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# Role of Gamma Glutamyl Transferase (GGT) and Creatine Kinase MB (CK-MB) in predicting coronary atherosclerosis: A hospital based observational study

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## Abstract

**Objectives:** To evaluate the role of gamma glutamyl transferase (GGT) and creatine kinase MB (CK-MB) in predicting coronary atherosclerosis; and to identify variables associated with levels of gamma glutamyl transferase, creatine kinase MB and percent coronary angiogram lesions. **Methods:** This was a prospective observational study conducted in the outpatient department and inpatient wards of the Department of General Medicine, tertiary healthcare facility in south India between March 2022 and December 2022. **Results:** The mean (SD) levels of GGT was 66.2 (19.4) and CK-MB was 72.7 (18.9). The levels of GGT and CK-MB increased with age, though the difference was not found to be statistically significant. Similarly, the levels of GGT and CK-MB was not statistically associated with gender and degree of vascular involvement. The mean (SD) age of the patients (54.7 (8.3) vs 37.9 (9.2)), gamma glutamyl transferase levels (69.5 (10.4) vs 46.9 (13.2)), and creatine kinase levels (74.7 (10.7) vs 52.3 (11.4)) were significantly higher among patients with coronary angiogram lesion more than 50.0%, in comparison with patients having coronary angiogram lesion less than 50.0% – a statistically significant difference ($p<0.05$). Correlation analysis showed that age had a significant positive moderate correlation; levels of GGT had significant positive strong correlation; levels of CK-MB had significant positive mild correlation; and ejection fraction had significant negative mild correlation with percent coronary angiogram lesion. Importantly, when the levels of GGT and CK-MB were combined, it showed a significant positive strong correlation with percent CAL, Pearson's coefficient being 0.831. The sensitivity and specificity of GGT ($\geq$52.5) to identify coronary atherosclerosis was 73.4% and 74.2%; of CK-MB levels ($\geq$66.0) was 56.8% and 58.2%, respectively. **Conclusion:** Incorporating these findings into clinical guidelines and screening protocols may enhance the accuracy of identifying individuals at risk of coronary atherosclerosis.

**Keywords:** Gamma Glutamyl Transferase, Creatine Kinase MB (CK-MB), Coronary atherosclerosis, India, Predictors

## Introduction

Gamma glutamyl transferase (GGT) is an enzyme responsible for the extracellular breakdown of glutathione, a major antioxidant in mammalian cells.(1) It is found on the outer surface of the plasma membrane in various cell types and in blood. In blood, it forms complexes with plasma components, including albumin and lipoproteins.(2) The measurement of serum GGT activity is a well-established diagnostic test for hepatobiliary diseases and is utilized as a sensitive marker for alcohol consumption and abuse.(3) Numerous studies have recognized the predictive value of serum GGT for both all-cause and cardiovascular mortality.(4)

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Coronary artery disease (CAD), also known as Ischemic Heart Disease (IHD), stands as the primary cause of death globally.(5) Atherosclerosis is the primary cause of Acute Coronary Syndrome (ACS), with most cases attributed to the rupture of an atherosclerotic plaque in a coronary artery, leading to thrombus formation. This thrombus results in coronary artery occlusion, restricting blood flow to the heart muscle. Various mechanisms, notably oxidative stress and inflammation are associated with atherosclerosis pathogenesis.(6)

Serum GGT, also known as gamma glutamyl transpeptidase, is a second-generation hepatic function test widely employed as a diagnostic indicator of liver dysfunction due to its role in glutathione catabolism.(7) Glutathione catabolism releases precursor amino acids in the extracellular membrane, transported to the intracellular compartment, forming glutathione. Simultaneously, the reactive thiol of cysteinyl glycine generated by GGT initiates an iron-dependent redox-cycling process, producing reactive oxygen species like superoxide anion and hydrogen peroxide.(8) These GGT-mediated prooxidant reactions catalyse the oxidation of LDL lipoproteins, contributing to the formation of inflammatory atheroma within the vascular endothelial wall. Thus, GGT-induced oxidative stress plays a central role in atherosclerotic plaque pathogenesis.(9) With targeted intervention to reduce GGT, it can be considered a modifiable risk factor.(10) Lowering GGT levels in at-risk patients may prevent myocardial infarction. Against this background, the objectives of the present study were to evaluate the role of gamma glutamyl transferase and creatine kinase MB in predicting coronary atherosclerosis; and to identify variables associated with levels of gamma glutamyl transferase, creatine kinase MB and percent coronary angiogram lesions.

