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Platelet Membrane γ-Glutamyl Transferase-Specific Activity and the Clinical Course of Acute Coronary Syndrome

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Abstract

γ-Glutamyl transferase (GGT) participates in oxidative and inflammatory reactions inside the atheroma plaque and platelets. We evaluated whether platelet membrane γ-glutamyl transferase (Plt-GGT) activity is a predictor of major adverse cardiac events (MACEs) during 3 months follow-up of patients with acute coronary syndrome (ACS; MACE-3M). We included 105 patients who were hospitalized consecutively with the diagnosis of ACS. Patients with an MACE-3M were older, more likely to have hypertension, hyperlipidemia, family history of coronary artery disease(CAD), thrombolysis in myocardial infarction (TIMI) risk score >4, higher Plt-GGT and serum GGT activities, serum C-reactive protein level, and lower left ventricular ejection fraction (LVEF) when compared to those without MACE-3M (all *P* values $\leq$.05). By receiver–operator characteristic (ROC) curve analysis, 265 mU/mg for Plt-GGT, 30 U/L for serum GGT, and 45% for LVEF were determined as cutoff values to discriminate MACEs. Platelet GGT activity >265 mU/mg, TIMI risk score >4, and family history of CAD were independent predictors of MACE-3M (all *P* values <.05). Platelet GGT activity was as an independent predictor for MACEs in patients with ACS during the 3 months follow-up.

Keywords

acute coronary syndrome, MACE, platelet, γ-glutamyl transferase

Introduction

Coronary artery disease (CAD), which accounts for the majority of cardiovascular diseases (CVDs), causes >7 million deaths per year worldwide.[1] The most important cause of acute coronary syndrome (ACS) is plaque rupture.[2] The lipid content released by the rupture of the fibrous capsule possesses thrombogenic activity and contains high amounts of tissue factor.[2] After the erosion of endothelial cells, collagen exposure leads to adhesion and activation of platelets via von Willebrand factor (deposited with P-selectin in platelets).[3] Platelet activation stimulates the thrombotic cascade intertwined with inflammatory pathways.[3]

Serum γ-glutamyl transferase (GGT) levels are used as a marker of alcohol consumption and impaired liver function and have been shown to correlate with oxidative and inflammatory events.[4] γ-Glutamyl transferase activity has been confirmed within atheromatous plaques by histopathological examination.[5] γ-Glutamyl transferase is also known to have prognostic significance in patients with myocardial infarction (MI).[6]

However, the tissue and cellular sources of elevated serum GGT in CVDs have not yet been established. The different isoforms of GGT have been determined based on relative mobility on electrophoresis (GGT1-GGT5).[7] These isoforms can be found in serum in different amounts in various clinicopathological conditions.[8]

γ-Glutamyl transferase 4 isoforms have been found in the platelets and neutrophils.[7] It is known that GGT converts leukotriene C4 to leukotriene D4 in the platelet cell membrane, and these products are also prothrombotic.[9] The concentration of GGT in the platelet membrane may reflect the level of platelet activation.[9] The activity of GGTs in the platelets and their electrophoretic behaviors are different from those in the serum.[7] γ-Glutamyl transferase in the platelets produces a distinct electrophoretic band and has different substrate interactions than those seen in the serum. It is understood that the

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activity measured in the serum is due to the composition of GGT isoforms originating from many tissues.[7,9,10]

The aim of this study was to investigate the predictive value of platelet membrane GGT (Plt-GGT) activity for the development of major adverse cardiac events (MACEs; recurrent angina pectoris, MI, rehospitalization due to ACS, and death) after a 3-month follow-up (MACE-3M) in patients hospitalized with ACS.

Methods

Patients hospitalized (n = 105) with a prediagnosis of ACS at Baskent University Cardiology Clinic, between May 2007 and July 2007, were included in the study consecutively after obtaining written informed consents. The follow-up continued till the end of October 2007. The study was approved by Baskent University Faculty of Medicine Clinical Research Ethics Committee (approval dated February 05, 2007, and number 07/90). Patients diagnosed with an increased concentration of liver enzymes, active hepatobiliary disease, active use of alcohol, who underwent major surgery (vascular, pulmonary, cerebral, hepatobiliary, or genitourinary) within the last 4 weeks, definite diagnosis of pulmonary embolism, deep vein thrombosis, cerebrovascular event, peripheral arterial embolism and thrombosis, disseminated intravascular coagulation, sepsis and active malignancy, active tuberculosis, AIDS, and other immunodeficiency were excluded from the study.

