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CARDIOVASCULAR SURGERY AND INTERVENTIONS

Gamma-glutamyl transferase levels and coronary artery disease severity assessed by SYNTAX score: Impact of premature atherosclerosis

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ABSTRACT

Objectives: Gamma-glutamyl transferase (GGT) has emerged as a biomarker reflecting oxidative stress and low-grade inflammation, both of which play key roles in the development and progression of coronary artery disease (CAD). However, its association with angiographic CAD severity, particularly in patients with premature atherosclerosis, remains incompletely defined.

Patients and methods: A total of 454 consecutive patients with angiographically confirmed CAD managed with an invasive strategy were included. The study aimed to investigate the relationship between serum GGT levels and CAD severity assessed by the SYNTAX score, with a particular focus on premature CAD. Patients were categorized into four age groups: ≤49 years, 50-59 years, 60-69 years, and ≥70 years. Demographic characteristics, cardiovascular risk factors, and laboratory parameters including GGT levels were recorded. Coronary lesion complexity was quantified using the SYNTAX score. Correlation analysis was performed to evaluate the association between GGT levels and SYNTAX score.

Results: GGT levels showed a significant decreasing trend with advancing age ($p<0.001$). Serum GGT demonstrated a weak but statistically significant positive correlation with SYNTAX score ($r=0.136$, $p=0.05$). Notably, patients with premature CAD (≤49 years) exhibited the highest GGT levels compared to older age groups.

Conclusion: Serum GGT levels are positively associated with CAD severity as assessed by the SYNTAX score, particularly in patients with premature atherosclerosis. GGT may serve as a simple, widely available biomarker reflecting coronary atherosclerotic burden, with potential utility in risk stratification, especially in younger patients.

Keywords: Gamma-glutamyl transferase, coronary artery disease, premature atherosclerosis, SYNTAX score.

Gamma-glutamyl transferase (GGT) has emerged as a biomarker reflecting oxidative stress and low-grade inflammation, both of which contribute to the development and progression of coronary artery disease (CAD).[1-3] Coronary artery disease remains the leading cause of morbidity and mortality worldwide despite advances in preventive and therapeutic strategies.[4-6]

Beyond its traditional role as a marker of hepatobiliary dysfunction and alcohol consumption, increasing evidence suggests that GGT is associated with endothelial dysfunction, oxidative stress, and atherosclerotic processes.[1-3] Elevated serum GGT levels have also been linked to adverse cardiovascular outcomes and cardiovascular mortality in patients with established CAD.[4,5]

The severity and complexity of coronary atherosclerosis can be objectively evaluated using angiographic scoring systems. In this context, the SYNTAX score is widely used to assess coronary lesion complexity and overall atherosclerotic burden.[7] However, the relationship between serum GGT levels and angiographic CAD severity, particularly in patients with premature atherosclerosis, remains incompletely understood.

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Premature CAD represents a distinct clinical phenotype characterized by accelerated atherosclerosis and increased oxidative stress burden. Whether circulating GGT levels reflect angiographic CAD severity differently across age groups remains unclear. Therefore, the present study aimed to investigate the association between serum GGT levels and CAD severity assessed by the SYNTAX score, with particular emphasis on premature CAD.

PATIENTS AND METHODS

Study Population

This single-center observational study included 454 consecutive patients with angiographically confirmed CAD who underwent invasive coronary angiography and were managed with an invasive strategy. Consecutive enrollment was used to minimize selection bias. Patients were categorized into four age groups: Group 1: ≤49 years, group 2: 50-59 years, group 3: 60-69 years, group 4: ≥70 years. Premature CAD was defined as age ≤49 years, consistent with prior literature.[7]

Clinical and Laboratory Data

Baseline demographic characteristics, cardiovascular risk factors, and laboratory parameters were obtained.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as percentages. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. For variables showing normal distribution, One-Way ANOVA was used for group comparisons, whereas for non-normally distributed variables, the Kruskal-Wallis test was applied. Pearson correlation analysis was performed to assess the relationship between serum GGT levels and SYNTAX score. A p-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of serum GGT levels for CAD severity. The area under the curve (AUC) with 95% confidence intervals (CI) was calculated. The optimal cut-off value was determined using the Youden index. Sensitivity and specificity values corresponding to the optimal cut-off point were reported. Variables with p<0.10 in univariate analysis were included in the multivariate logistic regression model. This study was approved by the Ethics Committee of İzmir Bakırçay University Faculty of Medicine (approval no: 2234, date: 07 May 2025). Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