## Materials and methods

This was a prospective observational study conducted in the outpatient department and inpatient wards of the Department of General Medicine, tertiary healthcare facility in south India between March 2022 and December 2022. The study was approved by the Institute Human Ethics Committee (IHEC). The content of Participant Information Sheet (PIS) in local language was provided to the participants (and their attenders) and contents were read to them in their own language to their satisfaction. The participants were enrolled in the study after obtaining written informed consent. The present study included patients presenting with acute coronary syndrome; of age 30 to 80 years (adults); and both gender. However, patients with history of past and/or current alcohol consumption, hepatitis B or C infection, other known hepatobiliary diseases or kidney diseases, use of hepatotoxic drugs, pregnancy and malignancies were excluded.

The study population was very specific – we resorted to purposive sampling. All accessible patients with acute coronary syndrome satisfying the inclusion criteria were included in the study using consecutive sampling technique. The minimum estimated sample size was 100 patients. We used a purpose predesigned, semi structured, pretested proforma to collect the patient sociodemographic characteristics, history, findings of general physical and clinical examination, laboratory parameters (including liver function tests, renal function tests, serum gamma glutamyl transferase, hepatitis B surface antigen (HbsAg), HCV antibody test (anti-HCV)), electrocardiogram (ECG), and coronary angiogram.

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The research hypothesis was that serum gamma glutamyl transferase levels will be elevated in patients presenting with acute myocardial infarction. The data obtained was manually entered into Microsoft Excel, coded, and recoded. Analysis was done using Statistical Package for the Social Sciences (SPSS) v23. Descriptive analysis was presented using numbers and percentages for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. To test for association, Chi-square test or Fisher's exact test (two sided) was used for categorical data; independent 't' test (two sided) was used for continuous data. To assess the correlation between independent study variables and percent coronary angiogram lesion, we used Pearsons's correlation coefficients. Area under the curve (AUC) values were estimated for gamma glutamyl transferase and CK-MB levels to predict atherosclerosis. Statistical significance was considered at $p<0.05$.

## Results

The present study included a total of 100 patients presenting with acute coronary syndrome. The mean (SD) age of the patients 49.7 years (11.5); ranging between 26 and 78 years with a median (IQR) of 50 years (14). More than half the patients (58.0%) were between 41 and 60 years of age; one in four (26.0%) were less than 40 years and 16.0% patients were elderly (more than 60 years). Majority (70.0%) of the patients were males. The distribution of vascular involvement showed that 22.0% had minimal disease, 44.0% had single vessel involvement, 14.0% had double vessel involvement, and 20.0% had triple vessel involvement.

The mean (SD) levels of gamma glutamyl transferase was 66.2 (19.4); ranging between 22.6 and 139.3 with a median (IQR) of 64.3 (19.7). Though the results showed that levels of gamma glutamyl transferase increased with age – 57.3 (26.3) in patients less than 40 years, 65.9 (24.0) in patients 41 to 60 years, and 68.7 (16.9) in patients more than 60 years of age – the difference was not found to be statistically significant. Similarly, the levels of GGT did not differ significantly by gender and vascular involvement ($p>0.05$).

The mean (SD) levels of CK-MB was 72.7 (18.9); ranging between 31.5 and 129.3 with a median (IQR) of 70.6 (22.4). The levels of creatine kinase MB increased with age – 63.3 (20.5) in patients less than 40 years of age, 72.5 (25.7) in patients 41 to 60 years, and 74.7 (18.5) in patients more than 60 years of age – the difference was not found to be statistically significant ($p>0.05$). Similarly, the levels of creatine kinase MB was not statistically associated with gender and degree of vascular involvement ($p>0.05$).

