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RESEARCH

Association between aspirin resistance and indices of inflammation and platelet activity in patients with acute coronary syndrome

Akut koroner sendromlu hastalarda aspirin direncinin inflamasyon indeksleri ve trombosit aktivitesi ile ilişkisi

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Abstract

Purpose: Aspirin resistance (AR) has been linked to increased cardiovascular morbidity and mortality in patients with acute coronary syndrome (ACS). Both ACS and AR have also been associated with enhanced platelet activity and inflammatory responses. This study aimed to evaluate the power of the levels of uric acid (UA), non-high-density lipoprotein (non-HDL) cholesterol, high-sensitivity C-reactive protein (Hs-CRP), and gamma-glutamyltransferase (GGT) and the mean platelet volume (MPV), to predict AR in patients with ACS.

Materials and Methods: This study included543 patients with ACS. AR was identified by whole blood aggregometry. Predictors of AR were determined through multivariate regression analyses and the receiver operating characteristic (ROC) curve analysis.

Results: The levels of UA, GGT, non-HDL cholesterol, MPV, and Hs-CRP were significantly higher in patients with AR compared to those without AR (5.6±1.5 vs.6.8±3.1, 20 vs 34 (median), 162.3±43.2 vs. 143.2±37.1, 8.2 ±0.9 vs. 8.9 ±1.1, 5.0 vs 14.7 (median)). A multivariate regression analysis identified MPV, UA, Hs-CRP and presence of clopidogrel resistance as independent predictors of AR.

Conclusion: In patients with ACS, AR was found to be associated with elevated platelet activity and inflammation, suggesting that these factors might contribute to the development of AR or might be underlying mechanisms of AR. These findings highlight potential benefit of a routine workup to assess the oxidative status, inflammation, and thrombogenicity that may help risk stratification and treatment decision-making in clinical Practice, in patients with AR.

Keywords: Aspirin resistance, gamma-glutamyltransferase, high-Sensitivity C-Reactive Protein

Öz

Amaç: Akut koroner sendrom (AKS) hastalarında aspirin direnci (AD), artmış kardiyovasküler morbidite ve mortalite ile ilişkilidir. Hem AKS hem de AD, artmış trombosit aktivitesi ve inflamatuar yanıtlarla da ilişkilidir. Çalışma, AKS hastalarında AD'yi tespit etmede ürik asit (UA), ortalama trombosit hacmi (MPV), yüksek yoğunluklu lipoprotein olmayan (non-HDL) kolesterol, yüksek duyarlılıklı C-reaktif protein (Hs-CRP) ve gama-glutamiltransferazın (GGT) öngörü gücünü değerlendirmeyi amaçladı.

Gereç ve Yöntem: Çalışmaya 543 AKS hastası dahil edildi. AD, tam kan agregometri yöntemi ile tespit edildi. AD varlığının prediktörleri, çok değişkenli regresyon analizleri ve alıcı işletim karakteristiği (ROC) eğrisi analizi ile belirlendi.

Bulgular: AD'li hastalarda UA, GGT, non-HDL kolesterol, MPV ve Hs-CRP seviyeleri anlamlı derecede daha yüksekti (5,6±1,5 - 6,8±3,1, 20 - 34 (medyan), 162,3±43,2 - 143,2±37,1, 8,2 ±0,9 - 8,9 ±1,1, 5,0 - 14,7 (medyan), sırasıyla; tüm parametreler için p<0,001). Çok değişkenli regresyon analizi, MPV, UA, Hs-CRP ve klopidogrel direncinin varlığının AD'nin bağımsız öngörücüleri olduğunu tespit etti.

Sonuç: AKS hastalarında AD, artmış trombosit aktivitesi ve inflamasyon ile ilişkilidir ve bu faktörler, AD'ye katkıda bulunan altta yatan mekanizmalar olabilir. Bu bulgular, AD olan hastalarda klinik uygulamada okdidatif durumun, inflamasyonun ve trombojenitenin değerlendirmesi için rutin tetkiklerin potansiyel faydasını vurgulayarak, risk sınıflandırmasına ve tedavi karar alma sürecine yardımcı olmaktadır.