Three months after discharge, the patients were investigated for recurrent angina or angina equivalent symptoms, hospitalization due to ACS and death (MACE-3M), either during follow-up examinations or via telephone calls. If any death was reported within this 3-month period, the cause of death (cardiac or non-cardiac) was recorded.

Hypertension (HT) was defined as documentation of a systolic blood pressure of $\geq$140 mm Hg and/or a diastolic blood pressure of $\geq$90 mm Hg in at least 2 measurements or active use of any antihypertensive agent. Diabetes mellitus was diagnosed as a fasting plasma glucose level over 126 mg/dL or glucose level over 200 mg/dL at any measurement or active use of an antidiabetic agent. Hyperlipidemia (HL) was defined according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report.[11]

Venous blood samples were obtained from the patients using a thick needle (20G = 0.9 mm) and were placed in tubes containing acid–citrate–dextrose (ACD; composition: 38 mmol/L citric acid, 75 mmol/L sodium citrate, and 124 mmol/L dextrose) in a ratio of 1.5 mL ACD/8.5 mL blood. After the sample was "rested" for 15 minutes, it was centrifuged at 1500 rpm for 8 minutes to obtain platelet-rich plasma.[9,12] This plasma was then centrifuged at 4000 rpm for 30 minutes to remove the remaining platelet cell pellet. The precipitate thus obtained was washed 3 times with cell washing solution (0.003 mmol/L Tris–HCl buffer+0.12 mmol/L NaCl+0.005 mmol/L EDTA, adjusted to pH 7.4) and was recentrifuged at 4000 rpm for 30 minutes. The washed platelet precipitate was mixed with distilled water. It was then frozen and thawed 4 times with addition of distilled water for cell lysis. Frozen and thawed platelets were centrifuged for 15 minutes at 10 000 rpm. The precipitate was suspended in 0.01 mmol/L Tris-HCl buffer containing 1% Triton X-100, aiming a cool incubation for 5 hours at 4°C with gentle stirring, and then centrifuged at 10 000 rpm for 15 minutes at 4°C to give a clear supernatant.[13]

The enzymatic colorimetric test was performed for measuring GGT activity at 37°C in patients' serum and obtained supernatant. L-γ-glutamyl-3-carboxy-4-nitroaniline was used as the substrate. The analysis was performed using a Roche-Hitachi analyzer (Mannheim, Germany). γ-Glutamyl transferase values were measured in units per liter (U/L). Total protein was determined in the obtained supernatant according to the Bradford method[13] and also with enzymatic colorimetric assay at 37°C, using a Roche-Hitachi analyzer (Mannheim, Germany). Because of the identical measurements of protein amounts by these 2 methods, colorimetric assay had been used in entire cases. Serum high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride values were measured using an enzymatic colorimetric assay at 37°C, using a Roche-Hitachi analyzer (Mannheim, Germany), and the concentrations were measured in mg/dL.

The following formula was used to calculate the "Plt-GGT-specific activity" and expressed in mU/mg for easy comparison of the small numbers (Plt-GGT: U/mg = 1000 mU/mg):

$$\text{Plt} - \text{GGT}\ \frac{\text{U}}{\text{mg}} = \frac{\text{GGT activity in platelet membrane protein solution U/L}}{\text{total protein in platelet membrane protein solution}\ \frac{\text{mg}}{\text{L}}}.$$

Statistical Analysis

All calculations were performed using Statistical Program for the Social Services Version (13.0) software. The continuous variables were expressed as mean (standard deviation) and median (interquartile range). The categorical variables were reported as frequency and percentage. The data were tested for normal distribution by Kolmogorov-Smirnov test. The comparison of differences between the groups was done using χ^2 (chi-square) test for categorical variables and independent sample *t*-test for continuous variables. The cutoff values for the parameters investigated were calculated using the receiver–operator characteristic (ROC) curve analysis. Single Cox regression analysis was used to analyze parameters that were determinant for MACE-3M. Independent determinants of MACE-3M were recorded using the multiple Cox regression analysis. All *P* values were 2 sided, and $P \leq .05$ was considered significant.

