Association of Serum Gamma Glutamyl Transferase Level with Acute Coronary Syndrome and Its Correlation with Major Adverse Cardiovascular Outcomes - A Single Center Cross Sectional Study from a Tertiary Care Centre in Kerala

Baiju Rajan[1], Praveen Velappan[2], Abdul Salam[3], Sivaprasad Kunjukrishnapillai[4], Kapil Rajendran[5], Binu Thankappan Gomathy[6], Ashis Ranjan[7], Girish[8]

[1, 2, 3, 4, 5, 6, 7, 8] Department of Cardiology, Government TD Medical College and Hospital, Alappuzha, Kerala, India.

ABSTRACT

BACKGROUND

Gamma glutamyl transferase (GGT) is a biomarker elevated in various cardiovascular diseases due to oxidation mediated free radical damage. It has been recently used in patients presenting with acute coronary syndromes (ACS) for predicting major adverse cardiovascular events and in hospital adverse outcomes. The application of gamma glutamyl transferase to the traditional set of biomarkers like troponin I and T, creatinine kinase-MB (CKMB) adds to the value that it helps in reclassifying the patients into high and low risk and plan the appropriate treatment strategy.

METHODS

Patients presenting with acute coronary syndromes were classified into STEMI (ST elevation myocardial infarction), NSTEMI (Non-ST elevation myocardial infarction) and unstable angina based on cardiac biomarkers and electrocardiographic changes. Serum gamma glutamyl transferase of these patients were measured by photo spectrometry and were monitored for 5 days for major adverse cardiovascular events.

RESULTS

Of the study population (N = 210), 41 % presented with STEMI, 24 % unstable angina, 25 % NSTEMI. The normal range of GGT in our study population was 15 - 70 U/l. values more than 70 U/l was considered raised GGT major adverse cardiac events (MACE) was present in 35 % of the study population. 58 % of the patients with MACE had raised GGT (> 70 U/l) which was statistically significant (P < 0.001). The ROC (receiver operator characteristic curve) for GGT to predict MACE was to the left of the reference line and the area under the curve (AUC) was 0.915. The optimal cut-off for GGT to predict MACE from our study was 50.5 with a sensitivity and specificity of 0.813 and 0.868 respectively.

CONCLUSIONS

Raised GGT was significantly associated with MACE and in hospital adverse outcomes (ventricular arrythmias, heart failure, recurrent angina). GGT can be used as a prognostic marker in patients presenting with ACS.

KEYWORDS

Gamma Glutamyl Transferase, Acute Coronary Syndromes, St Elevation Myocardial Infarction, Non-ST Elevation Myocardial Infarction, Unstable Angina

Corresponding Author:
Dr. Baiju Rajan,
Baiju Bhavan, TC 5/2065 PNRA F11,
Kokkode, Kawdiyar P.O-695003,
Thiruvananthapuram, Kerala, India.
E-mail: baijurajan2001@gmail.com

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BACKGROUND

Acute myocardial infarction is traditionally diagnosed using standard biomarkers like cardiac troponin/creatine kinase (CKMB).[1] The prognostic value of these diagnostic biomarkers is uncertain. Identifying and stratifying patients presenting with acute coronary syndrome into high and low risk based on biomarkers is important therapeutically for planning the appropriate intervention strategy.[2] The increased quantity of gamma glutamyl transferase found in atherosclerotic plaques predisposes these plaques to oxidative stress accelerating plaque rupture, apoptosis and thrombosis.[3] Data regarding gamma glutamyl transferase in south Indian Kerala population is rare. Our current study highlights the importance of gamma glutamyl transferase in prognostifying of patients presenting with acute coronary syndromes and its role in predicting major adverse cardiovascular events. Since gamma glutamyl transferase also correlated with the risk factors and severity of coronary artery disease,[4,5] it helps in categorising patients into high and low risk and plan the earliest intervention strategy as per the risk.

The aim of our study was to determine the incidence of raised GGT in various subsets of ACS and its association between major adverse cardiovascular events and in hospital outcomes.

METHODS

This is a single centred cross-sectional study conducted on 210 (> 18 years) patients with acute coronary syndrome admitted in cardiac intensive coronary care unit (ICCU), Department of Cardiology, TDMCH, Vandanam (Kerala-India) after obtaining informed consent.

