

SERUM GAMMA GLUTAMYL TRANSFERASE AS A MARKER OF ISCHEMIC HEART DISEASE AND ITS RELATIONSHIP WITH RISK FACTORS

Mustafa Mohammed Abd Alwahid*¹ and Dr. Ala Hussain Haider²

¹(M.B.Ch.B.) Merjan Teaching Hospital.

²Consultant Physician Professor of Internal Medicine (M.B.Ch.B, F.I.C.M.S) Babylon University, Hammurabi College of Medicine.

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*Corresponding Author: Mustafa Mohammed Abd Alwahid

(M.B.Ch.B.) Merjan Teaching Hospital.

ABSTRACT

Background

Serum gamma glutamyl transferase is an enzyme involved in glutathione metabolism, has been implicated in oxidative stress and inflammation, both key contributors to atherosclerosis and coronary artery disease. **Aim of the study to** Evaluate gamma glutamyl transferase's predictive role in coronary disease severity and establish correlations with coronary heart disease risk factors. **Patients and Methods** a cross-sectional study conducted in Merjan teaching hospital and Shaheed Al-Mehrab Cardiovascular center from the 1st Jan 2023 to the 1st Oct 2023. The study involved the assessment of 100 patients scheduled for coronary angiography due to suspected coronary artery disease. The gamma glutamyl transferase measurements were conducted using established laboratory techniques. An elevated level was deemed to be present when it exceeded 71 IU/L in male patients and 42 IU/L in female patients according to laboratory reference values. **Results** The mean age of the patients was 60.5 ± 11.3 , regarding sex distribution, 60 percent were male and 40 percent were female. In this study, gamma glutamyl transferase levels, with a median of 40.5 (IQR: 21.0-56.2), showed elevation in 24.0% of patients. A comparison between normal and abnormal angiography revealed significantly higher gamma glutamyl transferase levels (46.0 vs. 23.0, $p < 0.001$) in the latter group. **Conclusion** The current study concluded that serum gamma-glutamyl transferase is prevalent among those with ischemic heart disease, revealing a significant association with positive angiography findings.

KEYWORD: Serum gamma glutamyl transferase; Coronary heart disease.

INTRODUCTION

As of the latest available data, there are approximately 126.5 million cases of ischemic heart disease worldwide, making it a widespread and significant global health issue.^[1,2] Ischemia, characterized by inadequate oxygenated blood flow to the myocardium, can result from decreased oxygen in the blood or reduced blood flow. Predisposing risk factors for coronary heart disease (CHD), defined as those that worsen independent risk factors include^[3], family history of premature CHD, occurring in a first-degree male relative < 55 years of age, or first-degree female relative < 65 years of age, metabolic or insulin resistance syndrome (defined as ≥ 3 of the following: abdominal obesity [male >102 cm waist, female > 88 cm], fasting glucose ≥ 110 mg/ dL, systolic pressure >130 mm Hg, diastolic ≥ 85 mm Hg, triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL in males and < 50 mg/dL in females), obesity (body mass

index > 30 kg/m²), physical inactivity and other factors.^[4] Gamma-glutamyl transferase (GGT) is a glycosylated protein embedded in the outer surface of the plasma membrane. It has a role in the homeostasis of both glutathione and cysteine.^[5] GGT is a microsomal enzyme that is responsible for transferring the glutamyl groups from gamma-glutamyl peptides to other peptides. With the exception of muscle cells, GGT is distributed in all other organs. GGT catalyzes the synthesis and transmembrane transport of proteins, counteracts oxidative stress by providing cysteine for regeneration of intracellular glutathione, and contributes to the detoxication of ammonium of some drugs.^[6] GGT has been proposed to be a predictive biomarker for cellular antioxidant deficiency and several disease states.^[7] GGT makes a significant contribution to oxidant activity. In addition, there are variations in GGT levels based on gender, ethnic, and regional differences and an upward

trend in levels which suggests an environmental factor.^[8] Whether GGT offers prognostic information that is incremental to the information provided by conventional risk factors remains questionable. Despite using coronary angiography—the gold standard for diagnosis of CHD—studies that assessed GGT in patients with established CHD included smaller numbers of patients and had a short follow-up. Furthermore, teasing out the intricate relationship and interdependence between CVD risk factors, GGT and CHD remains difficult.^[9,10] The confounding impact of percutaneous coronary intervention—suggested to abolish the association of GGT with coronary events should be considered.^[11]

