Original Research Article

Study on association of gamma glutamyl transferase with acute coronary syndrome and correlation with in-hospital outcome

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Abstract

Background: Although traditionally associated with alcoholic liver disease, recent studies have shown evidence of correlation between elevated Gamma-glutamyl transferase (GGT) and atherosclerotic heart disease. This is said to be due to its role in the generation of reactive oxygen species in the presence of iron. It is independently correlated with conditions associated with increased atherosclerosis, such as obesity, elevated serum cholesterol, high blood pressure and myocardial infarction. It is also demonstrated that serum GGT activity is an independent risk factor for myocardial infarction and cardiac death in patients with coronary artery disease.

Aim: To study the correlation between rise in GGT levels and different subsets of Acute Coronary Syndrome. To study the correlation between GGT and risk of Major Adverse Cardiovascular Events (MACE).

Materials and methods: This was a cross sectional study conducted at Government Medical College, Omandurar Government Estate, Chennai and patients admitted with Acute Coronary syndrome in our ICU were selected. GGT levels were measured for all patients in a standardized manner and cases were observed for five days in the hospital for adverse events. This study was done for a time period between May 2019 to March 2020 and 75 patients with ACS were included.

Results: Serum GGT levels were significantly elevated in both the STEMI and NSTEMI subsets but not in the unstable angina subset. The mean GGT value for patients who suffered complications was 90.22. The mean value for patients without MACE was a significantly less 46.44. There was also

found to be correlation between GGT and presence of hypertension, LV dysfunction, total cholesterol and LDL levels.

Conclusion: Gamma glutamyl transferase levels were significantly elevated above normal in patients presenting with acute coronary syndrome. GGT levels were independently correlated with STEMI and NSTEMI but had no correlation with unstable angina. There was a significant correlation between GGT levels and incidence of left ventricular systolic LV dysfunction. The mean value of GGT was significantly elevated in patients who suffered from major adverse cardiovascular events. Patients with significantly elevated GGT values may, in future, be referred for early invasive revascularization procedures like PCI/CABG. In conclusion, as concerns ischemic heart disease, GGT assay seems to have the features of a good prognostic marker with optimal sensitivity of the diagnostic assay and it helps improve our ability to predict adverse events in CAD. Further its prognostic impact can be utilized in risk stratification and the need for urgent therapeutic intervention.

Key words

Gamma Glutamyl Transferase, Acute Coronary Syndrome, LDL oxidation, Atherosclerotic plaque, MACE.

Introduction

Sudden onset chest pain is one of the commonest causes for presentation to the hospital casualty. Even though acute onset chest pain is very often assumed to be acute coronary syndrome (ACS), after further workup only 15% to 25% of patients with acute chest pain have MI [1, 2]. The diagnosis of ACS is overlooked in about 2% of patients, which can lead to negative consequences. The acute coronary syndromes constitute a range of heart diseases from unstable angina to ST elevation myocardial infarction. The basic pathophysiology is similar for the entire spectrum in the form of a thrombus overlying a plaque. Several recent advances, have enhanced the accuracy and efficiency of the evaluation of patients with acute chest pain, mainly owing to better biomarkers of cardiac injury [3].

A variety of molecules have been used to diagnose and prognosticate acute coronary syndromes ranging from LDH and myoglobin to creatine phosphokinase and troponins. The current management particulars are centered around the measurements of troponins which are both highly specific and sensitivity to acute cardiac insult. However the search is still ongoing for other molecules and enzymes which will help in assessing the severity of various forms of myocardial infarction. Stratification of ACS into high and low risk is imperative not only regarding the adequacy of treatment but also in avoiding unnecessary costs and inconvenience to the patient.

Among the latest armamentarium of molecules being investigated for diagnosing and more importantly, prognosticating myocardial infarction is an enzyme called Gamma Glutamyl Transferase (GGT) [4]. Well recognized as a marker of alcohol induced liver injury, GGT has gained importance in recent years as a marker of acute cardiac injury and has shown correlation with a host of risk factors responsible for macrovascular diseases, primarily coronary artery disease. GGT shows promise as a new tool in the risk stratification of various types of acute myocardial infarction.

Aim and objectives

- To determine the frequency of raised serum Gamma Glutamyl Transferase levels in cases presenting with acute coronary syndromes.
- To determine the possible association between raised GGT levels and different subsets of ACS.
- To determine the association between raised serum GGT levels and in hospital adverse cardiovascular outcomes.

- To determine the association between raised GGT levels and risk factors for acute coronary syndrome.