Anahtar kelimeler: Aspirin direnci, gama-glutamiltransferaz, hCRP

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INTRODUCTION

Platelet aggregation plays a significant role in the pathogenesis of acute coronary syndrome[1]. Therefore, it is crucial to establish optimal dual antiplatelet therapy in order to reduce mortality rates and the risk for recurrent thrombotic events, in patients experiencing acute coronary syndrome[2]. However, cardiovascular events can still occur despite treatment with recommended doses of antiplatelet agents, indicating a phenomenon known as antiplatelet resistance that has been associated with recurrent cardiovascular events[1,3-5]. Aspirin, an acetylated salicylate, irreversibly inhibits the conversion of arachidonic acid (AA) to thromboxane A2 (TXA2) by blocking platelet cyclooxygenase-1 (COX-1), thereby reduces platelet function and exerts an antithrombotic effect[6]. Aspirin resistance (AR) is a form of antiplatelet resistance closely associated with cardiovascular ischemic events, such as myocardial infarction, stroke, and death[7,8]. However, the pathophysiology of AR remains incompletely understood. Mechanisms underlying aspirin resistance include medication non-adherence, increased inflammation, increased platelet turnover, and platelet receptor gene polymorphisms[7].

Chronic inflammation, increased platelet turnover, and oxidative stress are pivotal mechanisms involved in the development of atherosclerosis[9]. The role of inflammation in atherosclerosis is well-established[10]. High-sensitivity C-reactive protein (Hs-CRP), an inflammation marker, is mainly produced by hepatocytes and regulated by cytokines such as tumor necrosis factor-alpha and interleukin-6 (IL-6)[11]. Extensive evidence indicate that Hs-CRP is linked to major adverse cardiovascular events (MACE) in individuals with heart disease[12].

Gamma-glutamyl transferase (GGT) is crucial in the metabolism of glutathione, an important cellular antioxidant, and it plays a role in the oxidation of low-density lipoprotein (LDL) cholesterol, contributing to the development of atherosclerosis[13]. Previous studies have shown that the serum GGT level is a predictor for MACE[14,15]. Similarly, although uric acid (UA), a xanthine metabolite, acts as an antioxidant, elevated serum UA levels are observed in coronary artery disease and are linked to MACE[16]. Despite considerable evidence suggesting that patients with aspirin resistance (AR) have poorer survival outcomes, there are limited studies investigating the effects of markers of atherosclerosissuch as inflammation, oxidation, and thrombotic statuson AR in patients with acute coronary syndrome (ACS). This study provides new insights into the associations between AR and UA, MPV, GGT, Hs-CRP, clopidogrel resistance in patients with ACS. Our findings demonstrating significant associations between AR and these parameters of inflammation, oxidation, and thrombogenicity suggest that UA, MPV, GGT, Hs-CRP may serve as valuable, simple, and low-cost markers of AR and may contribute to early diagnosis and management of patients with AR at risk for adverse cardiovascular events. We hypothesized that patients with AR would havehigher levels of inflammation, oxidation, and thrombogenicity compared to patients without AR, and this might be associated with adverse cardiovascular events. Therefore, this study aims to evaluate potential associations between AR and the levels of UA, GGT, high-sensitivity C-reactive protein (Hs-CRP) and the mean platelet volume (MPV)in patients presenting with ACS.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of Suleyman Demirel University Faculty of Medicine (Decision No.66 of January 9, 2013). This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent. This prospective study is a subgroup analysis of a study evaluating aspirin and clopidogrel resistance in patients from the Isparta region of Turkey[17,18].