RESULTS

The study population consisted of 454 patients, of whom 165 (36.3%) were female. Hypertension was present in 60.4%, diabetes mellitus in 40.7%, hyperlipidemia in 39.4%, and 31.5% were active smokers. Percutaneous coronary intervention was performed in 63.2% of patients, while 36.8% underwent coronary artery bypass grafting. Premature CAD patients constituted 8.8% of the cohort. The distribution of patients across age groups was as follows: ≤49 years (n=40), 50-59 years (n=121), 60-69 years (n=159), and ≥70 years (n=134). Serum GGT levels showed a weak but statistically borderline significant positive correlation with SYNTAX score (r=0.136, p=0.05) (Figure 1). SYNTAX score did not differ significantly across age groups (p=0.189). Although a statistically significant correlation was observed between age and SYNTAX score, the strength of this association was very weak (r=0.093, p=0.049) and is unlikely to be clinically meaningful (Figure 2). HDL cholesterol increased with age, while triglyceride and GGT levels decreased significantly across age groups. Detailed clinical, laboratory, and angiographic characteristics according to age groups are presented in Table 1. ROC curve analysis was performed to evaluate the ability of serum GGT levels to predict premature atherosclerosis (Figure 3). The AUC was 0.610 (95% CI: 0.519-0.701, p=0.021), indicating a modest discriminatory performance. At the optimal cut-off value of 30.5 U/L, GGT demonstrated a sensitivity of 70% and a specificity of 53.4% for predicting premature atherosclerosis. While the sensitivity was relatively acceptable, the limited specificity suggests a restricted ability to accurately distinguish between patients with and without premature disease. Overall, these findings indicate that GGT has a statistically significant but clinically modest predictive value for premature atherosclerosis.

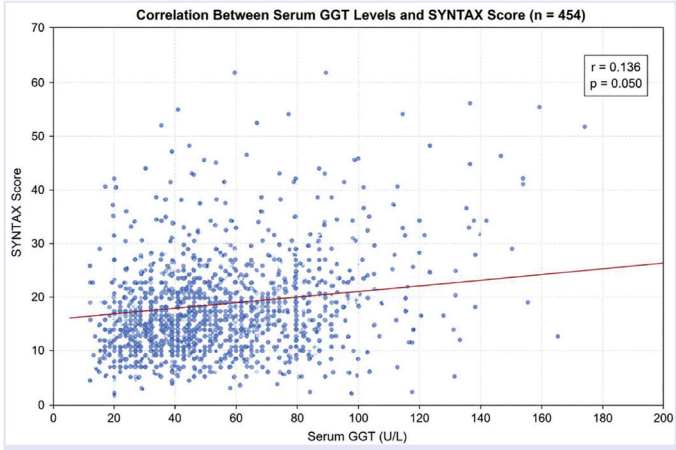

Figure 1. Scatter plot illustrating the relationship between serum gamma-glutamyl transferase (GGT) levels and SYNTAX score.

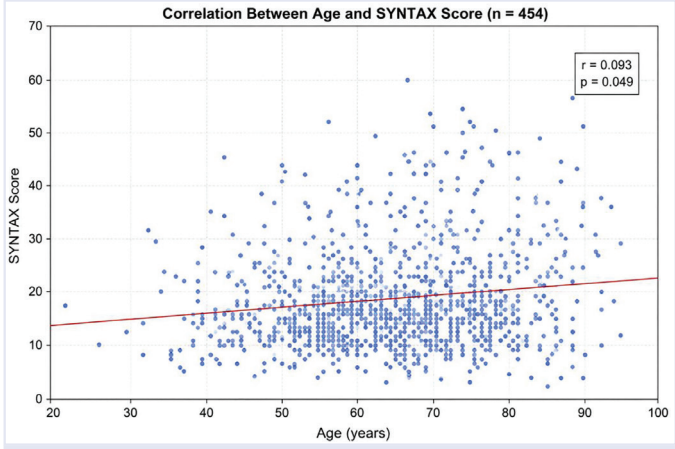

Figure 2. Scatter plot demonstrating the relationship between age and SYNTAX score.