Sample size (N = 210) was calculated by using the formula $4pq/d^2$ from the gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk - The Framingham heart study (2006) with a cumulative incidence of age/sex adjusted incident cardiovascular event rate was 32 %.

The research protocol was approved by the institutional research committee (IRC) & institutional ethics committee (IEC). The study period was from 5 – 7 - 2020 to 5 – 1 - 2021 for a duration of 6 months. Patients with history of any alcohol intake within 24 hours, history of hepatobiliary disease, surgical conditions causing obstructive jaundice, alanine transaminase (ALT) > 40 U/L, coarse liver echotexture on ultrasonography, history of taking drugs such as barbiturates, phenytoin, anti-tubercular drugs were excluded from the study. Risk factors like diabetes, hypertension, hypercholesterolemia were defined by routine standard criteria. Serum samples for TROP I, GGT, liver function test (LFT), renal function test (RFT) was collected. Serum GGT was measured and quantified by FUJI DRI-CHEM SLIDE GGT-PIII (reflective photo spectrometry). GGT values > 70 U/l were considered abnormally high. Patients were classified into STEMI/NSTEMI/UA based on electrocardiogram (ECG) and troponin measurements. Patients were followed up in ICCU for 5 days for monitoring in hospital outcomes.

Statistical Analysis

Statistical significance between GGT and risk factors, MACE was assessed by the chi square test. P value < 0.05 was considered statistically significant at 95 % confidence interval. Fisher's exact test was used when the expected value in any of the cell was found to be less than 5. The ability of gamma glutamyl transferase in predicting major adverse cardiovascular events was analysed with a receiver operator characteristic curve and area under the curve (AUC). The optimal cut-off for gamma glutamyl transferase to predict MACE was derived with its sensitivity and specificity. Results were calculated and analysed using SPSS - 18.

RESULTS

210 patients were enrolled for the study of which 39.7 % of patients was STEMI, 29.2 % NSTEMI, 31.1 % UA. Baseline characteristics of the study population are described in table 1

	Distribution of Study Subjects	
Age - years	Mean	57.48 ± 12.77
	Median	58 (48-66)
Gender - n (%)	Male	112 (53.6)
	Female	97 (46.4)
T2DM - n (%)	Yes	106 (50.7)
	No	103 (49.3)
Hypertension - n (%)	Yes	110 (52.6)
	No	99 (47.4)
Smoking - n (%)	Yes	48 (23)
	No	160 (76.6)
BMI - kg/m2	Mean	23.12 ± 2.84
	Median	22.6 (20.80-25.90)
Type of ACS - n (%)	STEMI	83 (39.7)
	NSTEMI	61 (29.2)
	UA	65 (31.1)
TROP I - n (%)	Positive	108 (51.7)
	Negative	101 (48.3)
RWMA - n (%)	NIL	85 (40.7)
	IW/IS	59 (28.2)
	AW/AS	65 (31.1)
Cholesterol - mg/dl	Mean	186.15±29.31
	Median	180 (164-213)
Cholesterol – n (%)	<175	86 (41.1)
	175-200	68 (32.5)
	>200	55 (26.3)
LDL- mg/dl	Mean	133.05±30.18
	Median	139 (109-157)
HDL- mg/dl	Mean	39.56±7.32
	Median	39 (33-46)
GGT- U/L	Mean	47.07±21.67
	Median	43 (28-64)
GGT- n (%)	<70	167 (79.9)
	>70	42(20.1)
MACE - n (%)	Yes	80(38.3)
	No	129(61.7)

Table 1. Demographics and Baseline Characteristics of Study Subjects

Gamma Glutamyl Transferase and MACE

The mean GGT was 47.07 ± 21.67. 20.1 % (N = 42) (Table 1) patients had raised GGT. 20.1 % of the total study population had a GGT of more than 70 IU/L and the remaining 79.9 % had a GGT of less than 70 IU/L. MACE

was found in 38.3 % (N = 80) of the patients with raised GGT.

