous coronary intervention (PCI) as the "STEMI group" and consecutive individuals with NCAs who were scheduled for elective coronary angiography as the "control group." Patients who were admitted to the emergency department with typical myocardial ischemia symptoms and whose electrocardiography exhibited ST-segment elevation in two consecutive derivations with reciprocal ST-segment changes were diagnosed with STEMI. The Third Universal Definition of Myocardial Infarction document was used to diagnose MI [16]. Patients in the control group were referred for coronary angiography according to the anginal symptoms and noninvasive stress test results. The exclusion criteria were patients who reported to the clinic more than 3 h after the emergence of symptoms; those with a diagnosis of non-STEMI, unstable angina, myocarditis, pericarditis, and Tako-Tsubo syndrome; those with a previous history of stable coronary artery disease (CAD); those diagnosed with decompensated heart failure, diseases related to kidney and liver, autoimmunity disorders, malignancy, any hematological symptoms, severe valvular disorders, or diseases characterized by chronic inflammation and infection.

*Laboratory Measurements*

We obtained blood samples from the median cubital vein by applying atraumatic puncture during the phase of diagnosis, before sending the patients to the cardiac catheterization laboratory. We used the centrifugation technique for separating the serum at 4,000 rpm for 10 min and stored the serum samples at –80°C until conducting analysis, besides checking the blood count variables by using the automated cell counters (Beckman Coulter LH 750; Beckman Coulter Inc., USA). Levels of troponin I, high-sensitivity C-reactive protein (hs-CRP), total cholesterol, triglyceride, creatinine, and low-high-density lipoprotein cholesterol were estimated in an automated analyzer (Beckman Coulter Inc.). Serial troponin measurements were done every 6 h in patients with STEMI to detect the peak troponin level. A single troponin level was measured in the control patients, Afterward, we measured serum RvD1 levels using a sandwich ELISA technique (SunRed Biotechnology Company, Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China). Based on our preliminary data, we determined the intra-assay and inter-assay coefficients of variability for RvD1 as 10.0% and 12%, respectively. All patients underwent a bedside transthoracic echocardiography in the emergency room to exclude a type A aortic dissection. Standard transthoracic echocardiography was performed in all participants 24 h after the PCI by using a transducer 3.5-MHz (Vivid 7; GE-Vingmed Ultrasound AS, Horten, Norway); we used Simpson's rule for calculating the left ventricular ejection fraction (LVEF).

*Angiographic Analysis*

Selective coronary angiography was performed using the Standard Judkins technique and Siemens Axiom Sensis XP device (Munich, Germany), after which quantitative analysis was done by recording all coronary angiographic images to establish cause-effect relationships among variables. We followed the PCI procedures within the scope of the clinical practice guidelines by using iopromide, a low osmolar, nonionic X-ray contrast agent used for intravascular administration. Later, we applied a 600 mg loading dose of clopidogrel or 180 mg ticagrelor and 300 mg acetylsalicylic acid

