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The Predictive Value of R Wave Peak Time to Detect Thrombus Burden in ST-segment Elevation Myocardial Infarction: A Retrospective Cohort Study in a Tertiary Medical Center

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ABSTRACT

Background: Patients with higher thrombus burden have higher procedural complications and more long-term adverse cardiac events. Detecting patients with high thrombus burden (HTB) before coronary intervention could help avoid procedural complications. **Objective:** The research aimed to analyze the R wave peak time (RWPT) on the electrocardiogram to predict thrombus burden before coronary angiography in patients with acute ST-segment elevation myocardial infarction (STEMI). **Materials and Methods:** A total of 159 patients with STEMI were included in the study conducted at a tertiary medical center. The thrombolysis in myocardial infarction (TIMI) thrombus scale was applied to assess the thrombus burden. TIMI thrombus grades 0, 1, 2, and 3 were accepted as low; 4 and 5 had HTB. RWPT was measured from the beginning of the QRS complex to the R-peak from the leads pointing to the infarct-related artery. **Results:** Patients were divided into two groups according to their angiographically defined thrombus burden as low and high. The low thrombus burden group (LTB) comprised fifty-four patients, whereas the HTB group comprised 105 patients. In the LTB group, RWPT was 47.96 ± 9.17 ms, and in the HTB group was 53.58 ± 8.92 ms; it was significantly longer ($p < 0.01$). Receiver operating characteristic analysis showed that a cut-off value of pre-procedural RWPT of > 46.5 ms predicted the occurrence of HTB with a sensitivity and specificity of 87.62% and 51.85%, respectively (AUC 0.682, 95% CI 0.590-0.774, $p < 0.001$). **Conclusion:** The present study evaluated the relationship between the RWPT and thrombus burden in STEMI patients. Based on the results, RWPT is an independent predictor of HTB. (REV INVEST CLIN. 2023;75(4):212-20)

Keywords: R wave peak time. Thrombus burden. ST-segment elevation myocardial infarction. High thrombus burden.

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INTRODUCTION

The primary pathophysiology of acute myocardial infarction (AMI) is rupture or erosion of atherosclerotic plaque followed by thrombus formation in coronary vessels resulting in total occlusion or an abrupt decrease in coronary blood flow. The disruption of atherosclerotic plaque triggers the coagulation cascades with the inflammatory pathways as well. The amount and the extensiveness of the thrombus depend on the counteraction of the thrombotic and thrombolytic pathways and can be variable from a limited lesion to complete occlusion. Percutaneous coronary intervention (PCI) is the preferred strategy for the treatment of AMI in adjunction with periprocedural antithrombotic therapies[1-4].

Higher thrombus burden in the course of AMI worsens outcomes both during the procedure and in the long term[5]. Despite the developing interventional techniques and more potent antithrombotic treatments, patients with higher thrombus burden have higher procedural complications such as no-reflow and distal embolism also; these patients have a more extended hospital stay, increased risk of stent thrombosis, recurrent AMI, heart failure (HF) and malignant arrhythmias[6]. Therefore, detecting patients with high thrombus burden (HTB) before coronary intervention could help to reduce procedural complications.

The electrocardiogram (ECG) is the most used noninvasive diagnostic tool in cardiology practice. R wave peak time (RWPT) on ECG is the time interval from the onset of the QRS to the peak of the R wave and is also called intrinsicoid deflection (ID). It represents the early phase of ventricular repolarization, the conduction time of the electrical activity from the endocardium to the epicardium. MacLeod, Wilson, and Barker reported ID in 1930[7]. So far, prolonged RWPT has been associated with left ventricular hypertrophy (LVH), left ventricular overload, myocardial ischemia, HF, and sudden cardiac death (SCD)[8-12]. Recent studies have shown the relationship between the RWPT and no-reflow and coronary artery disease severity in AMI patients[13,14].

Consistent with these data in the present study, we sought to show the role of RWPT on the ECG to predict thrombus burden before coronary angiography (CAG) in patients with AMI.