Results

Of all the patients, 77 (73.3%) were male, 28 (26.7%) were female, and the mean age of the patients was 61.9 (10.5) years. The median Plt-GGT level of the patients was 170.3 (88.3-355.0) mU/mg. A total of 105 patients were followed

Table 1. Baseline Clinical and Laboratory Characteristics of the Study Population and the Comparison of Groups With and Without MACE-3M.[a]

Clinical Characteristics	Total Population, n = 105	No MACE-3M, n = 75	MACE-3M, n = 30	*P* Values
Age, years	61.86	60.2 (10)	66 (11)	.010
Age ≥70 years	28 (26%)	14 (18.7%)	14 (46.7%)	.003
Male gender	77 (73%)	52 (69.3%)	25 (83.3%)	.143
Traditional risk factors				
Hypertension	67 (63.8%)	43 (57.3%)	24 (80%)	.029
Diabetes mellitus	52 (49.5%)	40 (53.3%)	12 (40%)	.217
Hyperlipidemia	69 (65.7%)	45 (60%)	24 (80%)	.050
BMI ≥30	37 (35.2%)	23 (30.7%)	14 (46.7%)	.121
History of CAD	50 (47.6%)	29 (38.7%)	21 (70%)	.004
Family history of premature CAD	49 (46.7%)	28 (37.3%)	21 (70%)	.002
History of PAD	21 (20%)	8 (10.7%)	13 (43.3%)	<.001
History of CVE	4 (3.8%)	2 (2.7%)	2 (6.7%)	.322
Smoking	77 (73.3%)	53 (70.7%)	24 (80%)	.329
TIMI score ≥4	43 (41%)	17 (22.7%)	26 (86.7%)	<.001
Mean Days of Hospitalization	4.64 (3.6)	3.3 (2.3)	8 (4.5)	<.001
Hospitalization Time ≥5 days	42 (40%)	16 (21.3%)	26 (86.7%)	<.001
Medications				
ASA	94 (89%)	67 (89.3%)	27 (90%)	.920
Clopidogrel	37 (35%)	25 (33.3%)	12 (40.0%)	.518
Intravenous Heparin	45 (43%)	28 (37.3%)	17 (56.7%)	.071
Low-molecular-weight heparins	43 (40.9%)	26 (34.7%)	17 (56.7%)	.038
Tirofiban	15 (14.3%)	10 (13.3%)	5 (16.7%)	.659
Statin	82 (78%)	58 (77.3%)	24 (80%)	.765
Beta-Blocker	66 (62.8%)	44 (58.7%)	22 (73.3%)	.160
Calcium antagonists	26 (24.7%)	19 (25.3%)	7 (23.3%)	.830
ACE inhibitor/ARB	62 (59%)	46 (61.3%)	16 (53.3%)	.451
Nitrates	50 (47.6%)	29 (38.7%)	21 (70%)	.004
Laboratory variables				
LVEF, %	47.82 (9.5)	49.9 (8.4)	42.5 (10.3)	<.001
Plt-GGT, mU/mg	170 (88-355)	125 (72-300)	267 (192-641)	<.001
Serum GGT, U/L	29 (15)	27 (13)	33 (17)	.050
Serum CRP, mg/L	9.3 (12.2)	7.8 (11)	13 (14.2)	.044
HbA_{1c}, %	6.5 (1.4)	6.6 (1.5)	6.2 (1.1)	.283
Serum HDL cholesterol, mg/dL	41 (9)	41 (10)	41 (7)	.802
Serum LDL cholesterol, mg/dL	115 (34)	117 (35)	109 (30)	.275
Serum Triglyceride, mg/dL	186 (113)	180 (112)	199 (117)	.445
Serum AST, U/L	27 (15)	27 (11)	30 (22)	.064
Serum ALT, U/L	24 (10)	23.4 (11)	26 (9)	.578
Serum ALP, U/L	184 (54)	182 (46)	187 (71)	.157