Association of Risk Factors with Acute Coronary Syndromes

The incidence of T2 DM and SHT was higher in the NSTEMI subset which was not statistically significant (T2DM→ P = 0.378 / SHT→ P = 0.252). The incidence of hypercholesterolemia (> 200 mg/dl) was 41.8 %, 21.8 %, 36.4 % in the NSTEMI, STEMI, UA subsets respectively, the difference was not statistically significant (P = 0.407) (table 2). The incidence of MACE higher in the NSTEMI subset (66.2 %), 21.2 % in STEMI group, 12.5 % in UA group, the difference was statistically significant (P < 0.001) (table 2). Quantitative GGT > 70 U/l was found in higher incidence in NSTEMI (59.5 %), 26.2 % in STEMI, 14.3 % in UA, the difference of which was statistically significant (P < 0.006) (table 2).

	Risk Factors	ACS –n (%) NSTEMI	STEMI	UA	P Value
Gender	Male	43 (38.4)	33 (29.5)	36 (32.1)	0.906
	Female	40 (41.2)	28 (28.9)	29 (29.9)	
T2DM	Yes	47 (44.3)	29 (27.4)	30 (28.3)	0.378
	No	36 (35)	32 (31.1)	35 (34)	
Hypertension	Yes	38 (34.5)	36 (32.7)	36 (32.7)	0.252
	No	45 (45.5)	25 (25.3)	29 (29.3)	
Smoking	Yes	25 (52.1)	12 (25)	11 (22.9)	0.115
	No	57 (35.6)	49 (30.6)	54 (33.8)	
TROP I	Positive	49 (45.4)	59 (54.6)	0	0.001*
	Negative	34 (33.7)	2 (2)	65 (64.4)	
RWMA	NIL	0	37 (43.5)	48 (56.5)	0.001*
	IW/IS	35 (59.3)	10 (16.9)	14 (23.7)	
	AW/AS	48 (73.8)	14 (21.5)	3 (4.6)	
MACE	Yes	53 (66.2)	17 (21.2)	10 (12.5)	0.001*
	No	30 (23.3)	44 (34.1)	55 (42.6)	
GGT	< 70	58 (34.7)	50 (29.9)	59 (35.3)	0.006*
	>70	25 (59.5)	11 (26.2)	6 (14.3)	
Cholesterol	< 175	31 (36)	26 (30.2)	29 (33.7)	0.407
	175 - 200	29 (42.6)	23 (33.8)	16 (23.5)	
	> 200	23 (41.8)	12 (21.8)	20 (36.4)	

Table 2. Association of Risk Factors with ACS

Abbreviations: RWMA – Regional wall motion abnormality, AW- anterior wall, AS - anterospetum, IW -inferior wall, IS – inferospetum

38.3 % (80/210) of the study population had MACE. Ventricular tachycardia was the most common event followed by heart failure. 23.4 % (N = 39) of the patients with GGT 55 - 70 U/l had MACE. 97.6 % (N = 41) of the patients with GGT > 70 U/l had MACE in the form of ventricular arrythmia/heart failure/reucrrent angina, the results of which were statistically significant. (table. 3)

GGT	MACE Yes	No	P Value
< 70	39 (23.4)	128 (76.6)	0.001*
➢ 70	41 (97.6)	1 (2.4)	

Table 3. Association between GGT and MACE

*statistically significant at 5 % level

DISCUSSION

The current study showed a statistically significant association between raised GGT and major adverse cardiovascular outcomes. This study was conducted to assess the incidence of raised GGT in patients presenting with acute coronary syndromes in Kerala population.

In our study population, the incidence of STEMI, was proportionately higher than NSTEMI and unstable angina and the incidence of risk factors was also comparatively higher in the NSTEMI subgroup. Though the difference was not statistically significant, the incidence of higher risk factors could account for the observed higher GGT levels in NSTEMI subgroup compared to the other two subsets (STEMI and UA). Nearly 50 % of the study population had diabetes and hypertension which and about one fourth of the males were smokers. Although GGT was raised in only 20 % of the study population, 97 % (41) of the subjects with high GGT had major adverse cardio vascular events.

The ROC curve for gamma glutamyl transferase to predict major adverse cardiovascular events was to the left of the reference line (> 45-degree diagonal of the ROC space) (fig. 1) indicating good sensitivity and likelihood ratio to predict major adverse cardiovascular events.