MATERIALS AND METHODS

Study population

The study included 250 patients who had ST-segment elevation myocardial infarction (STEMI) and were treated at a tertiary health center. The enrollment was done retrospectively. All patient's data were evaluated from the hospital's digital database. Patients were diagnosed with STEMI according to the diagnostic criteria outlined in the 4th universal definition of myocardial infarction[15]. Patients who have coronary lesions more than > 50% lesions other than the infarct-related artery (IRA) or coronary ectasia; patients with a history of coronary intervention and coronary artery by-pass graft operation, QRS duration more than 120 ms, high-grade atrioventricular (AV) block (2nd and 3rd degree AV block), ventricular tachycardia/idioventricular rhythm, paced rhythm, moderate-to-severe-valvular-heart-disease, cardiomyopathies, pulmonary hypertension, abnormal thyroid or renal functions, abnormal serum electrolyte levels, congenital heart disease, chronic inflammatory disease, malignancy, previously diagnosed thrombophilia and patients on antiarrhythmic drug therapy were excluded from the study. Ninety-one of the 250 initially screened patients met the exclusion criteria, so 159 were included in the study. According to current guidelines, all participants were treated with acetylsalicylic acid, P2Y12 inhibitors, ACE inhibitors, beta-blockers, and statins, provided there were no contraindications[1-4]. According to the Declaration of Helsinki, the Local Ethics Committee of Ankara City Hospital reviewed and approved the study protocol.

Coronary angiography

Selective CAG and primary PCI with stenting and balloon dilatation, if necessary, were performed immediately at the time of diagnosis of STEMI by an experienced interventional cardiologist. Coronary interventions were performed via the radial approach or the femoral artery when the radial artery was unavailable, using the Judkins method. All patients received a loading dose of acetylsalicylic acid, P2Y12 inhibitor, and unfractionated Heparin with a dose of 50-100 IU/kg by the time of the procedure. In addition, Glycoprotein IIb/IIIa inhibitors were administered

during the intervention up to the operator's call. CAG recordings were stored in the hospital's PACS digital database and retrieved during analysis. Two interventional cardiologists individually evaluated all angiograms blinded to patients' data for thrombus burden. In case of divergency, a consensus decision was made.

Coronary blood flow was assessed by The thrombolysis in myocardial infarction (TIMI) blood flow classification as Grade 0, no contrast flow; Grade 1, a small amount of contrast material passes across the stenosis but fails to pass distally; Grade 2 opaque fluid runs through the obstruction and shows the distal end of the related coronary artery, but the flow is slower; Grade 3: Antegrade flow is the same as that in the normal coronary artery. The TIMI thrombus scale was applied to assess thrombus burden. Thrombus burden was scored as five grades based on the Gibson et al. classification, where grade 0 has no evidence of coronary thrombus and grade 5 total occlusion of the coronary artery by a thrombus[16]. Patients with total occlusion were re-quantified after the guidewire passage or a low-profile balloon dilatation if the coronary flow was restored[17]. TIMI thrombus grades 0, 1, 2, and 3 were accepted as low; 4 and 5 as HTB.

Electrocardiogram

Twelve lead ECGs with a speed of 25 mm/s and a voltage of 10 mm/mV were obtained pre-procedurally from all patients. ECG recordings were stored in the hospital's database as a digital file. At the time of analysis, ECG records were downloaded, and measurements were made using digital ECG caliper software (EP Calipers, https://www.epstudiossoftware.com). All measurements were performed by two experienced cardiologists blinded to patients' data. The QRS duration is calculated by measuring from the start of the QRS complex to the J point, while the QT duration is measured from the beginning of the QRS complex to the end of the T wave in leads D2, V5-6. The corrected QT interval is determined using Bazzet's formula, which involves dividing the QT interval by the square root of the R-R interval. RWPT from the beginning of the QRS complex to the R-peak. Specifically, in patients presenting with anterior STEMI leads V4 to V6, inferior STEMI leads D2- D3-AVF and high lateral STEMI leads D1-AVL were used for the analysis. The durations were given in milliseconds.

Other laboratory assessment

Transthoracic echocardiographic examination was performed on all patients included in the study during the index hospital stay. A skilled sonographer with Philips Epiq 7 echocardiography device carried out the echocardiographic evaluation. The left ventricular ejection fraction was measured by the modified Simpson's biplane method for all patients.

Fasting venous blood samples were obtained to measure the patients' glucose, HbA1c, renal functions, blood cell counts, and lipid profiles.