Abbreviations: ACE: angiotensin converting enzyme; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ASA: acetylsalicylic acid; AST: aspartate aminotransferase; ARB: angiotensin receptor blocker; BMI: body mass index; CAD: coronary artery disease; CRP: C-reactive protein; CVE: cerebrovascular event; GGT: γ-glutamyl transferase; HDL: high density lipoprotein; LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; MACE-3M: major adverse cardiac events at 3 months; PAD: peripheral artery disease; Plt-GGT: platelet γ-glutamyl transferase; TIMI: Thrombolysis In Myocardial Infarction.
[a]Data are given as mean (SD), n (%), or median (interquartile range).

up to investigate the development of MACE-3M after discharge. In all, 60 (57.1%) patients were diagnosed as unstable angina pectoris (USAP), 28 (26.7%) patients were diagnosed as non-ST-segment elevation myocardial infarction (NSTEMI), and 17 (16.2%) patients were diagnosed as ST-segment elevation myocardial infarction (STEMI). Of these patients, 30 (28.6%) developed MACE-3M (recurrent angina in 18 patients, MI in 10 patients, hospitalization due to ACS in 14 patients, and cardiac death in 4 patients). Clinical characteristics, medications used, and laboratory findings of the patients are shown in Table 1.

A significant difference was found between the patients with and without MACE-3M in terms of the mean age (66.2 [11.0] and 60.2 [10] years; $P = .01$), being older than 70 years (46.7% and 18.7%; $P = .003$), HT (80.0% and 57.3%; $P = .029$), and HL (80% and 60%; $P = .05$). The laboratory parameters that showed significant differences between the groups were Plt-GGT, 267 (191-640) mU/mg and 125 (72-300) mU/mg; $P < .001$], serum GGT (33 [17] and 27[13] U/L; $P = .05$, and serum C-reactive protein (CRP) levels (13 [8.2] and 7.8 [4.9] mg/L; $P = .044$). There were no significant differences between 2 groups about the other liver function tests such as aspartate

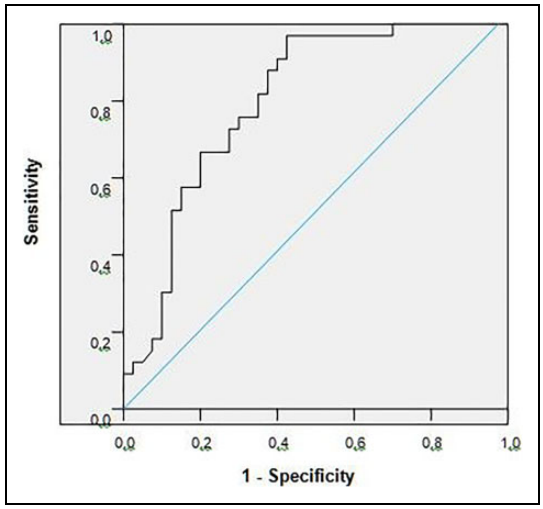

Figure 1. Receiver–operator characteristic (ROC) curve of platelet membrane γ-glutamyl transferase (Plt-GGT) activity and prediction of major adverse cardiac events-3 months (MACE-3M). Area under the curve: 0.800, $P = .001$.

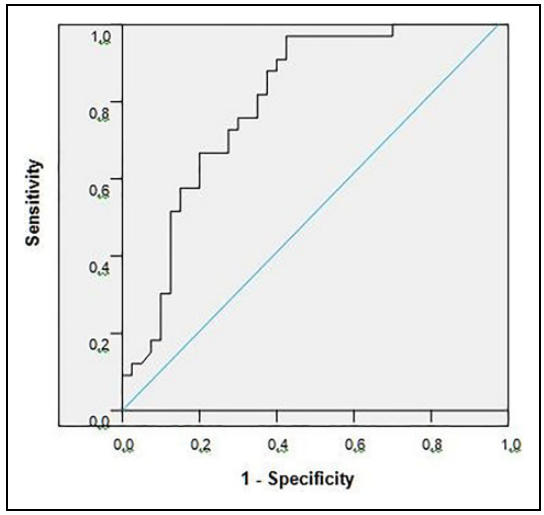

Figure 2. Receiver–operator characteristic (ROC) curve of left ventricular ejection fraction (LVEF) and prediction of major adverse cardiac events-3 months (MACE-3M). Area under the curve: 0.727, $P = .001$.