Study design and sample

The study was conducted in cardiology outpatient clinics of the Teaching Hospital at Suleyman Demirel University. A total of 628 patients with ACS who visited the Teaching hospital of Suleyman Demirel University between 2012 and 2014, were included in the study. All participants aged 18 years and older, underwent a percutaneous coronary intervention (PCI) with drug-eluting stents. Before stenting, patients received a loading dose of 600 mg clopidogrel and 300 mg aspirin, followed by maintenance doses of 75 mg of clopidogrel and 100 mg of aspirin daily. All patients aged 18 years and older were eligible for the study. Exclusion criteria included the need for a long-term heparin or

fondaparinux therapy, receiving ASA at doses >100 mg daily or clopidogrel at doses higher than 75 mg daily before the enrolment, rheumatic mitral valve disease, the requirement for oral anticoagulants, cardiogenic shock at the admission, NYHA Class III or IV heart failure at the admission, thrombocytopenia (<100 x 10^9 g/L), purpura, anemia (hemoglobin <100 g/L), active inflammation or stent thrombosis during interview or at the admission, and comorbidities with a life expectancy of less than one year. Patients' medical records and data were thoroughly examined by two expert cardiologists. Based on these criteria, 85 patients were excluded: 5 for thrombocytopenia, 40 for the use of high-dose clopidogrel, 30 for the use of oral anticoagulants, and 10 for cardiogenic shock. Eventually, 543 patients (51 with AR and 492 without AR) were included in this sub-study. None of the participants had severe infections, rheumatic diseases, liver or kidney disorders, or a history of active bleeding.

Definition of acute coronary syndrome

Diagnoses were recorded by participating physicians based on a combination of clinical evaluation, electrocardiographic findings, and biochemical markers, particularly elevated troponin levels. Myocardial infarcts classified as ST-elevation (STEMI) or non-ST-elevation (NSTEMI), as well as unstable angina, were uniformly defined according to current guidelines. As for electrocardiographic findings, ST-segment changes were defined as either a depression of at least 1 mm or a transient ST-segment elevation of at least 1 mm lasting less than 20 minutes. Additionally, an inverted T-wave was defined as a negative T-wave exceeding 2 mm. The diagnosis of STEMI was based on a rise and/or fall in cardiac biomarker levels, preferably troponin, with at least one value exceeding the 99th percentile of the upper reference limit. Additionally, the diagnosis of STEMI required at least one of the following criteria: ischemic symptoms, new or presumably new significant ST-T changes (measured at the J point and observed in two contiguous leads with an elevation of ≥0.2 mV in men or ≥0.15 mV in women in leads V2–V3, or ≥0.1 mV in other leads), or the presence of a new left bundle branch block[19,20].

Medications and traditional risk factors

Medications and traditional risk factors were assessed as indicated in previous studies[17,18]. During the examination, a comprehensive medical history with the focus on cardiovascular risk factors such as diabetes, hypertension, and smoking habits, was collected from eachstudy patient. The body mass index (BMI) was calculated for each patient, with obesity defined as a BMI of 30 kg/m² or higher. Other risk factors were classified according to current guidelines. Former smokers at the admission were classified as smokers.

Blood sampling and analysis

Platelet function analysis was conducted once the patient received a loading dose of 600 mg of clopidogrel along with premedication with ASA. Blood samples were collected 24 hours after the PCI. Five milliliters of whole blood were collected in a Lithium Heparin tube (without gel) using heparin as anticoagulant. Blood samples were analyzed using a Multiplate Platelet Function Analyzer, to evaluate platelet function in whole blood through impedance aggregometry (Dynabyte Medical, Munich, Germany, 2006) with the addition of 20 µl of the activator. Tests included in the workup were: (i) the ADP test, using adenosine diphosphate (ADP), to evaluate P2Y12-dependent platelet aggregation, and (ii) the ASPI test, using arachidonic acid (AA), to evaluate cyclooxygenase-dependent platelet aggregation. The ASPI test reagent (20 µl of a 15 mM stock solution) contains arachidonic acid that induces platelet aggregation through platelet cyclooxygenase-an action inhibited by aspirin. The ADP test reagent (20 µl of a 0.2 mM stock solution) activates platelets via ADP receptors, specifically the P2Y12 receptor, which is inhibited by clopidogrel. All tests were completed within two hours of blood collection. Results were reported as the area under the curve (AUC) after the 6-minute measurement period, and an AUC of 500 min for ASA and 470 min for clopidogrel were considered the thresholds for minimal resistance in patients undergoing dual antiplatelet therapy.Asprin and clopidogrel resistance test were performed as described in previous studies[21,22]. MPV, UA, GGT and HS-CRP levels were measured as described in previous studies[23].