Table 1. Clinical, laboratory, and angiographic characteristics according to age groups

Parameter	Group 1	Group 2	Group 3	Group 4	p-value
Age (years)	43.9±4.5	55.1±2.6	64.9±2.9	75.2±4.2	<0.001
SYNTAX score	16.2±10.5	19.2±10.2	20.1±12.7	21.6±13.9	0.083
Total cholesterol (mg/dL)	201.8±51.1	203.2±51.7	196.8±45.4	191.1±43.3	0.161
LDL-C (mg/dL)	126.1±40.4	121.0±40.2	122.1±38.1	115.2±38.1	0.109
HDL-C (mg/dL)	35.7±6.3	41.4±11.4	42.1±11.8	42.5±12.1	0.003
Triglycerides (mg/dL)	217.3±160.3	193.4±137.9	158.2±79.5	156.5±92.5	0.031
Fasting glucose (mg/dL)	113.3±37.4	130.3±58.8	125.1±46.6	124.3±46.4	0.249
Uric acid (mg/dL)	5.9±1.2	5.9±1.4	6.2±1.5	5.8±1.5	0.212
GGT (U/L)	50.3±45.2	41.0±31.3	40.3±40.5	36.7±47.4	<0.001
TSH (µIU/mL)	1.37±0.86	1.56±1.57	1.43±0.91	1.73±1.63	0.661
HbA1c (%)	6.3±1.4	6.5±1.4	6.5±1.3	6.6±1.5	0.839
BMI (kg/m²)	28.4±4.3	29.3±5.2	28.2±4.2	29.0±4.4	0.282

LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; GGT: Gamma-glutamyl transferase; TSH: Thyroid-stimulating hormone; HbA1c: Glycated hemoglobin; BMI: Body mass index.

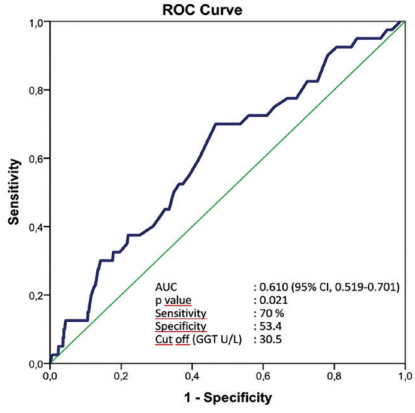

Figure 3. Receiver operating characteristic (ROC) curve analysis demonstrating the predictive performance of serum gamma-glutamyl transferase (GGT) levels for premature coronary artery disease. The area under the curve (AUC) was 0.610 (95% confidence interval [CI]: 0.519-0.701, p=0.021), indicating modest discriminatory ability.

DISCUSSION

In this angiographic study, serum GGT levels demonstrated a statistically borderline but positive association with CAD severity assessed by the SYNTAX score. Although the observed correlation coefficient was modest, this finding may still be biologically meaningful considering the multifactorial nature of coronary atherosclerosis and the complex determinants of angiographic disease burden.[2,3,6] Therefore, the present findings should be interpreted cautiously and considered hypothesis-generating rather than definitive evidence of a direct causal relationship between GGT and CAD complexity.

GGT is traditionally recognized as a hepatobiliary enzyme; however, accumulating evidence suggests that it may also reflect systemic oxidative stress, low-grade inflammation, and cardiometabolic risk burden.[1,2,8-10] Experimental and histopathological studies have demonstrated enzymatically active GGT within human atherosclerotic plaques, particularly in macrophage-rich and lipid-laden regions.[11-15] In this setting, GGT may contribute to oxidative modification of LDL cholesterol and promote plaque progression and instability through reactive oxygen species generation.[12,13] These mechanisms provide a biologically plausible explanation for the observed association between elevated GGT levels and more complex CAD.

Several previous studies have reported associations between GGT and cardiovascular outcomes, including myocardial infarction, heart failure, and cardiovascular mortality.[3-6,8] In addition, studies evaluating angiographic disease burden have demonstrated a relationship between elevated GGT levels and the extent of coronary atherosclerosis in patients with acute coronary syndromes and stable CAD.[16] Our findings are generally consistent with these reports, although the strength of the observed association was relatively weak. This is not unexpected, since SYNTAX score is influenced by numerous clinical and anatomical factors, including age, diabetes mellitus, hypertension, dyslipidemia, smoking, inflammatory activity, and genetic predisposition.[6,7] Accordingly, GGT should not be interpreted as an independent marker of CAD severity based solely on the present study, but rather as a potential adjunctive biomarker reflecting oxidative and metabolic risk.