aminotransferase, alanine aminotransferase, and alkaline phosphatase levels. There were no significant differences between 2 groups regarding the medication used such as acetylsalicylic acid, clopidogrel, and statins which could affect platelet function and atherosclerotic plaque stabilization. Among the study population, 77 (73.3%) patients were smoking. There was no significant difference regarding smoking between the patients with and without MACE-3M, 24 (80%) and 53 (70.7%); $P = .329$. Platelet GGT and serum GGT levels were significantly higher in the smoking group compared to nonsmokers (for Plt-GGT: 245 [111-415] mU/mg vs 111 [60-240] mU/mg; $P = .006$; for Serum GGT: 32 [15] vs 25 [13] U/L; $P = .036$, respectively). The clinical characteristics, medications used, and the laboratory parameters of patients with and without MACE-3M are given in Table 1.

It was seen that the Plt-GGT-specific activity at the time of admission increased proportional to the clinical severity of ACS. The analysis showed a statistically significant difference between the median Plt-GGT activities in each diagnostic step from USAP to NSTEMI and STEMI, USAP 126 (71-273) mU/mg, NSTEMİ 226 (106-353) mU/mg, and STEMİ 365 (287-516) mU/mg; $P = .01$, $P = .021$, and $P < .001$.

The cutoff values as calculated by ROC curve analysis were used in single and multiple regression analyses and are as follows: LVEF <45%, Plt-GGT >265 mU/mg, serum GGT activity >30 U/L, serum CRP levels >4 mg/L, and length of hospitalization >5 days. The ROC curves of these variables are provided in Figures 1 to 4 with the area under the curve (AUC) and P values. The parameters that determine the development of MACE-3M in single Cox regression analysis were LVEF >45%, Plt-GGT >265 mU/mg, thrombolysis in myocardial infarction (TIMI) risk score >4, the presence of HT and CAD, family history of CAD and peripheral artery disease (PAD), and the length of hospitalization >5 days (Table 2). For the

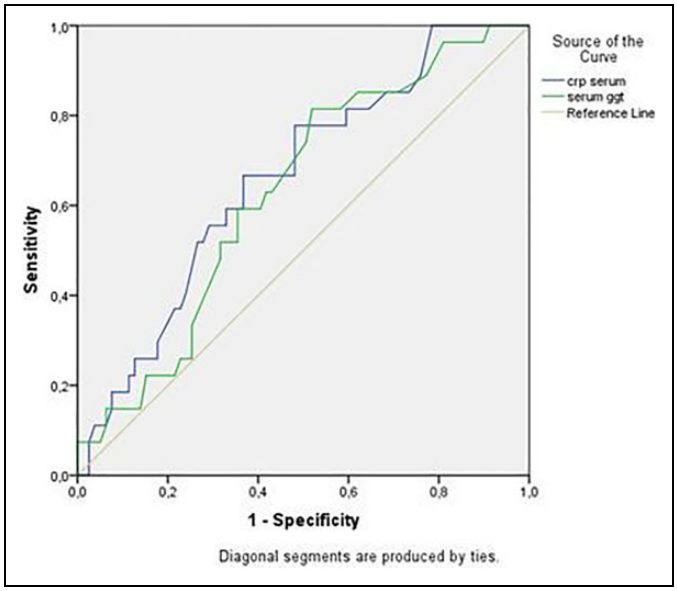

Figure 3. Receiver–operator characteristic (ROC) curve of serum γ-glutamyl transferase (GGT) and serum C-reactive protein (CRP) and prediction of major adverse cardiac events-3 months (MACE-3M). Area under the curve; GGT: [0.631, $P = .043$] CRP: [0.661, $P = .013$].

prediction of MACE-3M, the sensitivity and specificity were 83.3% and 82.7% for a Plt-GGT value >265 mU/mg, 74.7% and 63.3% for an LVEF >45, and 86.7% and 77.3% for a TIMI Risk Score>4, respectively.