Statistical analysis

Statistical analyses were performed using an SPSS software package version 16.0. Categorical variables were expressed as frequencies (%) and analyzed compared using the chi-square test. The chi-squared test was used for comparing the prevalence of: Male

gender, diabetes, hypertension smoking, hyperlipidemia, and other categorical variables. The Kolmogorov-Smirnov test assessed the distribution of numeric variables. Normally distributed data were expressed as mean ± standard deviation and analyzed using the independent sample Student's t-test. Specifically, the Student's t-test was applied to compare the following variables: Age, blood pressure, mean platelet volüme, uric acid and hemoglobin. Non normally distributed data were expressed as median (Interquartile Range (IQR) of 25%-75% percentiles) and analyzed using the Mann-Whitney U test. A p-value <0.05 was considered statistically significant. This test was employed for comparing non-normally distributed variables such as: Hs- CRP and GGT. Statistically significant parameters between the two groups were performed to univariate regression analysis and correlation analysis. The Pearson's correlation analysis determined relationships between AR and other variables. A univariate logistic regression analysis identified independent predictors of AR. Variables with a p value less than 0.1 in the univariate analysis were included in the multivariate logistic regression. To avoid multicollinearity, only the most statistically significant variable was included in cases where variables were correlated. The risk for AR and optimal cut-off points of the study variables were estimated using the receiver operating characteristic (ROC) curve analysis, with the sensitivity and specificity determined by the Youden J index. All ROC comparisons were performed using the DeLong test. All ROC comparisons were performed using the DeLong test. we performed power analysis with G-power (version 3.0.10, Franz Faul, Universitat Kiel, Germany), according to previous data[4,5]. It was calculated that a total of 157 subjects (143 control and 14 Aspirin resistance) were needed in order to fill the 2 groups at α err prob <0.05 and 1- β err prob of 0.95. Excess of this number was recruited to minimize risk of type II error.

RESULTS

Baseline characteristics, with the exception of oral anticoagulant use, were comparable between patients with and without AR. Table 1 presents the demographic and clinical characteristics of both groups. Patients with AR exhibited a higher prevalence of diabetes mellitus and hyperlipidemia compared to those without AR (p=0.005 and p=0.04, respectively).

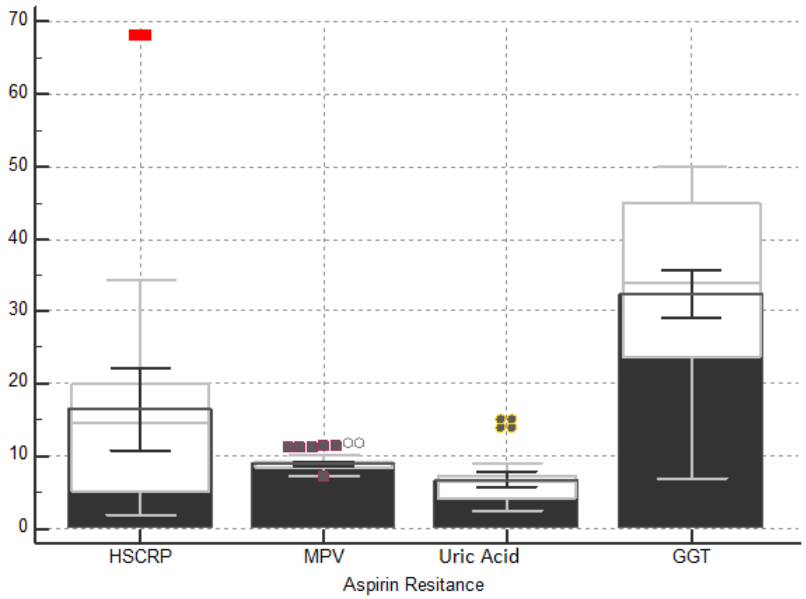

Figure 1. Indices of inflammation and platelet activity in each study groups.

hs-CRP = high-sensitivity C-reactive protein. MPV= mean platelet volüme, GGT= Gamma-glutamyltransferase.