Statistical analyses

All statistical analyses were performed using SPSS 23.0 Statistical Package Program for Windows. Of the continuous variables, those with normal distribution were given as mean + standard deviation, those without normal distribution were given as median (25^{th}–75^{th}), and categorical variables were presented as percentages. The Kolmogorov–Smirnov test was used to test the normality of distribution. Levene's test was used to evaluate homogeneity. Student t-test or Mann–Whitney U test were used to compare continuous variables. Categorical variables were compared ×2 test. Receiver operating characteristic curve (ROC) analysis was used to define the optimum cutoff level of RWPT to predict the HTB. The Youden index was used to determine the optimum cutoff value. Logistic regression analysis was used to find the predictors of HTB. Possible confounding factors were tested in a univariable regression model, and confounders with a $p < 0.05$ were tested in multivariable analysis, and $p < 0.05$ was considered to be statistically significant.

RESULTS

A total of 159 patients presented with STEMI formed the final population of the present study. The mean age was 60.7 ± 11.9, and 70.8% were males. Patients were divided into two groups according to their angiographically defined thrombus burden as low and high. The low thrombus burden group (TIMI 0-3) (LTB) comprised fifty-four patients, whereas the HTB (TIMI 4-5) (HTB) group comprised 105 patients. The patient's baseline clinical and laboratory

Table 1. Baseline clinical and laboratory characteristics of the study groups

Variables	All patients (n = 159)	Low thrombus burden (n = 54)	High thrombus burden (n = 105)	p-value
Clinical characteristics				
Sex, male n (%)	112 (70.8%)	35 (64.8%)	77 (73.3%)	0.265
Diabetes mellitus, n (%)	54 (34.0%)	19 (35.2%)	35 (33.3%)	0.815
Hypertension, n (%)	63 (39.6%)	23 (42.6%)	40 (38.1%)	0.583
Age, years	60.7 ± 11.9	62.0 ± 11.0	60.1 ± 12.4	0.348
Laboratory characteristics				
Serum glucose, mg/dL	129.0 (103.0-196.0)	115.0 (96.7-184.7)	131.0 (106.5-201.0)	0.055
Serum creatinine, mg/dL	0.85 (0.71-0.99)	0.78 (0.66-0.93)	0.89 (0.74-1.01)	**0.018**
Urea, mg/dL	30.0 (25.0-40.0)	29.0 (22.0-39.0)	31.0 (25.5-41.5)	0.113
LDL-cholesterol, mg/dL	132.9 ± 46.2	138.1 ± 51.0	130.3 ± 43.5	0.311
Potassium, mmol/L	4.2 (4.0-4.5)	4.1 (4.0-4.5)	4.2 (4.0-4.5)	0.597
WBC count, 10^3/mL	11.18 (9.04-14.09)	9.96 (8.54-12.44)	12.21 (9.74-14.80)	**0.006**
Hemoglobin, g/dL	13.8 ± 1.8	14.0 ± 1.7	13.8 ± 1.9	0.575
Platelet count, 10^3/mL	247.0 (208.0-295.0)	255.0 (207.7-306.7)	241.0 (208.5-288.5)	0.203
Baseline troponin, ng/mL	13.3 (3.51-25.0)	6.82 (1.75-19.80)	19.9 (5.13-25.0)	**0.002**

WBC: white blood cell count.

characteristics are presented in Table 1. There were no significant differences between the low and HTB groups regarding age, gender, and being diabetic or hypertensive. However, patients in the HTB group had higher troponin levels on admission than the LTB group. In addition, among the patients' baseline characteristics, there were findings that we should emphasize, namely white blood cell count and serum creatinine levels which were higher in the HTB group ([9.96 vs. 12.26 10^3/mL; p = 0.006]; [0.78 vs. 0.89 10^3/mL; p = 0.018], respectively) (Table 1).

Regarding the angiographic data, the IRA was the left anterior descending artery (LAD) in 75 patients (47.2%), the Circumflex artery (Cx) in twenty-three patients (14.5%), the Right coronary artery (RCA) in 61 patients (38.3%). In the LTB group, the distribution of IRA for LAD, Cx, and RCA were 44.4%, 20.4%, and 35.2%, respectively, while the rates were 48.6%, 11.4%, and 40.0% for LAD, Cx, and RCA in HTB group. There were no significant differences between the groups in terms of IRA. The mean left ventricular ejection fraction (LVEF) was 47.38 ± 10.68 in the LTB group and 43.85 ± 9.48 in the HTB group, which was statistically lower in the HTB group (p = 0.043) (Table 2).