***Factors associated with percent coronary angiogram lesion:*** The results showed that the mean (SD) age of the patients (54.7 (8.3) vs 37.9 (9.2)), gamma glutamyl transferase levels (69.5 (10.4) vs 46.9 (13.2)), and creatine kinase levels (74.7 (10.7) vs 52.3 (11.4)) were significantly higher among patients with coronary angiogram lesion more than 50.0%, in comparison with patients having coronary angiogram lesion less than 50.0% – a statistically significant difference ($p<0.05$).

***Correlation of independent study variables and percent coronary angiogram lesion:*** The results of correlation analysis showed that age (in years) had a significant positive moderate correlation ($r=0.447$; $p=0.015$); levels of gamma glutamyl transferase had significant positive strong correlation ($r=0.649$; $p=<0.001$); levels of CK-MB had significant positive mild correlation ($r=0.361$; $p=0.013$); and ejection fraction had significant negative mild correlation

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(r=-0.353; p=0.041) with percent coronary angiogram lesion (p<0.05). Importantly, when the levels of GGT and CK-MB were combined, it showed a significant positive strong correlation with percent coronary angiogram lesion (p<0.05), Pearson's coefficient being 0.831.

***Receiver operating curve (ROC) analysis:*** The serum gamma glutamyl transferase levels more than or equal to 52.5 was identified as a predictor of coronary atherosclerosis with area under the curve value of 0.781 (95% CI 0.521 to 0.905; p=0.001). At this cut off point, the sensitivity and specificity of gamma glutamyl transferase to identify coronary atherosclerosis was 73.4% and 74.2% respectively.

The results showed that the CK-MB levels more than or equal to 66.0 was a predictor of coronary atherosclerosis with area under the curve value of 0.697 (95% CI 0.592 to 0.872), though not statistically significant (p=0.062). At this cut off point, the sensitivity and specificity of creatine kinase MB to identify coronary atherosclerosis was 56.8% and 58.2% respectively.

## Discussion

The demographic profile of the study population revealed a mean age of 49.7 years, with a majority being males (70.0%). This aligns with existing literature, as cardiovascular diseases, including acute coronary syndrome (ACS), often manifest in the middle-aged and older population, and the prevalence is generally higher in males.(11) The distribution of vascular involvement in the study cohort showed varying degrees, with 22.0% having minimal disease, 44.0% single vessel involvement, 14.0% double vessel involvement, and 20.0% triple vessel involvement. This distribution is consistent with the diverse presentations of ACS, highlighting the multifactorial nature of coronary artery disease.(12) The study found that GGT levels increased with age, although the difference was not statistically significant. This observation is in line with some studies that suggest an age-related increase in GGT levels.(4, 13, 14) However, the lack of significance may imply that age alone may not be a robust predictor of GGT elevation in ACS patients. Additionally, no significant associations were observed between GGT levels, gender, and the degree of vascular involvement. The non-significant association might suggest that GGT alone may not be a reliable marker for predicting the extent of vascular involvement in ACS, which is consistent with findings in previous research.(15)

Similar to GGT, CK-MB levels increased with age, but the difference was not statistically significant. This aligns with the general understanding that age can influence cardiac biomarker levels.(16) The lack of significant association with gender and vascular involvement suggests that CK-MB might not be independently indicative of these factors in the context of ACS. While CK-MB has traditionally been used as a marker for myocardial infarction, its specificity has been challenged in recent years with the introduction of more sensitive cardiac troponin assays.(17) The findings imply that GGT and CK-MB, despite showing age-related variations, may not serve as stand-alone markers for predicting the severity of vascular involvement in ACS patients.(18)

The study results reveal significant associations between certain demographic and biochemical factors and the extent of coronary angiogram lesions. Patients with coronary angiogram lesions greater than 50.0% exhibited higher mean age, elevated levels of gamma glutamyl transferase (GGT), and increased creatine kinase (CK-MB) levels compared to those

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with less severe lesions. This aligns with existing literature indicating that age and certain biomarkers are associated with the severity of coronary artery disease.(19)