Table 1. Demographic, clinical and laboratory data from the study population with and without aspirin resistance

Variable	AR (+) n= 51	AR (-) n=492	P value
The type of acute coronary syndrome e			0.874
STEMI n, (%)	23 (%8.2)	257 (%91.8)	
NSTEMI n, (%)	10 (%9.0)	101 (%91.0)	
USAP n, (%)	12 (%8.6)	128 (%91.4)	
Age, years	59.8 ± 11.6	61.8 ± 11.8	0.254
Glu (mg/dl)	147.1 ± 63.8	156.7 ± 85.4	0.478
WBC, X 10^3/ mm^3	10.58± 3	11± 4	0.356
HGB (mg/dl)	13.9 ± 1.3	13.8 ± 1.8	0.686
Platelet count x 10^3/ mm^3	260,785 ± 64,549	227,964 ± 67,834	0.205
CRE (mg/dl)	1.0 ± 0.3	1.0 ± 0.3	0.442
TCHOL (mg/dl)	200.2 ± 46.5	182.7 ± 39.0	0.09
TG (mg/dl)	187.2 ± 103	159.8± 84	0.056
LDL (mg/dl)	121.8± 32.8	109.3± 34.1	0.019
HDL (mg/dl)	37.8± 8.9	39.5± 11.3	0.377
Non- HDL (mg/dl)	162.3± 43.2	143.2±37.1	0.02
BMI	26.9± 3.5	26.4 ± 3.2	0.334
Smoking n (%)	17 (37.8)	259 (53.3)	0.06
Diabetes Mellitus n (%)	25 (55.6)	162 (33.3)	0.005
Hyperlipidemia n (%)	23 (51.1)	144 (29.6)	0.04
Hypertension n (%)	27 (60.0)	204 (42.0)	0.27
Female Gender n(%)	19 (37.3)	100 (20.3)	0.006
Previous medication			
BB, n (%)	8 (15.7)	118 (24)	0.473
Statins , n (%)	7 (13.7)	56 (11.4)	0.379
ACEI , n (%)	6 (11.8)	79 (16.1)	0.281
ARB , n (%)	12 (23.5)	73 (14.9)	0.083
ASPI	666±218	148±107	<0.001
ADP	408± 210	234±180	<0.001
GGT (U/L)(median)	32±11 (34)	22±20 (20)	<0.001
MPV (fL)	8.9±1.1	8.2± 0.9	<0.001
Uric acid (mg/dl)	6.8± 3.1	5.6± 1.5	<0.001
Hs-CRP (mg/L) (median)	16.5± 15.7 (14.7)	7.3± 9.2 (5.0)	<0.001

STEMI: ST-Elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, USAP: Unstabil Angina Pectoris, Glu: Glucose, WBC: Wight Blood Cell, HGB: Hemoglobin, Cre: Creatinine, Tchol: Total Cholesterol, TG: Triglycerides LDL: Low density Cholesterol, HDL: High density cholesterol, BMI: Body Mass Index, BB: β-Blocker, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ASPI: Arachidonic acid, ADP: adenosine diphosphate, GGT: gamma glutamyl transferase, MPV: Mean Platelet Volume, HS-CRP: High sensitive C reactive protein

Additionally, low density lipoprotein (LDL)-cholesterol and non-high density lipoprotein (HDL) cholesterol levels were elevated in the AR group compared to the non-AR group (p=0.019 and p=0.02, respectively). Both arachidonic acid (ASPI) and ADP levels were significantly higher in the AR group compared to the non-AR group (p<0.001 for both parameters). Moreover, MPV, Hs-CRP, UA, and GGT levels were elevated in patients with AR compared to the non-AR group (p<0.001 for all parameters) (figure 1). In a univariate analysis, several factors including elevated levels of LDL and non-HDL cholesterol, uric acid, Hs-CRP, MPV, GGT, diabetes mellitus and hyperlipidemia, higher ADP levels, clopidogrel resistance, and female gender were significantly associated with a higher risk of AR, (Table 2 and Figure 3). A multivariate logistic regression analysis that included all factors associated with AR in the univariate analysis, revealed that the levels of uric acid, Hs-CRP, MPV, and non-HDL were independent predictors of AR (Table 2 and Figure 2). Table 3 provides a summary of the statistically significant correlations between AR and the levels of non-HDL cholesterol, uric acid, Hs-CRP, MPV, and GGT. Table 4 and Figure 3 illustrate the cut-off values, specificity, and sensitivity of study variables for predicting AR.

