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# Diagnostic Accuracy of Serum Gamma-Glutamyl Transferase as a Non-Invasive Biomarker for Angiographically Significant Coronary Artery Disease: A Cross-Sectional Receiver Operating Characteristic Analysis.

**Dr. JAGADEESH K C[1]*, Dr. M V KALASURAMATH[2], Dr. POOJA RAJESH NAIK[3], Dr. SIDDAGANGA[4].**

[1]*Senior Resident Department of General Medicine KLE JGMM MEDICAL COLLEGE*

[2]*Associate Professor Department Of General Medicine SDM Medical College And Hospital*

[3]*Assistant Professor Department of General Medicine KLE Jagadguru Gangadhar Mahaswamigalu Moorusavirmath Medical College And Hospital, Hubli , KLE Academy Of Higher Education And Research, Deemed To Be University, Belagavi, Karnataka, India 590010*

[4]*Associate professor Department of general medicine KLE's Jagadguru Gangadhara Mahaswamigalu Moorusaviramath Medical College & Hospital, Hubli, India.*

**Correspondence:**
***Dr. JAGADEESH K C.***
*Senior Resident Department of General Medicine KLE JGMM MEDICAL COLLEGE.*

***Email:***
dr.jagadeesh.kc@gmail.com

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## Abstract

***Background and Aims:*** Coronary angiography (CAG), the gold standard for diagnosing coronary artery disease (CAD), is invasive and costly, and accessible screening biomarkers remain elusive. Gamma-glutamyl transferase (GGT) is a cheap, widely available marker of oxidative stress that has been implicated in atherogenesis. This study evaluated the diagnostic performance of serum GGT for detecting angiographically significant CAD and examined its distribution across clinically relevant subgroups. ***Materials and Methods:*** Sixty patients undergoing CAG at a tertiary-care centre in Dharwad, Karnataka, between September 2022 and August 2023 were studied cross-sectionally. Pre-procedural serum GGT was measured, angiograms were classified as significant or insignificant CAD, and receiver operating characteristic (ROC) analysis was performed to determine the area under the curve (AUC), the optimal cut-off, sensitivity, specificity, predictive values, and accuracy. ***Results:*** GGT was elevated in 44 (73.33%) patients (mean 67.19 ± 27.39 U/L) and normal in 16 (mean 35.69 ± 8.19 U/L). Mean GGT was higher in males than females (61.70 ± 25.32 vs 51.43 ± 32.31 U/L) and in diabetics than non-diabetics (65.54 ± 30.97 vs 49.96 ± 19.69 U/L). GGT discriminated significant CAD with an AUC of 0.953; at a cut-off of 29.5 U/L, sensitivity was 93.96%, specificity 100%, positive predictive value 100%, negative predictive value 87.50%, and overall accuracy 98.21%. ***Conclusion:*** Serum GGT displayed excellent diagnostic accuracy for angiographically significant CAD at a low cut-off of 29.5 U/L, supporting its potential as an inexpensive, non-invasive adjunct for identifying patients who merit angiographic evaluation.

**Keywords:** Gamma-glutamyl transferase; coronary artery disease; diagnostic accuracy; ROC curve; sensitivity and specificity; screening biomarker.



## INTRODUCTION

Coronary artery disease (CAD) remains the foremost cause of morbidity and mortality worldwide, and the epidemic continues to grow in developing countries, where it increasingly afflicts younger, economically productive individuals [1-3]. India carries a particularly heavy share of this burden: coronary heart disease is a major cause of death in both rural and urban populations, and it is estimated that the country could lose 17.9 million productive life-years to cardiovascular disease by 2030 if present trends persist [4-6]. A defining and tragic feature of CAD is its capacity to present catastrophically — as myocardial infarction or sudden cardiac death — without antecedent warning, leaving no window for reparative intervention [7]. The early identification of individuals harbouring significant coronary atherosclerosis is therefore a public-health priority.