**Table 1.** Baseline characteristics and laboratory parameters of the study groups

| Variables | STEMI group (*n* = 88) | Control group (*n* = 52) | *p* value |
|---|---|---|---|
| Baseline characteristics | | | |
| Age, years, mean±SD | 60.8±10.6 | 55.1±9.5 | 0.002 |
| Gender, male, *n* (%) | 72 (81.8) | 26 (50) | <0.001 |
| Diabetes mellitus, *n* (%) | 23 (26.1) | 13 (25) | 0.882 |
| Hypertension, *n* (%) | 32 (36.4) | 22 (42.3) | 0.485 |
| Dyslipidemia, *n* (%) | 32 (36.4) | 18 (34.6) | 0.835 |
| Smoking status, *n* (%) | 63 (71.6) | 20 (38.5) | <0.001 |
| Family history of CAD, *n* (%) | 13 (14.8) | 2 (3.8) | 0.043 |
| LVEF, %, median (IQR) | 42 (38.5–47.5) | 60 (59.2–62) | <0.001 |
| Laboratory parameters | | | |
| Urea, mg/dL, median (IQR) | 36 (28–44) | 34 (27–43) | 0.320 |
| HDL-C, mg/dL, median (IQR) | 42 (35–46.5) | 45 (38.2–51.7) | 0.014 |
| LDL-C, mg/dL, median (IQR) | 127 (103.7–151) | 122 (90.7–133.7) | 0.065 |
| Triglyceride, mg/dL, median (IQR) | 103 (67–149.2) | 126 (99.5–188.5) | 0.011 |
| Total cholesterol, mg/dL, median (IQR) | 192 (160.2–218.7) | 196 (165.5–223.5) | 0.357 |
| WBC count, $\times 10^3$/μL, median (IQR) | 10.9 (8.6–13) | 7.9 (6.7–8.9) | <0.001 |
| Neutrophil count, $\times 10^3$/μL, median (IQR) | 8.8 (6.4–10.1) | 5.2 (3.9–5.7) | <0.001 |
| Lymphocyte count, $\times 10^3$/μL, median (IQR) | 1.5 (1.1–2.1) | 2.1 (1.6–2.6) | <0.001 |
| Hemoglobin, g/dL, median (IQR) | 14.3 (12.9–15.1) | 14.2 (12.5–15.1) | 0.578 |
| Hematocrit, %, mean±SD | 40.3±4.6 | 39.8±4.3 | 0.491 |
| Platelet count, $\times 10^3$/μL, median (IQR) | 223 (198–284) | 246 (212–290) | 0.183 |
| High-sensitivity CRP, mg/L, median (IQR) | 0.44 (0.32–0.78) | 0.3 (0.2–0.52) | 0.001 |
| Pro-BNP, ng/mL, median (IQR) | 231 (113–940) | 70 (70–71.7) | <0.001 |
| Peak troponin I, ng/L, median (IQR) | 24,909 (15,892–26,495) | 5 (8–12) | <0.001 |
| RvD1, ng/mL, median (IQR) | 3.18 (2.72–4.11) | 6.75 (6.05–8.98) | <0.001 |

BNP, brain natriuretic peptide; CAD, coronary artery disease; CRP, C-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; WBC, white blood cell.

to patients with an emergency diagnosis of STEMI before the intervention. After administering a bolus of 70 IU/kg of unfractionated heparin during the PCI procedure, the operator was left free to inhibit the platelet glycoprotein IIb/IIIa receptor by using tirofiban. Digital angiograms were examined by two independent experienced interventional cardiologists who were unfamiliar with the study. Intracoronary thrombus load was determined by the thrombus burden classification in addition to Thrombolysis in Myocardial Infarction (TIMI) after antegrade flow was achieved through balloon dilatation or a safe guidewire passage. As a result, interventional cardiologists did not detect any discrepancies regarding the outcomes of TIMI thrombus grading.

*Statistical Analysis*

Statistical analyses were conducted using SPSS software, version 22.0, for Windows (SPSS Inc., Chicago, IL, USA) while using the Kolmogorov-Smirnov test to analyze the variables on distribution patterns. While categorical variables were demonstrated using percentages and ratios, continuous variables are shown as mean ± standard deviations or as medians with the interquartile range, based on distribution patterns. Along with comparing nonparametric continuous variables by the Mann-Whitney U test, categorical variables were evaluated using Fisher's exact tests or Pearson's $\chi^2$. We evaluated the correlation between TIMI thrombus grade and RvD1 levels by using Spearman's correlation analysis. As for the analysis of multivariate regression, the variables with a $p < 0.05$ in univariate analysis were investigated through the logistic regression analysis to detect the independent predictors of STEMI. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. We used the analysis of the receiver operating characteristic curve to determine the optimal cut-point value of RvD1 levels in predicting STEMI and to evaluate the finding concerning specificity and sensitivity. Thus, a two-sided *p* value <0.05 was considered significant.