Table 2. Predictors of the development of AR in the univariate and multivariate logistic regression analyses.

Variable	Unadjusted Odds Ratio	Confidence interval (CI)	P-value	Adjusted Odds Ratio	Confidence interval	P-value
LDL-Cholesterol	1.009	1.001-1.018	0.026			
Non-HDL Cholesterol	1.011	1.003-1.019	0.007			
ADP	1.014	1.002-1.005	<0.001			
GGT	1.018	1.003-1.033	0.019			
Hs- CRP	1.053	1.025-1.082	<0.001	1.03	0.98-1.09	0.04
Uric Acid	1.32	1.38-2.32	<0.001	1.4	1.06-2.08	0.01
MPV	1.79	1.15-3.43	<0.001	1.4	0.99-2.18	0.04
Female Gender	2.32	1.26-4.2	0.007			
Presence of DM	2.88	0.92-0.97	<0.001			
Presence of CR	4.81	1.60-5.19	<0.001	4.19	1.40-12.5	0.01
Presence of HL	2.10	1.17-3.77	0.012			

OR: Odds Ratio, CI: Confidence Interval, LDL: Low density cholesterol, HDL: High density cholesterol, AR: Aspirin resistance, UA: Uric Acid, Hs-CRP: High sensitivity C Reactive Protein, MPV: Mean platelet volume, DM: Diabetes Mellitus, CR: Clopidogrel resistance, HL: Hyperlipidemia

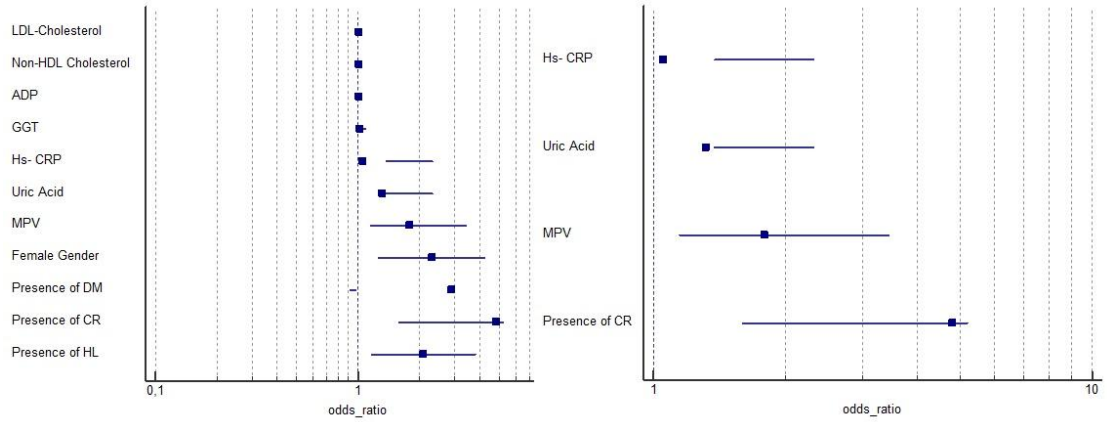

Figure 2. Forest Plot showing the the predictors of the development of AR in the univariate and multivariate regression analyses.

Table 3 Correlation between study variables

Variable		ADP	Hs CRP	GGT	MPV	UA	Non-HDL	Presence of CR
Presence of AR	r	0.266	0.277	0.318	0.188	0.100	0.121	0.221
	p	<0.001	<0.001	<0.001	<0.001	0.04	0.006	<0.001
ASP	r	0,380	0.158	0.123	0.163	0.063	0.088	0.225
	p	<0.001	0.007	0.019	<0.001	0.201	0.046	<0.001

AR: Aspirin resistance, UA: Uric Acid, Hs-CRP: High sensitivity C Reactive Protein, MPV: Mean platelet volume