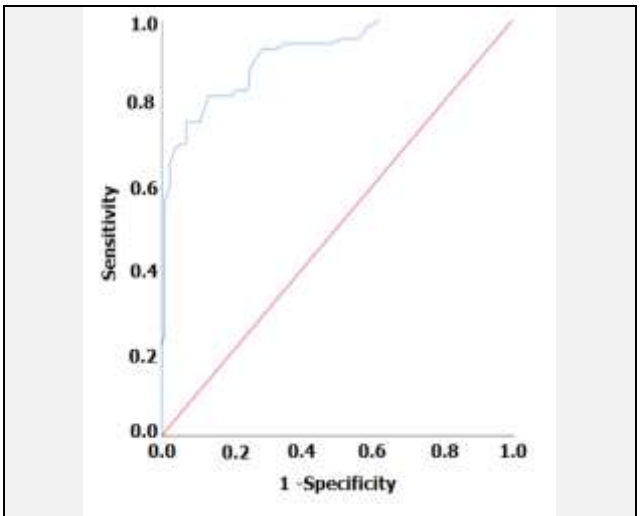

Figure 1. ROC Curve of RV GLS for Predicting MACE

Area under the Curve (AUC)

The AUC for gamma glutamyl transferase was 0.915 (traditional academic point system EXCELLENT→ 0.90 - 1.00 → A) which indicates that gamma glutamyl transferase has good accuracy to predict major adverse cardiovascular events. (table 4)

Area under the Curve	95 % CI	p Value
0.915	0.876-954	<0.001*

Table 4. Area under the Curve

*statistically significant

High GGT levels show a positive correlation with Framingham cardiovascular risk scores of adults with no diabetes or non-obese individuals.[6] Serum GGT level in hypertensive patients was associated with coronary flow reserve impairment and concluded that serum GGT was an independent predictor of end organ damage in hypertensive patients.[7]

Though the association between atherogenesis and GGT activity revealed by experimental studies were supported by

clinical and epidemiological data, the relation between severity of coronary artery disease and GGT levels had not been investigated previously. The largest study about the importance of GGT in patients with coronary artery diseases (CAD) was performed by Ruttmann et al. They found a strong association between high GGT levels and cardiovascular mortality, and suggested that high GGT is an independent risk factor for cardiovascular disease.[5]

Increased liver fat and carotid intima-media thickness, both indicative of atherosclerosis, are shown to be associated with normal or slightly elevated GGT levels.[8] Various biomarkers and risk stratification schemes have been developed and tested to predict prognosis of patients with acute myocardial infarction,[9] yet the risk stratification for short or long-term mortality after hospital discharge remains suboptimal.[10] Gamma-glutamyl transferase is a ubiquitous enzyme that is involved in the metabolism of glutathione which is a major physiological anti-oxidant in humans. Evidence available strongly suggests that GGT is involved in cardiovascular disease either in terms of association with incident coronary events or as an associate of all-cause or cardiac mortality.[11] GGT activity has been detected in human atherosclerotic plaques.[12] Notably, within-plaque GGT activity correlates with indices of plaque vulnerability and systemic GGT activity. Since vulnerable plaque is considered to be a key pathophysiological element in the pathophysiology of ACS, these findings strongly implicate GGT in the genesis of these syndromes[3].

Cardiac syndrome X (CSX) is a condition in which patients with no physical findings of CAD experience angina. Demir et al.[13] compared serum GGT levels between patients with CSX and asymptomatic healthy individuals. In this study, serum GGT activity in patients with CSX was confirmed to be higher than in healthy controls; moreover, GGT activity was further increased in patients with CSX who also had the metabolic syndrome. The relationship between serum GGT activity and carotid intima media thickness in patients with CSX was evaluated by Yagmur et al. Serum GGT activity in patients with CSX was shown to be as high as that in patients with CAD. A significant correlation was found between GGT activity and carotid intima media thickness measurements, but serum GGT activity did not correlate with serum CRP levels in patients with CSX. It was suggested that increased GGT levels play a role in the pathogenesis of the microvascular atherosclerotic process of CSX.[14]