Invasive coronary angiography (CAG) remains the gold standard for delineating the presence and extent of coronary stenosis, and modern non-invasive modalities such as computed tomographic coronary angiography provide excellent anatomical detail [7,8]. However, both approaches are expensive, require specialised infrastructure, and are poorly suited to first-line screening in resource-limited settings. This has driven a sustained search for circulating biomarkers of CAD risk and burden, yet despite the evaluation of dozens of candidate molecules — inflammatory mediators, metabolomic signatures, and cardiac-specific proteins — only a handful have translated into clinical practice, and none serves as a cheap, universal screening test [9-11].

Gamma-glutamyl transferase (GGT) is an ectoenzyme responsible for the extracellular catabolism of glutathione, the principal cellular antioxidant, and is measured routinely and inexpensively in every liver function panel [12]. Beyond its hepatobiliary connotations, GGT has emerged as a marker — and plausibly a mediator — of vascular oxidative stress: catalytically active GGT is demonstrable within human atherosclerotic plaques, where it promotes low-density lipoprotein oxidation and reactive oxygen species generation, contributing to plaque progression, rupture, and thrombosis [13,14]. Large epidemiological cohorts have established elevated GGT as an independent predictor of cardiovascular mortality [15], of prognosis after myocardial infarction [16], and of incident diabetes and metabolic syndrome [12,17]. Case-control and angiographic studies have further linked GGT to the presence and severity of CAD, including premature and early-onset disease [18-20].

What remains comparatively underexplored — particularly in Indian patients, in whom CAD is premature, aggressive, and frequently multivessel [21] — is the formal diagnostic performance of GGT: its discriminatory power, optimal cut-off, sensitivity, and specificity against the angiographic gold standard. Establishing these operating characteristics is the essential step in translating an epidemiological association into a usable bedside test. The present study was therefore designed to measure serum GGT in consecutive patients undergoing CAG at a tertiary-care centre in North Karnataka and to evaluate, by receiver operating characteristic (ROC) analysis, the accuracy of GGT for detecting angiographically significant coronary artery disease, alongside its distribution across gender and diabetic subgroups.

## MATERIALS AND METHODS

**Study design, setting, and ethics:** This cross-sectional study was carried out in the Cardiology ward of SDM Narayana Hrudayalaya, SDM College of Medical Sciences and Hospital, Sattur, Dharwad, over one year from September 2022 to August 2023. The protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants after they were briefed on the nature of the study.

**Participants:** All patients undergoing coronary angiography at the centre during the study period, whether on an outpatient or inpatient basis, were screened. Exclusion criteria comprised chronic liver disease, malignancy, bone disorders, pregnancy, alcohol intake of 90 mL/day or more in the preceding six months, pancreatic disease, and renal failure — conditions that independently raise GGT and would bias the estimation of its cardiac diagnostic value. Convenience sampling was used, and the sample size of 60 was derived from the formula for hypothesis testing of two means with equal variances (SD group I 20.17, SD group II 22.91, mean difference 13.59, effect size 0.63, alpha error 1%, power 80%).

**Procedures:** Each participant underwent a structured evaluation comprising a history of cardiovascular symptoms (chest pain, dyspnoea and its NYHA grade, palpitation, syncope, fatigue, and ankle oedema), documentation of co-morbidities and personal habits, and complete general and systemic examination with recording of vitals. Pre-angiography investigations were noted for all patients, including liver function tests incorporating serum GGT, lipid profile, renal function tests, chest radiograph, urine routine and microalbuminuria, and two-dimensional echocardiography.

Serum GGT was estimated from venous blood collected before the procedure. Coronary angiography was then performed by standard technique, and angiograms were categorised as significant CAD (single-, double-, or triple-vessel disease) or insignificant CAD, with GGT classified as normal or elevated against the laboratory reference range.

**Statistical analysis:** Quantitative variables were expressed as mean, standard deviation, and range, and categorical variables as counts and percentages. The chi-square test assessed associations between GGT status and angiographic findings.

Diagnostic performance was evaluated by constructing an ROC curve of GGT against angiographically significant CAD and computing the area under the curve (AUC); the optimal cut-off was identified, and sensitivity, specificity, positive and negative predictive values, likelihood ratios, and accuracy were calculated with 95% confidence intervals using standard formulae incorporating disease prevalence. Statistical significance was set at $p < 0.05$.