Table 4. The receiver operating characteristic curve analysis of study variables

Variable	Cut-off value	Sensitivity	Specificity	AUC	P-value
GGT (U/L)	>27	73	81	0.76 (0.72-0.81)	<0.001
Hs-CRP (mg/L)	>14	56	88	0.75 (0.70-0.80)	<0.001
UA (mg/dl)	>6,6	50	78	0.60 (0.55-0.64)	0.09
MPV (fL)	>8	85	47	0.68 (0.64-0.72)	<0.001
Non-HDL (mg/dl)	>187	40	80	0.61 (0.53-0.65)	0.02

GGT: gammaglutamyl transpeptidase UA: Uric Acid, Hs-CRP: High- sensitivity C Reactive Protein, MPV: Mean platelet volume, HDL: High density lipoprotein

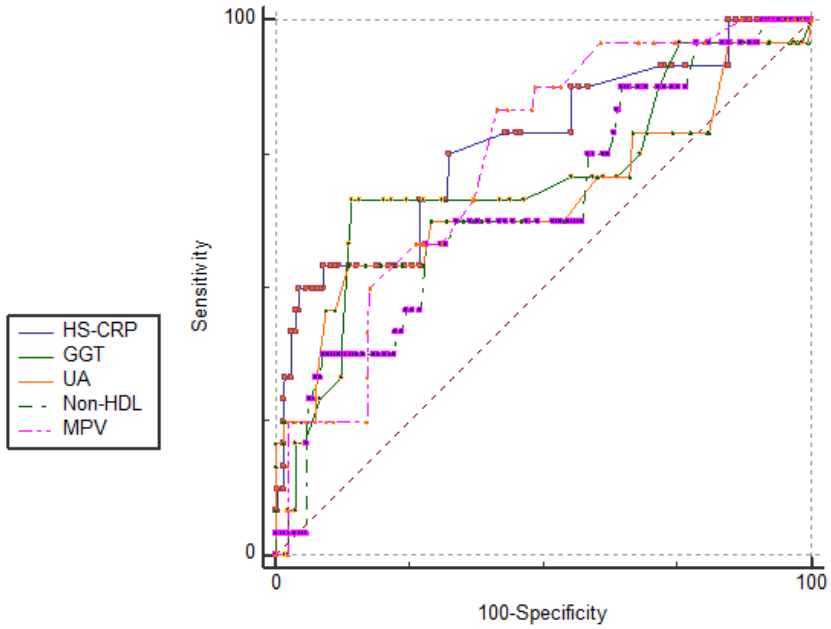

Figure 3. The receiver operating characteristic curve analysis of study variables.

GGT: gamma-glutamyl transpeptidase UA: Uric Acid, Hs-CRP: High- sensitive C Reactive Protein, MPV: Mean platelet volume, HDL: High density lipoprotein.

DISCUSSION

This study has demonstrated associations between the development of AR and several parameters of inflammation, oxidation, and thrombosis including hs-CRP, GGT, UA, non-HDL, and cholesterol levels and MPV, in patients with ACS.

GGT plays a crucial role in the oxidation of LDL cholesterol and in the breakdown of glutathione, which is a key antioxidant. It has been linked to the progression of atherosclerosis[13]. UA is a xanthine metabolite that acts as an antioxidant while the levels of UA may be elevated in coronary artery disease[16]. Previous studies have shown that serum GGT and UA levels were predictors for MACE[14-16]. In this study, patients with AR had higher levels of GGT and uric acid compared to those without AR, suggesting that oxidative processes might significantly contribute to AR development. Oxidative stress (OS) contributes to various stages of thrombosis, including platelet activation, and may reduce the bioavailability of nitric oxide, leading to an increased platelet activity and diminished aspirin efficacy[24]. Moreover, there is growing evidence that aspirin resistance may be mediated by 8-isoprotaglandin F2α produced through oxidative stress, further supporting the role of OS in AR[25].

Inflammation has a well-established role in the development of atherosclerosis[10]. Hs-CRP is mainly produced by hepatocytes and regulated by cytokines such as tumor necrosis factor-alpha and interleukin-6 and it has been associated with MACE in patients with heart disease[11]. In this study, the higher levels of Hs-CRP observed in patients with AR compared to patients without AR, indicate that inflammation may significantly contribute to the development of AR. The increased platelet turnover associated with infections, inflammation, diabetes mellitus, or hypertension can reduce the efficacy of aspirin[26]. As an indicator of thrombosis, MPV has been linked to MACE and several cardiovascular diseases[27,28]. In line with previous studies, MPV measurements were higher in patients with AR compared to patients without AR.