After multiple regression analysis, Plt-GGT >265 mU/mg, length of hospitalization >5 days, TIMI risk score >4, and family history of CAD were found to be independent predictors of MACE-3M with a positive predictive value of 65.8%, 61.9%, 60.5%, and 43% and negative predictive value of 92.5%, 94%, 93.5%, and 83.9%, respectively. We found that the risk of MACE-3M is 4.8 times higher in patients having a

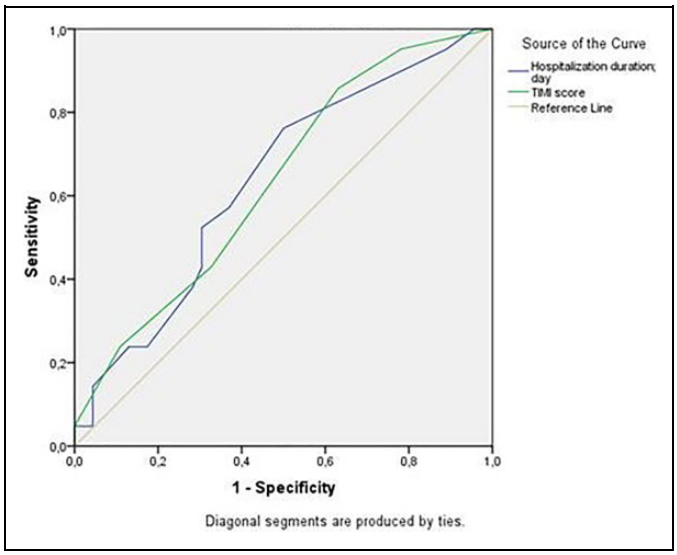

Figure 4. Receiver–operator characteristic (ROC) curve of hospitalization duration and thrombolysis in myocardial infarction (TIMI) score and prediction of major adverse cardiac events-3 months (MACE-3M). Area under the curve; Hospitalization day: [0.637 $P = .074$] TIMI score: [0.634 $P = .081$].

Table 2. Independent Variables Related MACE-3M Determination With Multivariate Cox Regression Analysis.

Characteristics of Patients	Hazard Ratio (95% Confidence Interval)	*P* Values
Hospitalization Time ≥5 days	5.9 (1.6-22.8)	.002
Plt-GGT ≥265 mU/mg	4.8 (1.5-14.7)	.006
TIMI score ≥4	3.5 (1.0-12.3)	.046
Family history of premature CAD	3.0 (1.1-8.1)	.028
Age ≥70 years	2.6 (0.8-8.5)	.114
History of PAD	1.8 (0.6-5.3)	.277
Serum GGT ≥30 U/L	1.7 (0.8-4.0)	.190
History of CAD	1.6 (0.6-4.2)	.307
CRP ≥4 mg/L	1.6 (0.6-4.2)	.311
Hypertension	1.5 (0.5-4.4)	.379
LVEF (%) ≤ 45	1.4 (0.6-3.4)	.374

Abbreviations: CAD: coronary artery disease; CRP: C-reactive protein; GGT: γ-glutamyl transferase; LVEF: left ventricular ejection fraction; MACE-3M: major adverse cardiac events at 3 months; PAD: peripheral artery disease; Plt-GGT: platelet γ-glutamyl transferase; TIMI: Thrombolysis In Myocardial Infarction.

Plt-GGT-specific activity >265 mU/mg at the time of admission (Table 2).

When the mean Plt-GGT-specific activities were compared using the clinical TIMI score groups, it was found that Plt-GGT-specific activity showed a steady increase toward the high-risk groups with a strong statistical significance (TIMI 1 to TIMI 6-8 analysis of variance; $P < .0001$; Figure 5).