GGT is an enzyme in the cell membrane that transfers gamma-glutamyl functional groups. The physiological role of GGT is to cleave the gamma-glutamyl amide bond of the tripeptide and hydrolysis of extracellular GSH to produce cysteine and other thiol ingredients. Also, GGT is a facilitator of the generation of ROS and transfer gamma-glutamyl moiety of glutathione to an acceptor such as amino acid, a peptide or water.[15,16]

In atherosclerosis, GGT can be slightly absorbed inside LDL-c and oxidized LDL inside the plaque (equivalent to GGT levels) by reducing Fe (III) to redox-active Fe (II)[16]. GGT is also involved in the formation of the fibrous cap, plaque rupture, erosion, increased platelet aggregation and thrombosis.[12] Bozbas et al. found a significant correlation between the level of GGT, CRP and metabolic syndrome.[17]

GGT is an overall marker of oxidation mediated free radical damage that can be elevated in any pathology that precipitates inflammation.[15] Acute coronary syndrome is an acute inflammatory state as well as the traditional risk factors like diabetes, hypertension, smoking, alcoholism can perpetuate the inflammation resulting in elevated GGT levels, thereby limiting its specificity in acute coronary syndrome. From our study, the optimal cut off score for gamma glutamyl transferase in predicting major adverse cardiovascular outcomes was 50.5 with a sensitivity of 0.813 and specificity of 0.868.

Sabri Demircan et al.[18] demonstrate that GGT activity is increased in patients with CAD. The association of GGT activity and cardiovascular mortality in these patients was related to LV function, clinical instability, and increased inflammatory activity rather than the extent of CAD. Their results suggest that GGT would be a useful and important biomarker to cardiovascular risk evaluation.

Dogan et al.[19] found that GGT levels were higher in patients with significant stenosis compared with those without significant stenosis in a study that investigated the association between significant stenosis and major cardiac events (MACE) in 237 non-ST elevation ACS patients. MACE-free survival was slightly poorer in ACS patients with GGT levels in the upper tertile compared with those with levels in the lower tertile at 12 months. Akpek et al.[20] 425 patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention, although the TIMI flow percentages were similar in the three GGT tertiles (32 %, 45 % and 42 %), serum GGT activity was associated with in-hospital MACE. Breitling et al.[21] reported that serum GGT level was associated with prognosis independent of a variety of established risk markers in patients with stable CAD in a study that included 1152 participants of an in-patient ACS rehabilitation program. The association appeared to be similar to that reported for primary cardiovascular disease, which should prompt additional studies of its clinical utility in cardiovascular patient care. In addition, serum GGT activity was found to be associated with higher occlusion rates of venous bypass grafts in a study investigating the relationship between serum GGT levels and saphenous vein bypass graft disease at least one year after coronary artery bypass graft surgery.[22] GGT levels have also been confirmed to be an independent predictor of early mortality in STEMI patients without previously known diabetes who underwent mechanical revascularization.[23]

The relationship between GGT and hepatic triglyceride accumulation in obesity, insulin resistance, metabolic syndrome, and type 2 diabetes was demonstrated by Ortego et al.[24] The liver derived proteins called hepatokines establishes the relationship between obesity, metabolic syndrome and cardiovascular disease.[25] GGT has been established as a marker of oxidative stress and a proinflammatory indicator.[26] The amplifying effects of GGT levels and highly sensitive C-reactive protein on metabolic syndrome and insulin resistance was reported by Kawamoto et al.[27] The catabolism of the major antioxidant glutathione