## Results

This study encompassed 140 patients, consisting of 88 patients showing the symptoms of STEMI and 52 individuals with NCA. Clinical characteristics and laboratory parameters of the patients with STEMI and control groups are presented in Table 1. Patients in the control group were younger than those in the group with STEMI

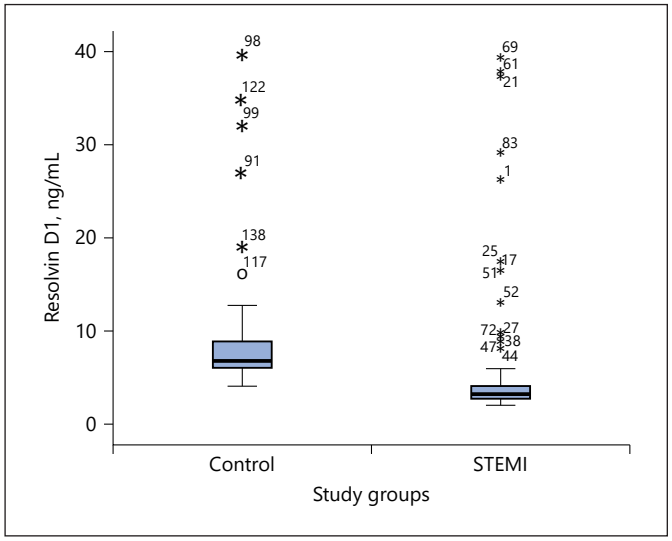


**Fig. 1.** Comparison of serum RvD1 levels of the study groups.

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**Table 2.** Spearman correlation analysis between RvD1 and laboratory parameters

| Variables | *r* | *p* value |
|---|---|---|
| High-sensitivity CRP, mg/L | −0.173 | 0.041 |
| Pro-BNP, ng/mL | −0.445 | <0.001 |
| Peak troponin I, ng/L | −0.481 | <0.001 |
| LVEF, % | 0.486 | <0.001 |
| TIMI thrombus grade | −0.347 | 0.001 |
| WBC | −0.231 | 0.006 |
| Neutrophil | −0.260 | 0.002 |

BNP, brain natriuretic peptide; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; *r*, correlation coefficient; TIMI, Thrombolysis in Myocardial Infarction.

($p = 0.002$). The rates of male patient ratio, family history of CAD, and tobacco use were significantly higher in the group with STEMI ($p < 0.05$). We detected no statistically significant differences in terms of hypertension, diabetes mellitus, and dyslipidemia between the two groups ($p > 0.05$). Additionally, we identified the results of the two groups as showing a statistically significant difference in the LVEF recorded 24 h after the PCI (42 [38.5–47.5] vs. 60 [59.2–62]; $p < 0.001$). Additionally, total white blood cell (WBC), neutrophil and lymphocyte counts, hs-CRP, pro-brain natriuretic peptide (pro-BNP), and peak troponin I were significantly higher in the STEMI group than in the control group (Table 1). Moreover, the serum RvD1 levels were significantly different between the two groups (3.18 [2.72–4.11] vs. 6.75 [6.05–8.98]; $p < 0.001$; Fig. 1).

Correlation analysis revealed that RvD1 levels presented a significant negative correlation with TIMI thrombus grade ($r = -0.347$, $p < 0.001$). Additionally, RvD1 levels negatively correlated with hs-CRP, pro-BNP, and peak troponin I levels (Table 2).

Factors considered significant in univariate analyses were evaluated within the multivariate logistic regression model to detect independent predictors of STEMI. It was observed that RvD1 was independently associated with the presence of STEMI. Furthermore, we observed that values of pro-BNP and neutrophil count served as independent predictors of STEMI (Table 3).

Investigation of the discriminative ability of the RvD1 levels in diagnosing STEMI with the receiver operating characteristic curve showed that the area under the curve was 0.852 (95% confidence interval: 0.784–0.921; $p < 0.001$). We detected an optimal intersection for Youden's index (J = max [Sensitivity + Specificity−1]) and an RvD1 level of 5.07 (ng/mL). A diagnosis of STEMI was predicted with a sensitivity of 79.5% and specificity of 96.2% (Fig. 2).

## Discussion

This study indicates that serum levels of RvD1 in the STEMI group were significantly lower compared to the levels in the control group. Additionally, RvD1 levels were negatively correlated with TIMI thrombus grade. We suggest that RvD1 could serve as a strong and independent predictor of STEMI.