Regarding the ECG parameters, the mean QRS duration was 94.0 (86.0-104.0) ms, the mean QT interval was 391.7 ± 43.5 ms, and the mean QTc interval was

Table 2. Baseline angiographic, echocardiographic, and electrocardiographic characteristics of the study groups

Variables	All patients (n = 159)	Low thrombus burden (n = 54)	High thrombus burden (n = 105)	p-value
Angiographic and echocardiographic characteristics				
IRA, n (%)				
LAD	75 (47.2)	24 (44.4)	51 (48.6)	0.622
CX	23 (14.5)	11 (20.4)	12 (11.4)	0.129
RCA	61 (38.4)	19 (35.2)	42 (40.0)	0.554
LVEF, (%)	45.05 ± 10.01	47.38 ± 10.68	43.85 ± 9.48	**0.043**
Electrocardiographic characteristics				
RWPT	51.67 ± 9.37	47.96 ± 9.17	53.58 ± 8.92	**< 0.001**
HR	76.7 ± 17.9	75.2 ± 15.9	74.4 ± 18.8	0.471
QRS	94.0 (86.0-104.0)	93.0 (87.5-100.0)	96.0 (86.0-104.0)	0.453
QT	391.7 ± 43.5	395.2 ± 41.4	390.0 ± 44.7	0.473
QTC	422.4 ± 26.7	422.8 ± 26.8	422.2 ± 26.7	0.890

IRA: infarct related artery; LAD: left anterior descending artery; CX: circumflex artery; RCA: right coronary artery; LVEF: left ventricular ejection fraction.

422.4 ± 26.7 ms, which were all similar between groups. Furthermore, the mean RWPT was 51.67 ± 9.37 ms; in the LTB group, RWPT was 47.96 ± 9.17 ms, and in the HTB group was 53.58 ± 8.92 ms, it was significantly longer ($p < 0.001$) (Table 2).

In addition, univariable and multivariable regression analysis models were performed for possible covariables using HTB as the dependent variable. The multivariable regression analysis revealed that RWPT is an independent predictor for HTB (OR: 1.078; 95% CI: 1.0333-1.125; $p = 0.002$) (Table 3). ROC analysis showed that a cut-off value of preprocedural RWPT of > 46.5 ms predicted the occurrence of HTB with a sensitivity and specificity of 87.62% and 51.85%, respectively (AUC 0.682, 95% CI 0.590-0.774, $p < 0.001$) (Fig. 1).

DISCUSSION

Based on the results of the present study, RWPT is an independent predictor of angiographically defined HTB in patients presenting with STEMI. To the best of our knowledge, this is the first study evaluating the relationship between the thrombus burden and RWPT in STEMI patients. In addition, we showed a statistically significant difference between the HTB and LTB groups in terms of LVEF, white blood cell count, serum creatinine, and troponin levels.

Occlusion of the coronary artery or abrupt decrease in coronary flow by an intracoronary thrombus is the nature of AMI. Therefore, reassessing the coronary blood flow is the cornerstone of treating AMI mechanically and pharmacologically. The extent of thrombus can be variable according to the underlying inflammatory process and thrombotic thrombolytic balance. Clinical studies demonstrated that intracoronary thrombus challenges periprocedural success regardless of the underlying mechanism. HTB is related to distal embolization, no-reflow microvascular obstruction, inadequate reperfusion, subsequent myocardial damage, and deterioration of ventricular function[5,6,18-20]. However, patients with HTB experience more stent thrombosis, recurrent MI, and recurrent

Table 3. Univariable and multivariable logistic regression analysis showing the independent predictors for the high thrombus burden

Variables	Univariable analysis		Multivariable analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Serum creatinine	5.086 (1.209-21.398)	0.027	3.093 (0.689-13.891)	0.141
WBC	1.102 (1.011-1.202)	0.028	1.017 (0.919-1.126)	0.738
Baseline troponin	1.052 (1.017-1.089)	0.003	1.031 (0.991-1.073)	0.129
LVEF	0.964 (0.932-0.998)	0.037	0.981 (0.943-1.021)	0.356
RWPT	1.078 (1.033-1.125)	**0.001**	1.072 (1.022-1.123)	**0.004**