The correlation analysis further elucidates the relationship between individual study variables and the percent coronary angiogram lesion. Notably, age demonstrated a significant positive moderate correlation, corroborating the understanding that age is a risk factor for coronary artery disease.(20) GGT levels exhibited a significant positive strong correlation, affirming the potential role of GGT as a marker for cardiovascular risk.(21) Similarly, CK-MB levels showed a significant positive mild correlation, emphasizing its association with myocardial injury.(22) The negative mild correlation of ejection fraction with percent coronary angiogram lesion is consistent with the expected relationship, as reduced ejection fraction is indicative of impaired cardiac function.(23) The most striking finding is the significant positive strong correlation observed when combining GGT and CK-MB levels. This suggests that the combination of these two biomarkers may enhance the predictive value for the extent of coronary angiogram lesions. Such synergistic effects of multiple biomarkers have been reported in cardiovascular risk assessment.(24, 25) The identified associations and correlations carry important clinical implications. Elevated GGT and CK-MB levels, along with advanced age, could serve as indicators for clinicians to anticipate a more extensive coronary angiogram lesion. This information may contribute to risk stratification and guide therapeutic decisions in managing patients with acute coronary syndrome.(26)

The results of the Receiver Operating Characteristic (ROC) analysis indicate that elevated serum gamma glutamyl transferase levels, specifically equal to or exceeding 52.5, serve as a significant predictor of coronary atherosclerosis. The area under the curve (AUC) of 0.781 suggests a moderate to good discriminatory power of GGT in identifying individuals with coronary atherosclerosis.(27) At the identified cut-off point, GGT demonstrates a sensitivity of 73.4% and specificity of 74.2%. On the other hand, the analysis also identifies CK-MB levels equal to or exceeding 66.0 as a potential predictor of coronary atherosclerosis, though the statistical significance is borderline ($p=0.062$). The AUC value of 0.697 suggests a fair discriminatory ability, and at the determined cut-off, CK-MB shows a sensitivity of 56.8% and specificity of 58.2%. The identified cut-off for GGT aligns with previous research that has implicated elevated GGT levels in cardiovascular risk. Studies have shown that GGT, as a marker of oxidative stress and inflammation, may play a role in the pathogenesis of atherosclerosis.(28) Similarly, CK-MB has been traditionally used as a marker for myocardial infarction, but its specificity has been challenged by newer cardiac biomarkers like troponins.(26) The borderline significance in the current study could be influenced by various factors, including sample characteristics and the sensitivity of the CK-MB assay used. Comparing the AUC values for GGT and CK-MB, GGT demonstrates a relatively higher discriminatory ability. This reinforces the idea that GGT may be a more robust biomarker in the context of coronary atherosclerosis, whereas CK-MB might be less specific. The combined use of multiple biomarkers could be explored to improve diagnostic accuracy.(29)

## Conclusion

Our study has provided valuable insights into the role of serum gamma glutamyl transferase (GGT) and creatine kinase MB (CK-MB) in predicting coronary atherosclerosis among patients presenting with acute coronary syndrome. We observed that elevated GGT levels, specifically

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at or above 52.5, were identified as a significant predictor of coronary atherosclerosis, demonstrating a moderate to good discriminatory power. This finding aligns with existing literature suggesting GGT as a potential marker for cardiovascular risk and oxidative stress. Additionally, while CK-MB levels at or above 66.0 were identified as a potential predictor of coronary atherosclerosis, the statistical significance was borderline. This underscores the evolving landscape of cardiac biomarkers, with traditional markers like CK-MB facing challenges from newer, more specific markers such as troponins. The clinical utility of CK-MB in predicting coronary atherosclerosis may benefit from further validation in larger cohorts.

The combined analysis of GGT and CK-MB levels revealed a significant positive strong correlation with percent coronary angiogram lesion, emphasizing the potential synergistic effects of these biomarkers in assessing the extent of coronary artery disease. The established cut-off points for GGT and CK-MB, along with associated sensitivity and specificity values, offer clinicians a practical tool for risk stratification and timely intervention. Incorporating these findings into clinical guidelines and screening protocols may enhance the accuracy of identifying individuals at risk of coronary atherosclerosis.