Discussion

The most valuable finding of our study was that Plt-GGT activity seems to be a strong predictor of MACE-3M in patients

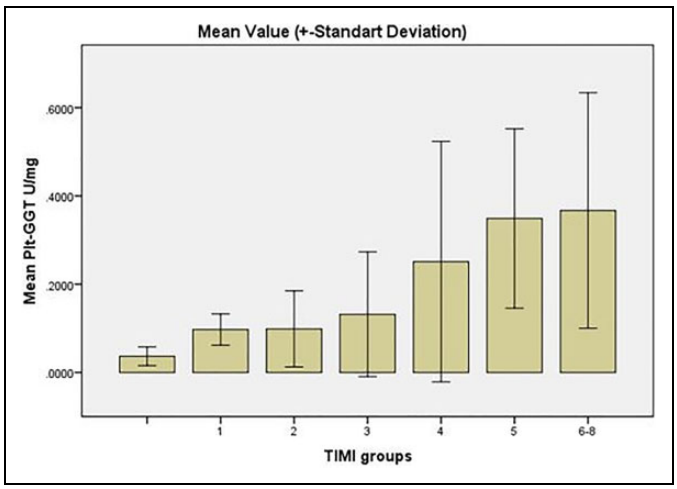

Figure 5. Mean platelet γ-glutamyl transferase (Plt-GGT) activities according to thrombolysis in myocardial infarction (TIMI) clinical score groups.

hospitalized with ACS, correlating with known prognostic indicator TIMI risk score. The level of Plt-GGT specific activity was associated with the clinical severity of ACS.

Our study population consisted of high-risk patients, so the TIMI risk score was >4 in 41% of them. An increase in TIMI risk score was associated with Plt-GGT activity; a TIMI risk score >4 was associated with a 3.5-fold increase in MACE-3M. Therefore, the specific activity of Plt-GGT measured at hospital admission may help to identify and manage high-risk patients, since it was found to be an independent variable for the development of MACEs and to provide similar results with the globally accepted TIMI risk score.

Approximately 20% of all patients presenting to the emergency department with acute chest pain are diagnosed with ACS.[14] During admission and in-hospital follow-up in patients with an ACS, risk stratification is of paramount importance. We intend to investigate the Plt-GGT as a novel biochemical marker for risk stratification of ACSs.

The MACE-3M was significantly higher in the patients having a Plt-GGT-specific activity >265 mU/mg. Platelet GGT >265 mU/mg was found to be an independent predictor for MACE-3M by multiple regression analysis. Until now, no study has been published that emphasizes the prognostic significance of Plt-GGT for any CVD. Therefore, it is not possible to exactly compare with similar studies. However, previous studies have shown that high serum GGT activity has a prognostic value in patients hospitalized with a diagnosis of ACS[15] or after MI.[6]

γ-Glutamyl transferase has been shown to directly participate in oxidative events related to the formation of the atheromatous plaque.[16] It is considered that the migration of GGT into the plaque occurs via LDL.[16] γ-Glutamyl transferase is also present in the platelet membrane and converts leukotriene C4 to leukotriene D4.[9] An increased excretion of leukotriene D4 and E4 has been found in patients after MI and coronary artery bypass surgery.[17]

An important issue that determines long-term MACEs in the ACS clinic is multiple vulnerable lesions that produce greater risk for recurrent ischemic events.[18-20] In angiographic studies, it has been observed that even if the culprit lesion is successfully treated with an interventional approach, the remaining unstable plaques are responsible for recurrent events.[18-20] Platelet GGT activity, which is claimed to be a marker of platelet function,[9] may be thought to be mediated from platelets during plaque rupture thrombus formation in the ACS clinic. The view that the cumulative GGT activities in serum and platelets are related to the amount of thrombus supports our finding that Plt-GGT activity is associated with severity of ACS. It can be argued that the Plt-GGT-specific activity increased due to the excess amount of inflamed plaques (vulnerable plaques), which is not responsible for the ACS presentation at admission; however, it is constantly in contact with platelets in the coronary circulation and increases the tonic reactivity of platelets as a trigger for transient micro-thrombosis, while accelerating the platelet cycle. This also explains the fact that a Plt-GGT level >265 mU/mg was determined to be an independent variable for the development of MACEs in the following days and months.