Aim of the study

- 1- Assess the prediction of high gamma-glutamyl transferase levels on the severity of coronary heart disease.
- 2- Show the correlation between gamma-glutamyl transferase with the coronary heart disease risk factors.

PATIENTS AND METHODS

This study was designed as a cross-sectional study conducted in Merjan teaching hospital and Shaheed Al-Mehrab Cardiovascular center from the 1st Jan 2023 to the 1st Oct 2023. The study involved the assessment of 100 patients scheduled for coronary angiography due to suspected coronary artery disease. Nonrandomized convenient sampling was done to enroll patients.

Inclusion criteria

1. Patients who are scheduled for coronary angiography to evaluate coronary artery disease.
2. Aged 18 years or older.

Exclusion criteria

Patients with severe comorbidities such as advanced cancer, severe liver disease, defined by clinical criteria and liver function tests, or severe renal disease (eGFR < 30 mL/min/1.73 m²) or other conditions that may significantly affect the study results or their ability to undergo coronary angiography

1. Patients who had experienced a myocardial infarction within the last three months due to the potential acute effects on gamma-glutamyl transferase (GGT) levels.
2. Patients who had undergone coronary artery revascularization procedures (e.g., percutaneous coronary intervention or coronary artery bypass grafting) within the last three months.
3. Pregnant individuals due to the potential influence of pregnancy on GGT levels and the associated risk factors.
4. patients with a history of alcohol consumption were excluded, as alcohol is known to influence GGT levels.

Data collection and measurement

Detailed socio-demographic data, medical history, and clinical information had been obtained through patient

interviews and medical records. These information included age, sex, occupation, medical history, medication use, and lifestyle factors, such as smoking history (which included current and ex-smokers), and Family history of IHD (history of premature CHD, occurring in a first-degree male relative < 55 years of age, or first-degree female relative < 65 years of age).

BMI, an indicator of obesity, was calculated by measuring the participant's weight and height. The BMI was calculated using the formula:

$$\text{BMI} = \text{weight (kg)} / \text{height}^2 (\text{m}^2).$$

Blood pressure was measured using standard procedures to determine hypertension status, defined by systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the current use of antihypertensive medication.^[12] laboratory tests were conducted to assess various risk factors, including those associated with liver and renal function, the presence of diabetes mellitus, and dyslipidemia. The patient was considered to have diabetes mellitus if he had one of the following criteria: Hemoglobin A1C equal to or greater than 6.5%, Fasting plasma glucose equal to or greater than 126 mg/dl, Random blood sugar equal to or greater than 200 mg/dl or the patient had history of diabetes on treatment.^[13]

Liver function tests encompassed liver enzyme measurements (alanine transaminase and aspartate transaminase), while renal function was assessed by serum creatinine levels and blood urea nitrogen. Blood samples were analyzed to assess random blood sugar, and the lipid profile, which includes total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, to define dyslipidemia. Blood samples were collected to measure GGT levels, which serve as the primary focus of this study which had been correlated with angiographic findings and the various risk factors. The GGT measurements were conducted using established laboratory techniques. An elevated GGT level was deemed to be present when it exceeded 71 IU/L in male patients and 42 IU/L in female patients according to laboratory reference values of BS-230/ Mindray/ China. Coronary angiography was typically performed in a specialized cardiac catheterization lab. It is an invasive procedure in which a thin, flexible tube (catheter) is inserted into a blood vessel, usually in the groin or wrist, and threaded up to the coronary arteries. A contrast dye is injected through the catheter directly into the coronary arteries, which makes them visible on X-ray images. The procedure assesses the extent and severity of coronary artery disease. The images obtained can help doctors identify which coronary arteries are affected and to what degree.^[14] **Statistical analysis** Continuous variables were expressed as means and standard deviations. Categorical variables were expressed as frequency and percentages. univariate logistic regression was used to calculate the odds ratio for the risk of having three or four vessels of coronary disease. Pearson's rank correlation Coefficient

was used to study the correlation between study parameters. A P-value less than 0.05 was considered statistically significant. R software packages (dplyr, gt_summery and ggplot) were used for data processing, visualization, and statistical analysis ("R version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria").