Materials and methods

This study was done at Government Medical College, Omandurar Government Estate, Chennai between May 2019 to March 2020. The study was performed after procuring informed written consent from all the participants involved. Clearance was obtained from the Ethical Committee of Government Medical College, Omandurar Government Estate, Chennai.

Study design and patient selection

This was a cross sectional, comparative study in which seventy five cases presenting as Acute Coronary Syndrome to the coronary care unit of our hospital were selected.

Inclusion criteria

All patients admitted with an episode of Acute Coronary Syndrome in the coronary care unit of Government Medical College, Omandurar Government Estate, Chennai.

Exclusion criteria

- History of any alcohol intake
- History of hepatobiliary disease
- Surgical conditions causing obstructive jaundice
- Alanine transaminase (ALT)>40U/IL
- Coarse liver echotexture on ultrasonography
- History of taking drugs such as barbiturates, phenytoin, anti-tubercular drugs

Methodology

All patients presenting with acute coronary syndrome were included in the study. Gamma glutamyl tranferase levels were measured in all the patients using a standardized photometric method with the normal value noted as 0-45 IU/L. Blood samples were taken uniformly six hours from the time of presentation.

Patients were followed up for five days in the hospital from admission into CCU for in-hospital outcome. Major adverse cardiovascular events were recorded in the form of re-infarct, cardiogenic shock requiring inotropic support, ventricular arrhythmias requiring cardioversion, pulmonary edema and cardiac death. Changes in GGT levels in ACS and its prognostic value on the development of MACE were studied.

The following investigations were done in all the patients entering into the study: Gamma glutamyl transferase levels, 14 lead Electrocardiogram, 2D echocardiography with doppler, Total cholesterol, LDL and HDL cholesterol, FBS and PPBS, Troponin T estimation, Liver function tests and Ultrasonography for liver echotexture.

Statistical analysis

Data was entered in Windows Excel format. Frequency tables and measures of central tendency (mean) and measures of dispersion (Standard Deviation) were calculated by using the statistical package SPSS- 20. Correlation was assessed using the chi-square test.

Results

Correlation between GGT and Gender

A total of 75 (male 46 = pts and female = 29 pts) who met the inclusion criteria were studied during the study period. 20 out of 46 males had a positive value for GGT (43.5%). 17 out of 29 females were positive for GGT (54.1%). The p value was 0.201. There was no significant correlation between gender and GGT in this study.

Correlation between GGT and diabetes

35 patients out of 75 in the study population were diabetics and 40 nondiabetics. Twenty patients out of the diabetic group were positive for GGT. Pvalue was 0.206.There is no significant correlation between diabetic status and GGT levels in this study.

Correlation with GGT and hypertensive status

Out of the 75 subjects 36 were hypertensives. 24 out of 36 hypertensives were positive for GGT. P value was 0.004. There was significant correlation between hypertension and GGT.