Left ventricular ejection fraction (LVEF) is the most important determinant of MACEs in the patients with acute MI. Several studies have shown that the LVEF measured in intensive care unit is predictive of 1-year survival after acute MI.[21-24] It has been shown in previous studies that the rate of death increases within 6 months after acute MI when LVEF falls below 40%.[25] The mean LVEF values of patients included in the present study were higher than those in similar studies (mean [SD] = 47.9 [9.5]%). However, the rate of the development of adverse events within the 3-month follow-up period was significantly higher in patients with an LVEF <45% compared to those with an LVEF >45%. Unfortunately, LVEF <45% was not found to be an independent predictor of the development of MACE-3M in this study. This may be due to the short duration of the follow-up (3-months) and small sample size. This result could also be due to the fact that the LVEF values of patients in this study were better than those in the other studies.

The patients older than 70 years of age who are admitted with ACS are always at a high risk in the long term.[26,27] The age of >70 years was found to be the most important predictor of prognosis in patients with NSTEMI in a study[28] and STEMI in another study.[29] The rate of the development of adverse events within the 3-month follow-up period was significantly higher in patients older than 70 years when compared to those younger than 70 years of age in the present study, and this was in accordance with the literature. The age >70 years alone was found to be a predictor of MACE-3M.

Cigarette smoking induces inflammation and oxidative stress.[30,31] In this study, we found an increase in serum GGT and Plt-GGT in smokers confirming previous studies.[32] Nevertheless, smoking could not predict MACE-3M during our follow-up probably due to our small sample size. It has been shown that smoking increases serum GGT activity in a dose-dependent manner and with co-use of alcohol. Whitehead et al found that the effect of cigarette on serum GGT was significant in amounts up to 3 to 4 units/d of alcohol consumption.[33] They showed that cigarette smoking significantly increases the activity of GGT in drinkers. Those who consume alcohol at this level were not included in our study group. Our patients are usually teetotalers and occasional drinkers. These conditions might have weakened the relation between smoking and MACE-3M in our study. In addition, as a limitation of our study, the total amount of cigarettes smoked daily by our patients was not recorded. We think that smoking as a risk factor for coronary atherosclerosis is associated with increased serum GGT and Plt-GGT activities in patients with NSTEMI and STEMI with high thrombotic activity. In these patients, we tried to measure the Plt-GGT which we thought could be used as a platelet activation indicator and to investigate the relationship with MACE-3M. Further research should compare the amount of cigarette consumption with Plt-GGT in patients with ACS and distinguish which GGT isoenzyme is affected by smoking. The effect of various treatments also needs to be assessed.

Besides, significant statistical correlation was found between serum GGT level and MACE-3M in the present study, the risk coefficient and the predictive value of Plt-GGT-specific activity for MACE-3M were higher than the values obtained with serum GGT. This suggests that platelets might be a source of serum GGT activity.

It is not known whether the negative impact of Plt-GGT-specific activity on prognosis can be reversed by the drugs or surgical and percutaneous revascularization methods used in the treatment of atherosclerotic disease. It must be assessed in future studies whether any drug decreases the Plt-GGT activity; if found so, the effect of this decline on the prognosis must also be evaluated.

Our study is single centered, small scaled, and short termed in follow-up. Therefore, examination of the effects of risk-reducing drug treatments on MACE development was not possible. Also, the course of Plt-GGT-specific activity in patient groups during follow-up was not investigated.

Platelet GGT-specific activity was found to be an independent predictor of MACE-3M and a stronger prognostic marker than serum GGT activity. Platelet GGT>265 mU/mg, TIMI risk score >4, family history of CAD, duration of stay in coronary care unit (CCU) >5 days, and age >70 years were considered as independent predictors of the development of MACE-3M. In addition, the activity of Plt-GGT was increased with the clinical severity of ACS. New confirmative large-scale studies will be noteworthy for investigating the Plt-GGT (GGT4) as a novel biochemical marker for risk stratification of ACSs in a practical manner like giving way to a new Elisa kit design measuring Plt-GGT (GGT4) in serum.

Author contribution

All authors contributed to: (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

The study was approved by Baskent University Faculty of Medicine Clinical Research Ethics Committee (approval dated 02/05/2007 and number 07/90).

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