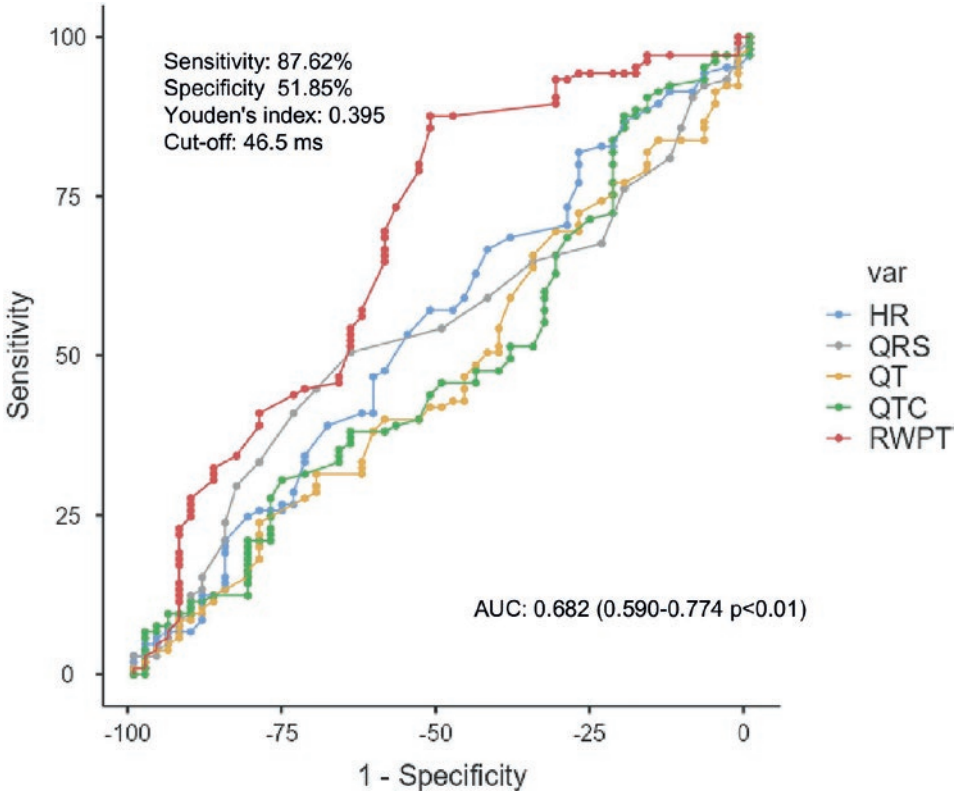
WBC: white blood cell count; LVEF: left ventricular ejection fraction; RWPT: R wave peak time.

revascularization[17,21]. Therefore, predicting the thrombus burden before the procedure is crucial to determine the patients at procedural and long-term risk. Choosing high-risk patients at the time of diagnosis of AMI with ECG simple, non-invasive, fast, and readily available tool is very convenient when the time is gold. Several ECG parameters have been associated with procedural success in the course of AMI, but none of them have been evaluated for thrombus burden.

We measured RWPT, QRS durations QT and QTC intervals in the present study. Only RWPT was related to the thrombus burden, according to our results. RWPT, a component of total QRS duration, presents the early phase of ventricular repolarization. Prolongation is thought to be related to intracellular K and Ca balance, which is vulnerable to ischemia[22]. The other proposed mechanisms in prolonged RWPT are the reduction of gap junction density, increasing interstitial fibrosis, and myocardial size in ischemic, hypertrophied, and overloaded myocardium[23]. The standard measurement of RWPT is made in leads V5-6 in a normal heart with an expected value of < 50 ms. Prior studies demonstrated that RWPT is prolonged in LVH, HF (both reduced EF and preserved EF), coronary heart disease, and SCD[9-12]. It is recommended to measure the RWPT in different leads of the ECG depending on the condition. In patients with LVH and HF with preserved EF, RWPT is measured in leads V5-6, while D1, AVL, and V1 are used to assess CRT response[8,9]. Since it is a dynamic parameter that shows alterations due to underlying conditions, we measure RWPT in leads with ST-segment elevation in STEMI patients[8]. In our study, RWPT was longer in the HTB group, showing that a larger myocardial mass is in jeopardy. Recent studies demonstrated that preprocedural RWPT was associated with no-reflow in STEMI patients, a procedural complication related to thrombus burden[14,24,25]. Furthermore, Rencuzogullari et al. reported that RWPT is related to coronary artery disease severity in NSTEMI patients, pointing to the ischemic burden[13]. Therefore, our findings in terms of RWPT are consistent with the previous studies.