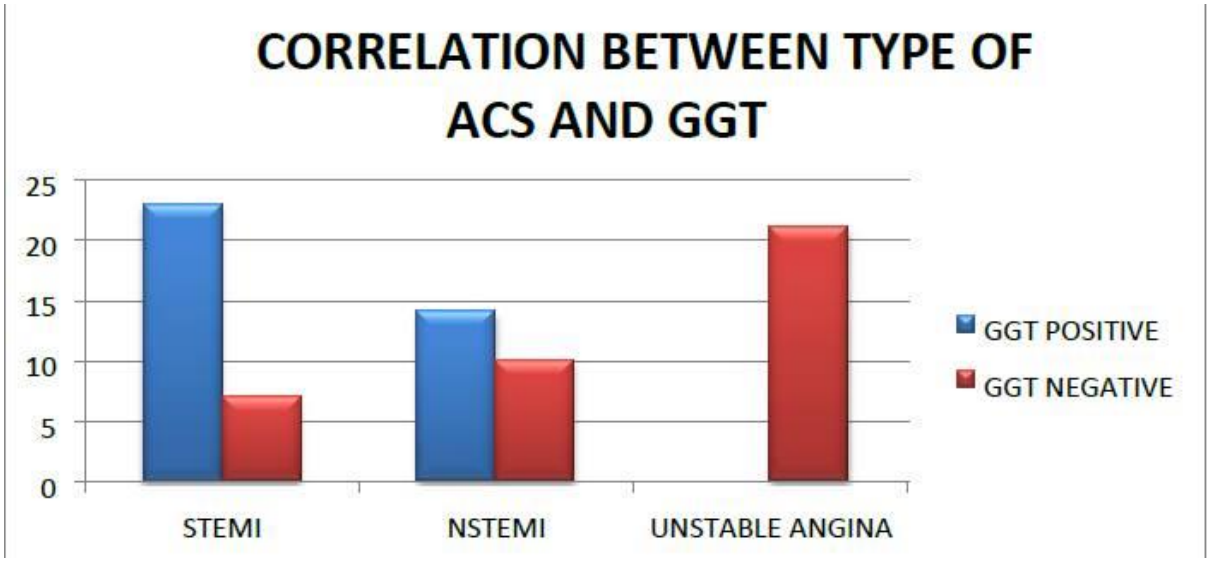
Correlation between GGT and smoking

30 subjects in the study population were chronic smokers. 17 of them turned out to be positive for GGT. The p value was 0.300. There is no significant correlation between smoking status and rise in GGT.

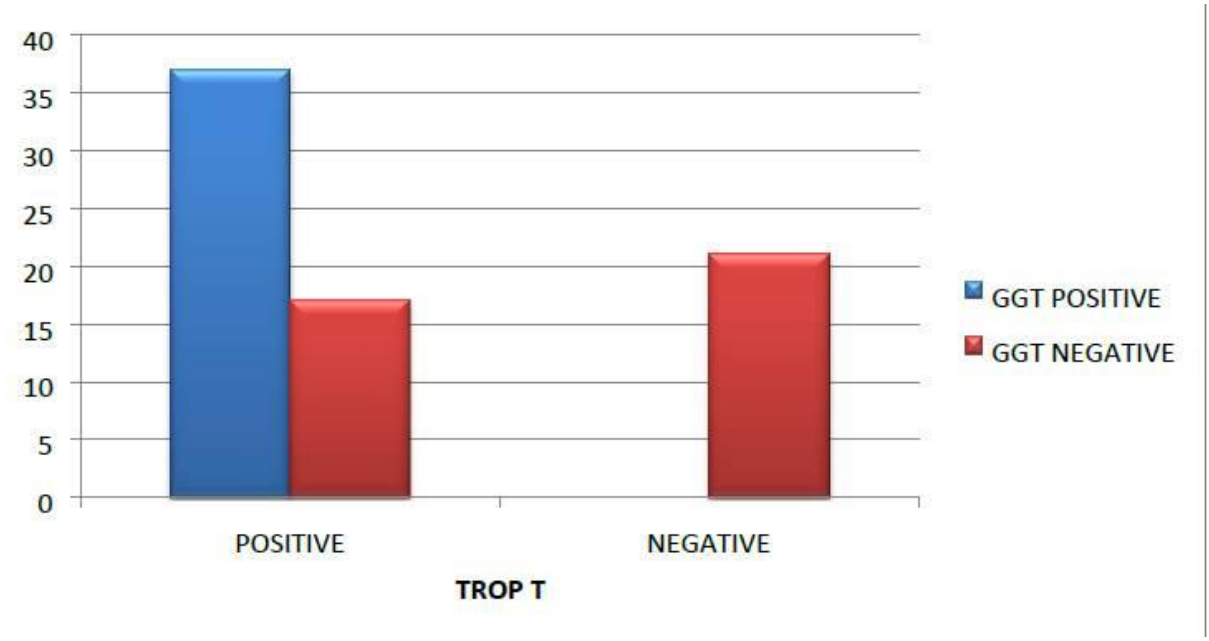
Correlation between GGT and type of ACS

In our study of 75 patients 30 had ST elevation in their ECGs, 24 subjects suffered from NSTEMI and 21 patients had unstable angina. 23 out of 30 patients with STEMI were positive for GGT. 14 out of 24 patients were positive for GGT while none of the unstable angina subset had a positive GGT value. P value was 0.001. Therefore there was a highly significant correlation between type of ACS and GGT levels with STEMI and NSTEMI showing positive values compared to unstable angina (**Graph – 1**).

Graph – 1: Correlation between type of ACS and GGT.



Graph – 2: Correlation between GGT and TROP T.



Graph – 3: Distribution of MACE in study population.