RESULTS

This study had enrolled 100 patients suspected to have ischemic heart disease. The mean age of the patients was 60.5 ± 11.3 , regarding sex distribution, 60 percent were male and 40 percent were female. The mean body mass index of the participants was 30.7 ± 5.3 . In regards to the occupation, the highest percentage (28.0%) were housewives, gainer (20.0%), and retired (19.0%).

Table 1: Description of socio-demographics of the patients.

Characteristic	Patients, N = 100 ¹
Age (years)	60.5 ± 11.3
Sex	
Male	60 (60.0%)
Female	40 (40.0%)
BMI (kg/m ²)	30.7 ± 5.3
¹ Mean ± SD; n (%)	

Regarding the comorbidities, hypertension was observed in (71%), and diabetes (60%). (49%) of the patients had a smoking history while (43%) had a positive family history of ischemic heart disease.

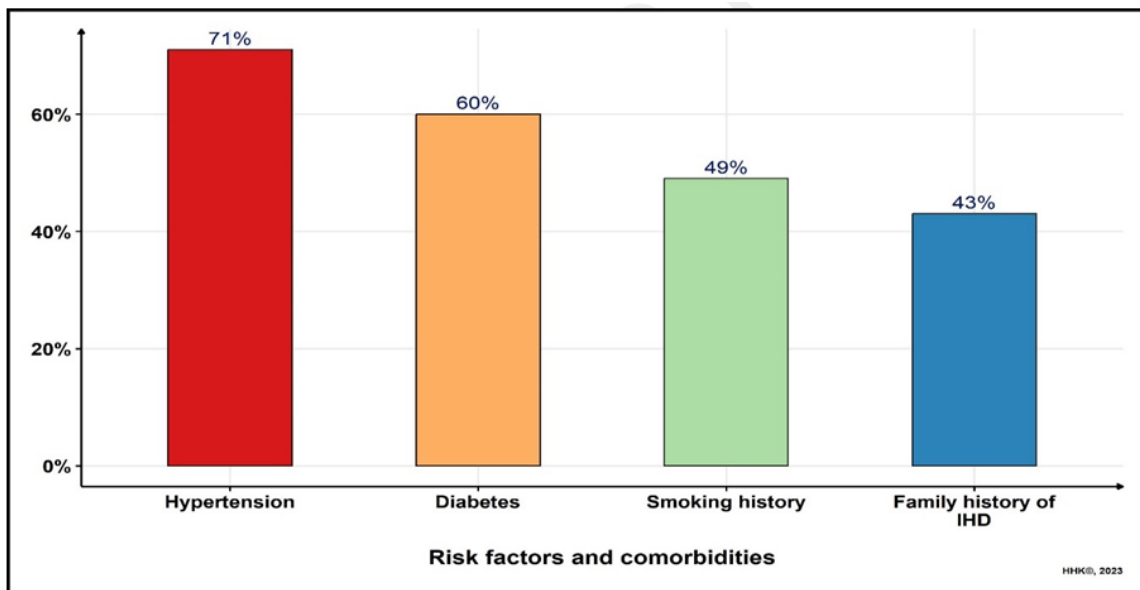


Figure 1: Bar chart showing the risk factors and comorbidities of ischemic heart disease among the participants.

The laboratory tests showed that the mean of the gamma-glutamyl transferase was 46.9 ± 30.8 , it was elevated in (24.0%) of the patients.