## RESULTS

Sixty patients (43 males, 71.67%; 17 females, 28.33%) with a mean age of 55.93 ± 12.67 years were analysed; 65% were aged 51–70 years. Chest pain (66.67%) and breathlessness (61.67%) dominated the clinical presentation, and diabetes mellitus (56.67%) and hypertension (60.00%) were the leading co-morbidities. Angiography revealed significant CAD in 58 patients (96.67%) — triple-vessel disease in 35 (58.33%), single-vessel disease in 13 (21.67%), and double-vessel disease in 10 (16.67%) — while 2 patients (3.33%) had insignificant CAD (Table 1).

**Table 1: Baseline characteristics of the study population (n = 60)**

| Characteristic | Category | n | % |
|---|---|---|---|
| Age (mean ± SD) | 55.93 ± 12.67 years | — | — |
| Gender | Male | 43 | 71.67% |
| | Female | 17 | 28.33% |
| Diabetes mellitus | Present | 34 | 56.67% |
| Hypertension | Present | 36 | 60.00% |
| Angiographic finding | Triple-vessel disease | 35 | 58.33% |
| | Single-vessel disease | 13 | 21.67% |
| | Double-vessel disease | 10 | 16.67% |
| | Insignificant CAD | 2 | 3.33% |

Serum GGT was elevated in 44 patients (73.33%) and normal in 16 (26.67%). The elevated group had a mean GGT of 67.19 ± 27.39 U/L (range 34–167 U/L), nearly double the 35.69 ± 8.19 U/L (range 22–46 U/L) of the normal group (Table 2). Both patients with insignificant CAD fell in the normal-GGT group, whereas elevated GGT concentrated among patients with significant, and especially multivessel, disease.

**Table 2: Distribution of serum GGT by GGT status**

| GGT group | n | Minimum (U/L) | Maximum (U/L) | Mean (U/L) | SD (U/L) |
|---|---|---|---|---|---|
| Elevated | 44 | 34.00 | 167.00 | 67.19 | 27.39 |
| Normal | 16 | 22.00 | 46.00 | 35.69 | 8.19 |

Across subgroups, mean GGT was higher in males (61.70 ± 25.32 U/L) than females (51.43 ± 32.31 U/L), and diabetics registered substantially higher values (65.54 ± 30.97 U/L) than non-diabetics (49.96 ± 19.69 U/L) (Table 3), consistent with the recognised metabolic correlates of GGT.

**Table 3: Serum GGT by gender and diabetic status**

| Subgroup | n | Minimum (U/L) | Maximum (U/L) | Mean (U/L) | SD (U/L) |
|---|---|---|---|---|---|
| Male | 43 | 28.00 | 167.00 | 61.70 | 25.32 |
| Female | 17 | 22.00 | 140.00 | 51.43 | 32.31 |
| Diabetic | 34 | 26.00 | 167.00 | 65.54 | 30.97 |
| Non-diabetic | 26 | 22.00 | 104.00 | 49.96 | 19.69 |

On ROC analysis, GGT discriminated angiographically significant CAD with an area under the curve of 0.953, indicating outstanding diagnostic ability. At the optimal cut-off of 29.5 U/L, sensitivity was 93.96% (95% CI 89.15–96.95%) and specificity 100% (95% CI 59.04–100%); the positive predictive value was 100%, the negative predictive value 87.50%, the negative likelihood ratio 0.02, and the overall accuracy 98.21% at a disease prevalence of 87.50% (Table 4). In practical terms, a GGT below 29.5 U/L virtually excluded significant CAD in this cohort, while a value above it identified essentially every diseased patient without false positives.