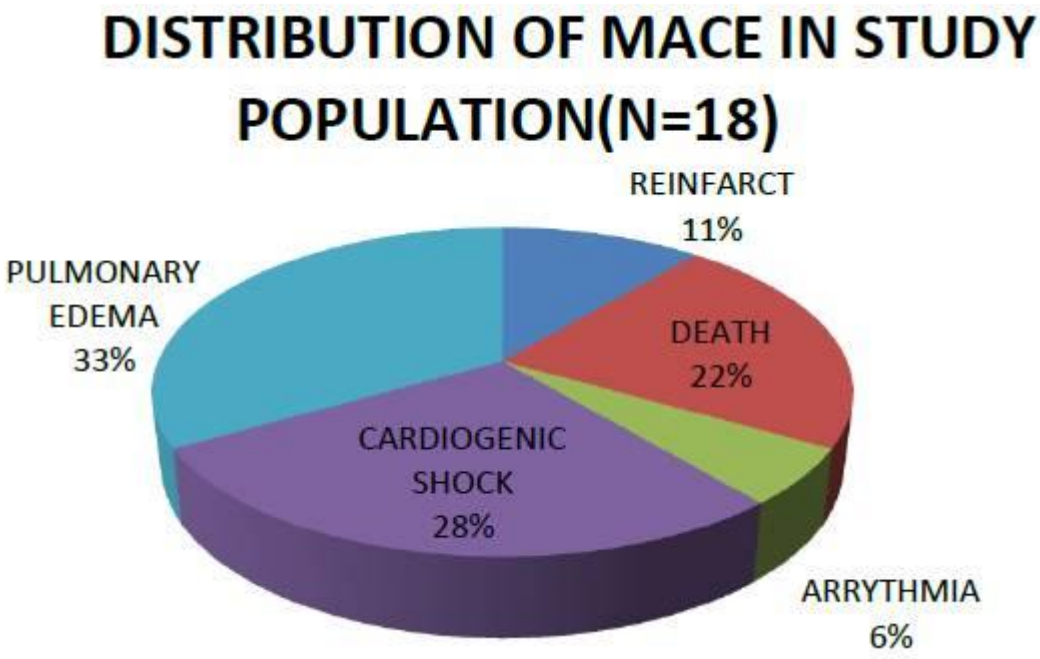


Table – 1: Correlation of GGT values in three types of ACS by ANOVA test.

	N	Mean	Std. Deviation	P value
STEMI	30	74.03	23.348	<0.001**
NSTEMI	24	54.88	23.058	
UA	21	34.90	7.609	

Table – 2: POST-HOC test.

(I) Type of ACS	(J) Type of ACS	Mean Difference (IJ)	Std. Error	p value
STEMI	NSTEMI	19.16(*)	5.515	0.002
	UA	39.13(*)	5.729	<0.001
NSTEMI	STEMI	-19.16(*)	5.515	0.002
	UA	19.97(*)	6.017	0.004
UA	STEMI	-39.13(*)	5.729	<0.001
	NSTEMI	-19.97(*)	6.017	0.004

Correlation between GGT and TROP T

In the study group of 75, people with Trop T positive were 54. Out of 54 subjects, 37 of them were positive for GGT. P value was 0.001. It shows a highly significant correlation between Trop T positivity and GGT positivity (**Graph – 2**).

Correlation between GGT and RWMA

Out of 75 study subjects 25 had demonstrable Regional wall motion abnormality of the ventricular wall on echocardiography. Out of this subset 20 patients had positive GGT values accounting for 80%. The p value was 0.001. Therefore there was highly significant correlation between RWMA on echocardiography and GGT levels.

Correlation between GGT and MACE

Out of the study population of 75, 18 subjects suffered from major adverse cardiovascular events (MACE) within their five day in-hospital period in the form of one of the following; reinfarct, ventricular tachycardia or fibrillation requiring defibrillation, cardiogenic shock requiring inotropic support, death. All 18 patients

had significantly positive GGT values. P value was <0.001. There was a significant correlation between incidence of MACE and GGT levels (**Graph – 3**).

18 subjects suffered from one of the major cardiovascular adverse events. The mean value for these patients was 90.22. The mean GGT value for patients without MACE was a significantly less 46.44. The p value was significant with 0.001.

Correlation of other variables with GGT

There was no significant correlation between increasing age, BMI and GGT positivity in this study. The p value was 0.799.

In comparing the total cholesterol levels and LDL cholesterol levels with GGT, the p value was significant <0.001. Therefore there was a highly significant correlation between total cholesterol, LDL cholesterol levels and GGT.

In comparing HDL levels and GGT, the p value was 0.183. Therefore there was no significant correlation between HDL levels and GGT positivity.

Correlation of GGT values in three types of ACS by ANOVA test

ANOVA test was used to look for correlation between the three types of ACS with their respective mean GGT values. The mean GGT values for the STEMI, NSTEMI and Unstable angina subsets were respectively 74.03, 54.88 and 34.90 respectively. The p value was significant for this test, <0.001. Therefore the difference in GGT values in the three subsets was statistically relevant (**Table – 1**).