Table 2: Description of laboratory parameters of the participants.

Characteristic	Patients, N = 100 ¹	Normal value
Lipid profile		
Total cholesterol (mmol/L)	3.7 ± 1.1	< 5.18 mmol/L
Serum triglyceride (mmol/l)	1.5 ± 0.9	< 1.82 mmol/L
Low-density lipoprotein (mmol/L)	1.6 ± 0.9	< 2.4 mmol/L
Serum gamma-glutamyl transferase (SGGT)	40.5 (21.0 - 56.2)	Male 10-71IU/L Female 6-42 IU/L
Elevated gamma-glutamyl transferase	24 (24.0%)	
¹ Mean ± SD; Median (IQR) n (%)		

In regards to the angiographic findings, it had been noticed that the left anterior descending artery was the

most vessel affected by ischemia (51%), while the left main stem was the least affected (17%).

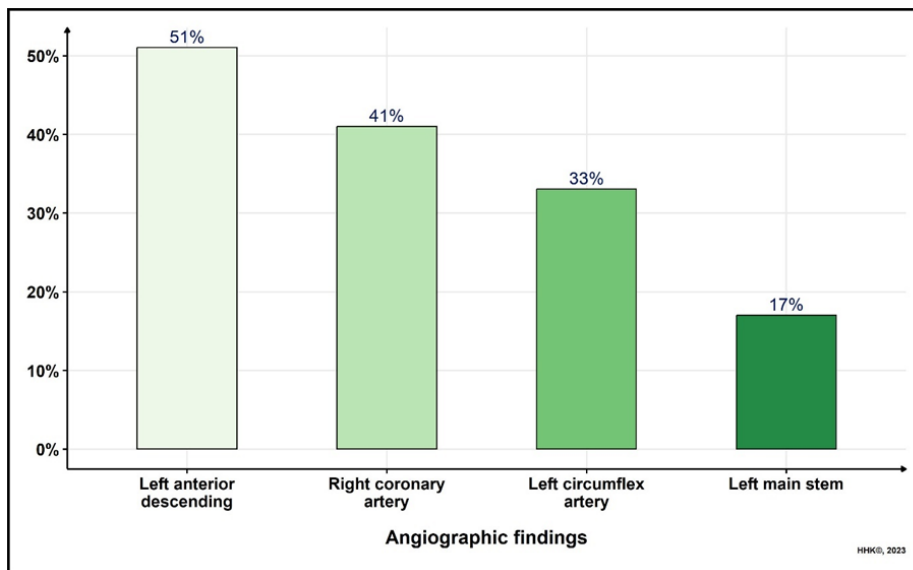


Figure 2: Bar chart showing the angiographic findings of the four vessels affected by ischemia.

The patients were grouped according to the angiographic findings into normal angiography (N = 37) and those with abnormal angiography (N = 63). The groups exhibited similar mean ages (60.2 ± 11.4 vs. 60.6 ± 11.3 years) and sex distributions, although the sex showed a trend towards significance (p = 0.076). Smoking history was significantly higher in the abnormal angiography group (p = 0.011). Other variables, including a family

history of ischemic heart disease, and BMI did not show statistically significant differences between the groups. However, random blood sugar levels (p = 0.014), lipid profile components (total cholesterol, p = 0.047; low-density lipoprotein, p = 0.017), and gamma-glutamyl transferase (p < 0.001) demonstrated significant associations with abnormal angiography.

Table 3: Patients Characteristics According to Angiographic Findings.