QRS duration is a well-known parameter and has prognostic significance in HF and AMI patients. In addition, recent studies have shown that prolonged QRS duration is associated with the angiographical no-reflow phenomenon[24-26]. However, there has yet to be any research in the literature to investigate the relation between the QRS duration and thrombus burden. In our study, the QRS duration in the HTB group was 96.0 ms (86.0-104.0) and 93.0 ms (87.5-100.0) in the LTB group. Although there was a slight prolongation in the HTB group, it was not statistical significance. The QRS duration represents the whole repolarization of the ventricles as a heterogeneous mass. Since the RWPT is a component of QRS duration, both are closely related. Still, RWPT is the duration more vulnerable to ischemia which can explain

Figure 1. Receiver operating characteristic curve analysis to detect the cut-off value of R wave peak time for high thrombus burden.



the results of the present study. However, the association of QRS duration and thrombus burden is another concern and should be investigated in a larger population. QT and QTc intervals are often used parameters to identify patients with the risk of ventricular arrhythmias and SCD[27]. They represent both repolarization and depolarization of ventricles and the prolongations are the earliest ECG parameter in response to ischemia[28]. Although studies have demonstrated a correlation between QT/QTC durations and outcomes during and after STEMI[29,30], as well as the severity of CAD[31], there has been no research evaluating the relationship with thrombus burden. In our study, we did not find a significant relationship between QT/QTc intervals and thrombus burden either. However, Onat et al. showed that the normalization of QT interval was a predictor of reperfusion after stenting in a cohort of 144 patients with chronic coronary syndrome[32]. Therefore, the value of QT/QTc interval in detecting no-reflow, thrombus burden, and reperfusion success should be investigated in larger cohorts.

According to our results, the WBC count is significantly higher in HTB patients, indicating inflammation. The inflammatory process plays a crucial role in the pathogenesis of atherosclerosis and thrombus formation, a well-known entity. Studies demonstrating the relationship between the inflammatory process and thrombus burden in AMI patients support our results regarding leukocyte counts[29-31].

Our study found that serum creatinine levels were higher in the HTB group than in the LTB group. As already shown, elevated serum creatinine level is a risk factor for atherosclerosis[32]. This is mainly attributed to its pro-inflammatory effect. Elevated serum creatinine levels result in increased vasotoxic substances and consequently increase oxidative stress, which provides the right environment for the development of atherosclerosis, plaque rupture, and subsequent thrombus formation[33].

Another finding of the present study is the higher troponin levels in the HTB group compared to the LTB

group. Higher basal troponin levels show the delay between symptom initiation and first medical contact. The more delay, the more thrombus formation, subsequently, more injured myocardial tissue. Hence, it is expected that HTB patients have higher troponin levels.

In the present study, LVEF was lower in the HTB group, supporting the early results, higher thrombus burden, and larger myocardial mass with ischemic risk. Napodano et al. evaluated the impact of the thrombus burden on myocardial damage during the primary PCI in patients presenting with STEMI by using contrast-enhanced cardiac magnetic resonance (CE-CMR). They found out that patients with large thrombus burden had larger infarct size detected by CE-CMR even in the absence of visual distal embolization[34]. O'neal et al. reported that RWPT > 50 ms predicted HF events in a large population without preexisting heart disease over 11 years of follow-up. However, he also claimed that each 10 ms increase in RWPT increases the HF event risk 1.42 times[10]. This is an important issue that needs further evaluation but is impressive to express the significance of RWPT in predicting adverse cardiac events.

In conclusion, RWPT is an emerging ECG parameter readily available and inexpensive, indicating the risk of adverse cardiac events in different conditions. In our cohort, we investigate the ECG parameters that can be related to thrombus burden. Among the QRS duration, QT, QTc intervals, and RWPT the only parameter that strongly related to thrombus burden was the RWPT in patients with STEMI. Even though the AUC was slightly lower, it was the most powerful parameter to predict the thrombus burden among the well-known ECG findings. Based on the ROC curve analysis, we established the cut-off value for RWPT at the point where the sensitivity was at its peak and the Youden index was 0.395. We anticipate that our research outcomes will be further validated in more extensive study groups. This is the first study in the literature indicating the interaction between RWPT and thrombus burden. Therefore, it will inspire further studies in this subject.

The retrospective design and the relatively small population are major limitations of our study. Hence, it will be better to test the subject in a large, prospectively designed study. Another limitation is the assessment of the thrombus burden visually. More quantitative methods such as optical coherence tomography or intravascular ultrasound would provide more accurate and objective results in terms of thrombus burden. Finally, the present study was not designed for long-term clinical outcomes. Therefore, these results should be re-evaluated for long-term clinical consequences, especially regarding LVEF in the future.

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The study was conducted according to the principles outlined in the Declaration of Helsinki and approved by Ankara City Hospital's Ethics Committee (E2-23-4082).

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