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Table 1: Association between independent variables, gamma glutamyl transferase and creatine kinase MB

| | | **N = 100** | **GGT** | **P value** | **CK-MB** | **P value** |
|---|---|---|---|---|---|---|
| | | **n (%)** | **Mean (SD)** | | **Mean (SD)** | |
| Age (in years) | Less than 40 | 26 (26.0) | 57.3 (26.3) | 0.102 | 63.3 (20.5) | 0.224 |
| | 41 to 60 | 58 (58.0) | 65.9 (24.0) | | 72.5 (25.7) | |
| | More than 60 | 16 (16.0) | 68.7 (16.9) | | 74.7 (18.5) | |
| Gender | Male | 70 (70.0) | 64.2 (19.2) | 0.753 | 69.5 (18.6) | 0.487 |
| | Female | 30 (30.0) | 68.6 (27.8) | | 75.6 (24.4) | |
| Vascular involvement | Minimal disease | 28 (22.0) | 55.2 (25.6) | 0.153 | 62.9 (20.1) | 0.492 |
| | SVD | 44 (44.0) | 67.9 (19.1) | | 73.1 (20.5) | |
| | DVD | 12 (14.0) | 66.8 (20.2) | | 69.7 (17.9) | |
| | TVD | 16 (20.0) | 70.3 (15.4) | | 78.4 (22.1) | |
| SVD, Single vessel disease; DVD, Double vessel disease; TVD, Triple vessel disease | | | | | | |

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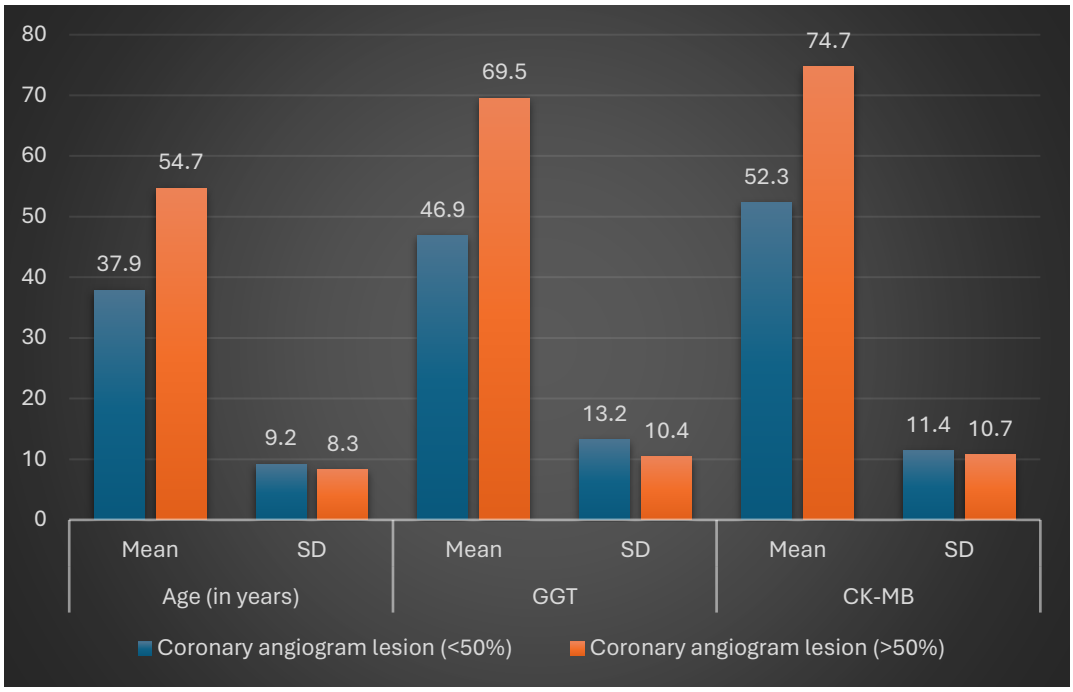


Figure 1: Association between independent study variables and percent coronary angiogram lesion

Table 2: Receiver operating characteristic (ROC) analysis

| | AUC | SE | P value | 95% CI |
|---|---|---|---|---|
| GGT | 0.781 | 0.082 | 0.001* | 0.521 to 0.905 |
| CK-MB | 0.697 | 0.114 | 0.062 | 0.592 to 0.872 |