RvD1 is derived from DHA metabolite via the regulation of enzymes involved in inflammation, such as COX-2 and 5-LOX, whereas its anti-inflammatory properties and cardioprotective outcomes consist of two different units [8]. While the former is related to the NF-κB pathway, the latter may involve the phosphoinositide 3 (PI3)-kinase pathway. RvD1 was shown to reduce inflammation in a lipopolysaccharide-induced model through a mechanism involving the inhibition of the peroxisome proliferator-activated receptor gamma/NF-κB pathway [17]. RvD1 was reported to reduce infarct size by activating the PI3-kinase/protein kinase B mechanism and neutrophil accumulation in the ischemic myocardium [18]. Thul et al. [19] demonstrated that the ratio of different lipid mediators (RvD1/leukotriene $B_4$) with opposing ef-

**Table 3.** Univariate and multivariate logistic regression analysis showing the independent predictors for the STEMI

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| Age | 1.055 (1.019–1.093) | 0.003 | | |
| Male gender | 4.500 (2.089–9.694) | <0.001 | | |
| Smoking | 4.032 (1.951–8.331) | <0.001 | | |
| WBC | 1.467 (1.249–1.724) | <0.001 | | |
| Neutrophil | 1.927 (1.525–2.436) | <0.001 | 1.720 (1.032–2.867) | 0.038 |
| Lymphocyte | 0.680 (0.480–0.963) | 0.03 | | |
| HDL | 0.954 (0.918–0.991) | 0.015 | | |
| hs-CRP | 2.139 (0.991–4.615) | 0.053 | | |
| Pro-BNP | 1.010 (1.005–1.016) | <0.001 | 1.009 (1.002–1.017) | 0.013 |
| RvD1 | 0.940 (0.896–0.988) | 0.014 | 0.901 (0.820–0.990) | 0.030 |

BNP, brain natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; OR, odds ratio; WBC, white blood cell.

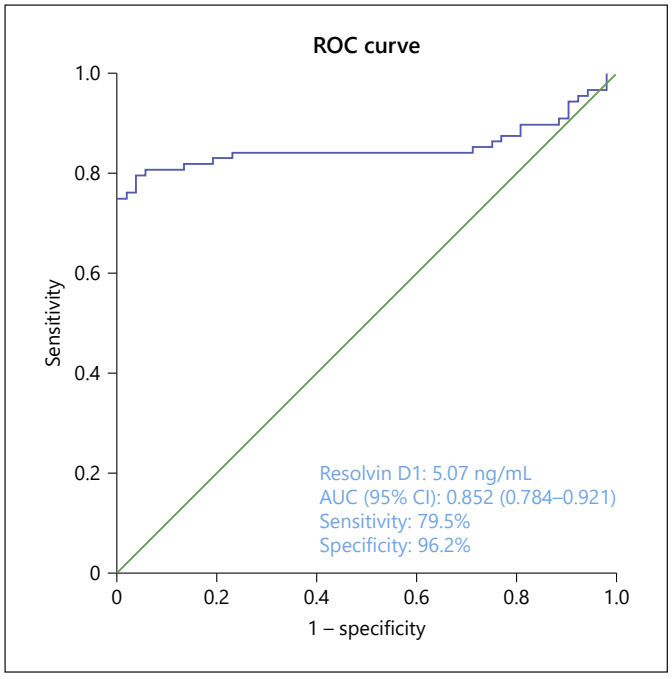


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**Fig. 2.** Receiver operating characteristic (ROC) curve analysis of RvD1 for the identification of ST-segment elevation myocardial infarction (STEMI).

fects on vascular inflammation may predict subclinical atherosclerosis.

Resolution of post-MI inflammation occurs as an evolving process that suppresses pro-inflammatory molecules, such as tumor necrosis factor (TNF), complement 5a, and CRP, without altering the host defense; in contrast, chronic and unresolved inflammatory responses often lead to ventricular dysfunction after an acute MI [20–22]. Deposition of the extracellular matrix (ECM) develops after the inflammatory response post-MI, directed by upregulation of ECM gene transcription. Kain et al. [23] showed that RvD1 stimulates the clearance of macrophages from sites of resolving inflammation, enhances the quick resolution of inflammation, and reduces the expression of ECM genes and deposition of collagens to stabilize the ECM, which supports cardiac remodeling by regulating the LOX and COX enzymes.