Characteristic	Normal Angiography, N = 37 ¹	Abnormal Angiography, N = 63 ¹	p-value ²
Age, years	60.2 ± 11.4	60.6 ± 11.3	0.9
Sex			0.076
Male	18 (48.6%)	42 (66.7%)	
Female	19 (51.4%)	21 (33.3%)	
Smoking history	12 (32.4%)	37 (58.7%)	0.011
Family history of IHD	13 (35.1%)	30 (47.6%)	0.2
BMI (kg/m ²)	31.8 ± 5.0	30.0 ± 5.5	0.10
Random blood sugar (mmol/l)	7.7 ± 2.9	9.6 ± 4.5	0.014
Lipid profile			
Total cholesterol (mg/dl)	3.5 ± 0.8	3.9 ± 1.3	0.047
Serum triglyceride (mmol/l)	1.4 ± 0.8	1.6 ± 0.9	0.3
Low-density lipoprotein (mg/dl)	1.3 ± 0.7	1.8 ± 1.0	0.017
Gamma-glutamyl transferase (SGGT)	23.0 (18.0 - 42.0)	46.0 (34.0 - 62.5)	<0.001
Elevated SGGT	6 (16.2%)	18 (28.6%)	0.2

¹Median (IQR); Mean ± SD; n (%)
²Wilcoxon rank sum test; Welch Two Sample t-test; Pearson's Chi-squared test

Patients with abnormal angiography were categorized into four categories according to the number of vessels affected. The mean ages across the groups were relatively similar, showing no significant differences (p = 0.8). Regarding sex distribution, a trend is observed (p = 0.11), with a higher percentage of males in the later groups. Smoking history, family history of ischemic heart disease, and lipid profile components (total cholesterol, triglyceride, LDL) did not exhibit significant differences among the groups. However, BMI showed

statistical significance (p = 0.007), with Group One having a higher mean BMI compared to the other groups. Random blood sugar (RBS) levels also demonstrate a marginal p-value (p = 0.095), with higher mean levels in Group Four. Gamma-glutamyl transferase (SGGT) levels did not significantly differ among the groups. The prevalence of elevated SGGT levels was consistent across the groups (p = 0.7).

Table 4: Classification of patients according to the number of vessels affected.

Characteristic	One, N = 22 ¹	Two, N = 14 ¹	Three, N = 16 ¹	Four, N = 11 ¹	p-value ²
Age, years	60.0 ± 13.7	59.6 ± 7.9	60.2 ± 9.8	63.6 ± 12.9	0.8
Sex					0.11
Male	11 (50.0%)	9 (64.3%)	12 (75.0%)	10 (90.9%)	
Female	11 (50.0%)	5 (35.7%)	4 (25.0%)	1 (9.1%)	
Hx of Smoking	12 (54.5%)	7 (50.0%)	9 (56.2%)	9 (81.8%)	0.4
FHx of IHD	12 (54.5%)	6 (42.9%)	8 (50.0%)	4 (36.4%)	0.8
BMI (kg/m ²)	33.0 ± 5.5	28.7 ± 6.0	27.3 ± 4.6	29.9 ± 3.2	0.007
RBS	8.3 ± 2.7	9.8 ± 4.1	9.1 ± 4.9	12.4 ± 6.4	0.095
Total cholesterol	3.8 ± 1.1	3.8 ± 1.2	3.9 ± 1.5	4.1 ± 1.6	0.9
Triglyceride	1.5 ± 0.7	1.4 ± 0.6	1.6 ± 1.3	1.9 ± 1.1	0.6
LDL	1.7 ± 0.8	1.8 ± 1.0	1.8 ± 1.2	1.8 ± 1.3	0.9
SGGT	40.5 (23.5 - 60.0)	45.5 (37.0 - 54.2)	50.5 (39.8 - 57.2)	47.0 (34.5 - 79.0)	0.5
Elevated	7 (31.8%)	5 (35.7%)	3 (18.8%)	3 (27.3%)	0.7
¹ Median (IQR); Mean ± SD; n (%)					
² Kruskal-Wallis rank sum test; One-way ANOVA; Fisher's exact test					

Upon stratifying patients based on their SGGT status, distinguishing between normal and high SGGT levels, a noteworthy association emerged in the comparison of patient characteristics, particularly concerning patient

sex (p-value = 0.01). However, no statistically significant associations were observed for the other variables under consideration.

Table 5: Comparison of Demographic Factors and Anthropometric Measures According to SGGT Status.