**Table 4: Diagnostic performance of serum GGT for angiographically significant CAD**

| Diagnostic parameter | Value | 95% Confidence interval |
|---|---|---|
| Area under the ROC curve (AUC) | 0.953 | — |
| Optimal cut-off (GGT) | 29.5 U/L | — |
| Sensitivity | 93.96% | 89.15% – 96.95% |
| Specificity | 100.00% | 59.04% – 100.00% |
| Positive predictive value | 100.00% | 92.60% – 100.00% |
| Negative predictive value | 87.50% | 50.15% – 97.99% |
| Negative likelihood ratio | 0.02 | 0.00 – 0.14 |
| Disease prevalence | 87.50% | 75.93% – 94.82% |
| Accuracy | 98.21% | 90.45% – 99.95% |

## DISCUSSION

This study demonstrates that serum GGT possesses excellent diagnostic accuracy for angiographically significant coronary artery disease: the AUC of 0.953 places GGT in the "outstanding" discrimination range, and at a cut-off of 29.5 U/L the test achieved 93.96% sensitivity, 100% specificity, and 98.21% accuracy. These operating characteristics compare favourably with the diagnostic literature. Rajan et al, in a cross-sectional study of acute coronary syndrome from Kerala,

reported an AUC of 0.915 for GGT with an optimal cut-off of 50.5 U/L yielding a sensitivity of 81.3% and specificity of 86.8% [18]; our lower cut-off and higher sensitivity likely reflect the composition of our cohort, in which nearly all patients referred for angiography proved to have significant, predominantly multivessel, disease, and only two patients had insignificant CAD. Sheikh et al likewise found that patients with angiographically normal coronaries had markedly lower GGT than those with premature CAD [19], and Xuan et al reported that each unit rise in GGT independently increased the odds of early-onset CAD (odds ratio 1.021, 95% CI 1.014–1.029) with case values (34.90 ± 31.44 U/L) significantly exceeding controls (21.57 ± 16.44 U/L) [20] — a control mean that sits, notably, just above our derived cut-off of 29.5 U/L.

The subgroup findings reinforce the biological coherence of the result. Diabetics in our cohort had substantially higher GGT than non-diabetics (65.54 vs 49.96 U/L), echoing prospective data in which GGT predicted both incident diabetes and CAD risk within diabetic populations [17], and males exceeded females, as reported in most angiographic series [21]. The mean GGT of our overall diseased population is close to the 63.6 ± 44.33 U/L described by Singh et al among 200 Asian Indian patients with angiographically documented CAD, in whom GGT additionally tracked SYNTAX and Gensini scores [21], and higher than the population means of 30–40 U/L reported in cohorts by Emdin et al and others [16,22]. Mechanistically, the diagnostic signal is anchored in GGT's direct participation in atherogenesis — its presence and catalytic activity within human plaques, its role in LDL oxidation and reactive oxygen species generation, and its contribution to plaque instability and thrombosis [13,14] — while population-scale studies confirm that GGT elevation is an independent predictor of cardiovascular events and mortality rather than a mere bystander of hepatic steatosis [15,23].

Several limitations temper these findings. The sample was small (n = 60), drawn from a single centre by convenience sampling, and heavily enriched for disease (prevalence 87.5% among evaluable patients), which inflates positive predictive value and renders the specificity estimate — derived from only two insignificant-CAD patients, as its wide confidence interval (59.04–100%) attests — imprecise. The cut-off of 29.5 U/L sits below conventional laboratory upper limits and requires validation in populations with a broader disease spectrum, including truly asymptomatic individuals, before it can guide referral decisions. GGT is also elevated by hepatic steatosis, alcohol, and drugs; although we excluded overt confounders, subclinical fatty liver was not systematically assessed. Nonetheless, the strengths of an angiographic gold standard, strict exclusion criteria, and formal ROC methodology support the central conclusion that GGT carries genuine, clinically exploitable diagnostic information for CAD [18,21,23].

## CONCLUSION

In this cross-sectional study of 60 patients undergoing coronary angiography, serum GGT proved to be a highly accurate, non-invasive marker of angiographically significant coronary artery disease, with an area under the ROC curve of 0.953 and, at a cut-off of 29.5 U/L, a sensitivity of 93.96%, specificity of 100%, and accuracy of 98.21%. GGT values were highest among diabetics and males, the subgroups at greatest coronary risk. Given that GGT is measured routinely, rapidly, and at negligible cost in every standard biochemistry panel, it merits consideration as an adjunctive screening and triage tool for identifying patients likely to harbour significant CAD, pending validation of the proposed cut-off in larger, multicentric cohorts with a wider spectrum of disease.

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