The metabolism of the omega-3 PUFA plays an essential role in providing cardioprotection. Dual LOX and COX inhibitors generate potent lipid mediators as key enzymes, which effectively promote the resolution of inflammation in pathophysiological conditions [24]. COX-2 inhibitors were shown to weaken the positive effect of omega-3 PUFA on myocardial ischemia, suggesting that boosting the levels of omega-3 PUFA metabolites can impact a potential therapeutic intervention [25]. In another study, a rich omega-3 PUFA concentration was observed to reduce infarct size [26].

Data on levels of RvD1 in patients with CAD are limited. Specialized pro-resolving lipid mediators (SPMs) such as lipoxins, resolvins, and protectins promote the resolution of acute inflammation by inhibiting the accumulation of neutrophils on tissues affected by ischemia and by inducing noninflammatory infiltration of monocytes, which differentiate into macrophages [22]. In a study of 6 patients by Elajami et al. [27], it was shown that patients with CAD have lower levels and/or absence of SPMs that were restored with Lovaza (an n-3 fatty acid); these low vascular SPMs could lead to chronic, uncon-

trolled vascular inflammation and predispose to coronary atherosclerosis and thrombosis.

This study suggests that RvD1 may be associated with MI and inflammation. As initially hypothesized by us, RvD1, an anti-inflammatory marker, appears to be linked with STEMI and markers of its poor prognosis. Our findings are compatible with our hypothesis. RvD1 levels were significantly lower in the STEMI group as compared to the NCA group. Low levels of RvD1 had a significant and negative correlation with high TIMI thrombus grade as assessed by the TIMI thrombus classification. Serum levels of RvD1 were negatively associated with WBC, neutrophil count, hs-CRP, pro-BNP, and peak troponin level. The correlation of low serum levels of RvD1 with other inflammatory parameters such as numbers of WBC and neutrophils indicates its role in the development of systemic inflammation. Furthermore, a cut-off RvD1 level of 5.07 (ng/mL) predicted STEMI with a sensitivity of 79.5% and specificity of 96.2%. Thus, our results demonstrated that serum RvD1 is associated with important prognostic markers like LVEF, peak troponin value, inflammatory markers, pro-BNP levels, and TIMI thrombus grade. Comprehensive studies will further clarify the role of low levels of RvD1 in the prognosis of STEMI.

Our results should be interpreted keeping in mind some limitations of this study. First, this was a single-center study conducted on a small sample. Due to the cross-sectional aspect of the study, we did not obtain follow-up data on adverse cardiovascular outcomes such as symptomatic heart failure or death, so we abstain from making any comment on the relationship between RvD1 levels and adverse cardiovascular events in patients with STEMI. Second, we were unable to perform serial measurements of RvD1 due to financial constraints. Thus, it is not possible to determine how RvD1 levels change in the event of MI. Within this context, the measurement of RvD1 after the acute MI can reveal additional data on the issue. Third, we could not perform a quantitative analysis of troponin levels, although we tried predicting the size of myocardial necrosis through the highest level of troponin.

## Conclusions

RvD1 levels are decreased in patients with STEMI compared to the control group. Serum levels of RvD1 are significantly associated with prognostic markers of STEMI such as LVEF, pro-BNP, peak troponin level, and TIMI thrombus grade. Prospective follow-up studies are needed to elucidate the prognostic value of RvD1 in patients with STEMI.

## Statement of Ethics

This study compiled was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient. The study protocol was approved by the Bozok University Ethics Committee, Yozgat, Turkey (2017/189_2021.12.09_02).

## Conflict of Interest Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


## Funding Sources

None.


## Author Contributions

Conceptualization of the study: Orhan Karayiğit; data collection: Serdar Gökhan Nurkoç and Funda Başyiğit; data analysis: Orhan Karayiğit and Emrullah Kızıltunç; and writing of the first draft: Orhan Karayiğit and Serdar Gökhan Nurkoç. All authors contributed substantially to the final draft of this paper and its revision. All the authors have read and approved the final manuscript.

## Data Availability Statement

All data relevant for this study will be provided upon specific request.

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