is mediated by gamma glutamyl transferase. Within atherosclerotic plaques, the active staining of gamma glutamyl transferase was demonstrated by Paolicchi et al.[28] and concluded that in addition to their synergistic role with conventional cardiovascular risk factors, GGT has a role as an independent prognostic factor. Although exact mechanism is not clear, the association between GGT and lipoproteins suggests that LDL lipoprotein can convey GTT activity inside the atherosclerotic plaque.[29] Due to unknown mechanisms, the relationship between GGT and apolipoproteins suggest that low density lipoproteins can accelerate GGT activity within atherosclerotic plaques.[29] The oxidative stress mediated by GGT perpetuate the development and progression of plaque vulnerability, erosion and subsequently rupture resulting in platelet aggregation and thrombosis.[16] Using coronary computed tomography angiography (CCTA), significantly higher levels of GGT was demonstrated in vulnerable atherosclerotic plaques by Celik et al.[30] In multivariable models, positive associations between GGT and CRP, interleukin - 6 (IL - 6), and soluble intercellular adhesion molecule - 1 (sICAM - 1) were demonstrated in the multi-ethnic study of atherosclerosis (MESA) study.[31] The independent association between coronary artery calcification (CAC) progression and GGT levels was demonstrated by Cho et al.[32] The association of low serum bilirubin, GGT as potential markers of atherosclerosis in Korean men was shown by Cho et al.[33] Age has a significant effect on GGT in predicting cardiovascular morbidity and mortality as shown in a nested case-control study, that in individuals more than 70 years the association between GGT and incident cardiovascular mortality was not established.[34] In a contemporary study done by Strasak et al. the significance of GGT in predicting cardiovascular mortality in younger individuals was established.[35] In younger men (< 55 years) when stratified by age group, Wannamethee et al. also showed a stronger association between GGT and CVD mortality.[36] The finding that the relationship between GGT and cardiovascular events being not found in older individuals was contradicted by Mahady et al. the relationship between ALT, GGT and cardiovascular mortality was found in older individuals but not in individuals < 59 years.[37] In the study done by a Kyung Mook et al.[38] relationship was significantly established between age, liver enzymes, GGT and cardiovascular events. They found that when compared to individuals with age ≥ 65, individuals with age < 65 demonstrated a remarkably higher risk of myocardial infarction and other cardiovascular events associated with GGT.[38] Small dense lipoproteins increase the cardiovascular risk in individuals with non-alcoholic steato hepatitis (NASH).[39] From the available literature, the possible explanations for GGT association with cardiovascular disease are summarized. Circulating GGT may be marker of oxidative stress and antioxidant inadequacy as complemented by the finding that it correlates with inflammatory markers like hs-CRP and indicate a amplified inflammatory state.[40] The role of increased oxidative stress, metabolic syndrome, insulin resistance, cardiovascular risk factors in promoting systemic inflammation has been previously established and with this context high GGT levels may be considered as a marker of cardiometabolic stress. The higher incidence of arrythmia's particularly atrial fibrillation may be explained by the higher levels of GGT found in individuals with high alcohol consumption.[41] But light and moderate alcohol consumption is inversely correlated with cardiovascular mortality. In about 70 % of diabetics, non-alcoholic fatty liver has been found to have more elevated levels of GGT in addition to the cardiovascular diseases.[42] Non-alcoholic fatty liver is associated with many cardio metabolic disorders (metabolic syndrome equivalent) may explain a probable link between fatty liver and accelerated atherosclerosis. The breakdown of glutathione by GGT in the extracellular space leads to production of cysteinyl-glycine dipeptide — even a stronger reducing agent than glutathione. The reduction of glutathione by GGT leads to production of cysteinyl-glycine dipeptide (stronger reducing agent than glutathione) which reduces Fe3 + to Fe2 + which catalyses formation of super-oxide and hydrogen peroxide. Super oxide and H2O2 promote peroxidation reactions (including low-density lipoproteins) which predisposes to an inflammatory milieu.[15,17]

Our study has important implications. This study did not find significant correlation between the incidences of risk factors in different subsets of acute coronary syndromes. Patients with high GGT (> 70 U/l) in NSTEMI/UA subsets prone to develop MACE (ventricular tachycardia (VT)/heart failure/recurrent angina) have to monitored more meticulously rather than premature discharge.

CONCLUSIONS

Raised GGT in patients admitted with acute coronary syndromes have a role in sub stratifying these patients into high and low risk and the emergent therapeutic strategy can be planned accordingly. Raised GGT patients in NSTEMI/UA subsets have to be monitored more cautiously as they are prone to develop MACE.

Limitations

The limitation of our study was small sample size and it was a single centred cross-sectional study. The observations arrived from the results of our study were based on a short term follow up. The effects of raised GGT on long term mortality could not be defined. A wide range of variation was observed in the levels of GGT measured in the study population. GGT is a general marker indicating oxidation mediated free radical damage; hence, its levels can be elevated in all pathological conditions accelerating inflammation, hence its limited specificity.

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