Hyperlipidemia and elevated LDL and non-HDL cholesterol levels were also more prevalent in patients with AR patients compared to those without AR.

Associations between cholesterol levels and aspirin resistance were reported in a prior research[29,30]. For instance, non-HDL cholesterol has been identified as an independent risk factor for AR, particularly in obese patients with type 2 diabetes mellitus, suggesting that blood lipid level monitoring is essential in patients with dyslipidemia[30].

Patients with AR are at a higher risk of adverse cardiovascular outcomes[4,15,27]. In this study inflammatory, oxidative, and thrombotic states were more common in patients with AR compared to patients without AR and this might explain the higher mortality rates observed in these patients.

In patients with stable cardiovascular disease, aspirin resistance has been associated with more than threefold increase in the risk of MACEs[4]. A meta-analysis conducted in 2014 with 1,889 patients with coronary heart disease(CHD) demonstrated that 622 out of these patients had aspirin resistance and patients with AR faced a significantly higher risk of adverse events compared to those who were responsive to aspirin therapy. Notably, even among patients with CHD who adhered well to aspirin treatment, the presence of aspirin resistance was associated with a 2.4-fold increase in the risk of experiencing MACEs[5].

In summary, AR is a significant clinical concern, particularly in patients with ACS, as it is associated with poorer clinical outcomes, including increased rates of recurrent cardiovascular events and mortality. AR is thought to result from a combination of factors that affect platelet function, including inflammation, thrombogenicity, and oxidative stress. As indicated by the elevated levels of the markers of inflammation such Hs-CRP, inflammatory processes play a crucial role in enhancing platelet activation and aggregation, which can diminish the efficacy of aspirin to inhibit the production of thromboxane A2. Thrombogenicity, characterized by an increased platelet reactivity and altered platelet morphology (e.g. increased mean platelet volume), further reduces the antiplatelet effects of aspirin. Additionally, oxidative stresswith markedelevations in the levels of reactive oxygen species, can exacerbate endothelial dysfunction and promote platelet aggregation, thatfurther compromises antithrombotic properties of aspirin. This interplay between inflammation, thrombogenicity, and oxidative stress underscores the multifactorial nature of AR and highlights the need for alternative therapeutic strategies or adjunctive treatments in patients who exhibit resistance to aspirin.

This study was not designed to detect differences in the occurrence of thrombotic events, such as stent thrombosis, when aspirin was omitted, and larger studies are required for such assessments. Further research is needed to elucidate the pathophysiological and clinical significance of increased oxidative stress and inflammation and to evaluate the effects of antioxidant and anti-inflammatory agents in patients with AMI. The sample size of this study is small but Future studies with larger sample size have been planned. Additionally, this study only assessed AR based on laboratory data but not clinical AR. Therefore, there is a need for future studies to correlate laboratory and clinical data for aspirin resistance. Another limitation of the study was that AR was not evaluated at different aspirin doses. Future studies should be designed to assess the resistance to aspirin at various doses

The findings of this study suggest that inflammation and a prothrombotic state are significantly more common in the presence of AR in patients with ACS. These results support the role of inflammation, thrombosis, and oxidative stress in the development of AR. Increased platelet activity and inflammation may be underlying mechanisms leading to an increased risk of atherosclerotic cardiovascular disease, mortality, and morbidity in patients with AR. The mortality and morbidity rates can be reduced through lifestyle changes and dietary supplements that decrease oxidative stress, inflammation, and thrombogenicity in patients with acute coronary syndrome. Additionally, our study will offer a new perspective on the development of novel therapies and encourage a more extensive research on these issues by focusing on these pathways in patients with aspirin resistance. This could help to develop strategies to prevent negative cardiac outcomes. Additionally, it might offer financial, social, and psychological advantages by reducing the length of hospital stays.

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Peer-review: Externally peer-reviewed.
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