Characteristic	Normal SGGT, N = 76 ¹	High SGGT, N = 24 ¹	p-value ²
Age	60.4 ± 10.9	60.8 ± 12.6	0.9
Sex			0.010
Male	51 (67.1%)	9 (37.5%)	
Female	25 (32.9%)	15 (62.5%)	
Body mass index (BMI)	30.4 ± 5.2	31.7 ± 5.7	0.3
¹ Mean ± SD; n (%)			
² Welch Two Sample t-test; Pearson's Chi-squared test			
Characteristic	Normal SGGT, N = 76 ¹	High SGGT, N = 24 ¹	p-value ²
Smoking history	39 (51.3%)	10 (41.7%)	0.4
Family history of IHD	32 (42.1%)	11 (45.8%)	0.7
¹ n (%)			
² Pearson's Chi-squared test			
Characteristic	Normal SGGT, N = 76 ¹	High SGGT, N = 24 ¹	p-value ²
Random blood sugar (mmol/l)	9.1 ± 4.5	8.4 ± 2.5	0.3
Lipid profile			
Total cholesterol (mmol/L)	3.6 ± 1.1	4.1 ± 1.4	0.2
Serum triglyceride (mmol/l)	1.5 ± 0.9	1.5 ± 0.8	0.8
Low-density lipoprotein (mmol/L)	1.5 ± 0.9	1.9 ± 1.1	0.093
¹ Mean ± SD			
² Welch Two Sample t-test			
Characteristic	Normal SGGT, N = 76 ¹	High SGGT, N = 24 ¹	p-value ²
Angiography			
Abnormal	45 (59.2%)	18 (75.0%)	0.2
Normal	31 (40.8%)	6 (25.0%)	
¹ n (%)			
² Pearson's Chi-squared test			

DISCUSSION

Accumulating evidence from epidemiological studies highlights the association between elevated γ -glutamyl transferase (GGT) levels and cardiovascular disease (CVD), including atherosclerosis, underscoring GGT's

potential as a biomarker for cardiovascular risk.^[15] In this study, patients had an average age of 60.5 ± 11.3 years, with 60% being male and a mean BMI of 30.7 ± 5.3. Aging, often linked with obesity, increases cardiovascular risk by contributing to arterial stiffness

and lipid metabolism changes, especially in males who generally face a higher IHD risk due to hormonal and non-hormonal factors.^[16, 17] Comparable findings from Christoffersen et al.^[18] reported a median age of 56 years in IHD patients and a BMI range of 23 to 28. Hypertension and diabetes were prevalent in 71% and 60% of participants, respectively, with 43% having a positive family history of IHD. These findings are consistent with Rashid et al.'s study^[19] in Malaysia, reinforcing the role of these comorbidities as significant IHD risk factors.^[20] Angiographic analysis revealed that 37% had normal results, while 22% had single-vessel disease, 14% had two vessels affected, and 16% had three-vessel disease. The left anterior descending artery was the most commonly affected vessel, followed by the right coronary artery and left circumflex artery, similar to findings in Kurdistan by Mohammad et al.^[21] and Haider et al.^[22] A significant association between smoking, random blood sugar levels, and abnormal angiography was observed, echoing results from Mathew et al.^[23] The study found a median GGT value of 40.5, elevated in 24% of patients, with higher GGT levels associated with abnormal angiography ($p < 0.001$) but not with the number of affected vessels.^[24] Previous studies by Singh et al.^[25] and Arasteh et al.^[26] reported progressive GGT increases with the severity of coronary artery disease, while Elahi et al.^[27] observed higher oxidative stress in patients with elevated GGT. No significant difference was noted in lipid profiles between patients with normal and elevated GGT, although LDL levels were marginally higher in the latter group.^[28] A significant association between GGT levels and sex was observed, with 62.5% of females exhibiting elevated levels, suggesting potential sex-related differences in GGT metabolism and cardiovascular pathology, warranting further research.

CONCLUSION

The current study concluded that serum gamma-glutamyl transferase is prevalent among those with ischemic heart disease, revealing a significant association with positive angiography findings.

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