One of the notable observations of this study was the higher GGT levels observed in patients with premature CAD. Premature coronary atherosclerosis has been associated with increased oxidative stress, metabolic dysregulation, insulin resistance, obesity, smoking, and hypertriglyceridemia, all of which are conditions closely linked to elevated GGT levels.[17,18] In addition, previous studies focusing on premature CAD populations have demonstrated distinct risk profiles and unfavorable cardiovascular characteristics in younger patients with coronary disease.[19,20] These findings suggest that GGT may be more informative in younger or middle-aged patients, in whom oxidative and metabolic mechanisms may contribute more prominently to accelerated atherosclerosis. However, because SYNTAX scores did not significantly differ across age groups, this observation should be interpreted carefully. Higher GGT levels in younger patients may reflect a distinct metabolic and inflammatory phenotype rather than directly indicating greater angiographic disease severity.

In our cohort, triglyceride levels also tended to decrease with advancing age, paralleling the decline in GGT levels. This observation further

supports the close relationship between GGT and metabolic risk profile described in previous studies.[16,17,18] Additionally, the inverse trend observed between bilirubin levels and CAD severity may support the proposed antioxidant role of bilirubin in atherosclerosis progression, although this relationship was not specifically designed as a primary endpoint of the study.

From a clinical perspective, GGT is an inexpensive, widely available, and routinely measured laboratory parameter. If confirmed in larger prospective studies, elevated GGT levels may help identify patients with increased oxidative stress burden and unfavorable cardiometabolic profiles, particularly among individuals with premature CAD. Nevertheless, GGT should not replace established cardiovascular risk markers or imaging-based assessments. Rather, it may serve as a complementary biomarker within a broader cardiovascular risk stratification approach.

Future studies should evaluate the relationship between GGT and CAD severity using clinically meaningful SYNTAX score categories, such as low, intermediate, and high SYNTAX groups.[7] Separate analyses in premature and non-premature CAD populations may further clarify whether GGT has differential relevance according to age-related atherosclerotic phenotype. In addition, prospective studies incorporating serial GGT measurements, plaque imaging, multivariable adjustment, and long-term cardiovascular outcomes are needed to determine whether GGT provides incremental prognostic value beyond established cardiovascular risk markers.

The present study has several limitations that should be considered while interpreting the findings. Due to its observational and cross-sectional design, a causal relationship between GGT levels and CAD severity cannot be established. Serum GGT levels were measured at a single time point, and serial measurements reflecting temporal changes in oxidative stress burden were not available. In addition, important confounding factors such as alcohol consumption, non-alcoholic fatty liver disease, hepatic dysfunction, and medications potentially affecting GGT levels were not systematically evaluated and the single-center design may limit the generalizability and external validity of the findings. The possible influence of cardiovascular therapies, including statins, antiplatelet agents, beta-blockers, and reninangiotensin system inhibitors, also could not be fully assessed.

Furthermore, previous coronary artery disease history, including prior percutaneous coronary intervention or coronary artery bypass grafting, was not analyzed separately, although these factors may affect both angiographic complexity and biochemical parameters. Concomitant atherosclerotic involvement in other vascular territories, such as carotid or peripheral artery disease, was not evaluated. Patients presenting with acute coronary syndromes and elective cases were analyzed together, and separate subgroup analyses according to clinical presentation were not performed, although acute ischemic conditions may influence inflammatory and oxidative biomarkers. Additionally, no multivariable regression analysis was performed to adjust for potential confounding variables, and additional inflammatory or oxidative stress biomarkers were not available. These limitations may have influenced the strength and interpretation of the observed associations.

Serum GGT levels were modestly and positively associated with SYNTAX score in patients with angiographically documented CAD. Higher GGT levels in patients with premature CAD may reflect an oxidative stress– and metabolism-related atherosclerotic phenotype. However, given the borderline statistical significance, modest correlation strength, and absence of multivariable adjustment, these findings should be interpreted cautiously and require confirmation in larger prospective studies incorporating multivariable adjustment and clinically relevant cardiovascular outcomes.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of İzmir Bakırçay University Faculty of Medicine (approval no: 2234, date: 07 May 2025).

Informed Consent: Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

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For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., B.E.; Concept: S.A.; Design: S.A.; Data Collection or Processing: B.E.; Analysis or Interpretation: S.A., B.E.; Literature Search: S.A.; Writing: S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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