POST-HOC TEST

A post hoc test was calculated to compare each type of ACS with the other two types and statistically correlate the difference between them. The p value was highly significant while comparing the difference in GGT levels in STEMI with both NSTEMI and Unstable angina. Likewise the p value was significant while comparing NSTEMI and unstable angina with the other two subsets (**Table – 2**).

Discussion

In our study, majority of patients were males (61%) and females accounted for 39% with a male: female ratio of approximately 3:2. 43.5% of males and 54.1% females had an elevated GGT value. However there was no significant correlation between gender and GGT in this study. The age group of our patients ranged from 37 to 84 and the mean age was 60.3 with peak incidence in the fifth and sixth decades. In this study there was no statistical correlation between age and GGT. In the study conducted by Emiroglu MY, et al. [6] comparing CRP and GGT, published in the North American Journal of Medical Sciences in 2010, the majority of the patients in each subset of ACS were males and male sex showed a positive correlation with GGT values. However the same study showed no correlation between age and GGT.

Our study showed no significant correlation between risk factors like presence of diabetes mellitus, hypertension, smoking and GGT positivity. In the study conducted by Emiroglu MY, et al. [6], no correlation between diabetes mellitus, hypertension, smoking and GGT levels was observed.

In our study of 75 patients 30 had ST elevation in their ecgs, 24 subjects suffered from NSTEMI and 21 patients had unstable angina. 23 out of 30 patients with STEMI were positive for GGT. 14 out of 24 patients were positive for GGT while none of the unstable angina subset had a positive GGT value. The mean GGT value for STEMI patients was 74.03 IU/L. The mean value for NSTEMI and unstable angina were respectively 54.88IU/L and 34.90IU/L. In comparing the correlation between types of ACS and level of GGT p value was significant <0.001. The mean value in unstable angina is within normal limits. Although the mean values in the other two subsets were elevated, the mean GGT in the STEMI subset was significantly higher than the

NSTEMI subset. This reveals that GGT shows promise as a sensitive diagnostic marker of STEMI. The study conducted by Emiroglu, et al. [6] showed positive correlation between types of ACS and GGT. However there was no correlation in this study between STEMI subset and NSTEMI subset. Mean value of GGT in unstable angina subset was similar to that of control group. In the study conducted by Dogan A, et al. [7] mean GGT level was higher in ACS group than control group (32 vs. 16 U/l, P=0.001).

Out of the 54 cases in the study that were positive for Trop T, 37 were positive for GGT. There was proven to be a significant correlation between Trop T and GGT. Further, GGT behaves similar to Trop T in that it is not elevated in any of the cases in the unstable angina subset. In the study conducted by Emiroglu, et al. [6] positive correlation was seen between Trop T and GGT with a p value of 0.001.

20 out of the 26 patients who were diagnosed to have systolic dysfunction on echocardiography were positive for GGT. There was a statistically significant correlation between GGT and LV dysfunction. Therefore high GGT values at presentation can assist in anticipating the complications of LV failure in patients presenting with ACS.

A total of 18 patients suffered from MACE in the study group. Two patients suffered from re-infarct, four patients died in the hospital, five patients had to be on dopamine support for cardiogenic shock. One patient went in for hemodynamically unstable ventricular tachycardia and six cases suffered from acute pulmonary edema. All the patients who suffered from MACE had an elevated GGT and the p value was highly significant. The mean GGT value of the MACE subset was 90.22+7.818 and mean GGT of the non-MACE group was 46.44+19.363. Comparing the two groups too, the p value was highly significant. Hence our study shows that an elevated GGT level at presentation can anticipate adverse cardiovascular outcomes in ACS patients. GGT therefore can be an important tool in prognosticating MI patients based on risk. In the study conducted by Dogan A, et al. [7] which included 237 cases, MACEfree survival was slightly poor in ACS patients with upper GGT tertile compared with those with lower GGT tertile (77 vs. 97%, P=0.06) even though p value was not significant. Asma Kamal, et al. [8] found that GGT values were higher than normal in the 36 subjects who suffered adverse cardiovascular events and a sizeable percentage of this subset suffered cardiac death, with a p value<0.001).

A post hoc analysis was done to assess the strength of GGT in predicting different types of acute coronary syndromes. The p value was highly significant while comparing GGT levels of one subset with each of the other subsets. This once again proves the utility of GGT in differentiating different types of ACS.

Conclusions

Gamma glutamyl transferase levels are significantly elevated above normal in patients presenting with acute coronary syndrome. GGT levels were independently correlated with STEMI and NSTEMI but had no correlation with unstable angina. There is a significant correlation between GGT levels and incidence of left ventricular systolic LV dysfunction. The mean value of GGT was significantly elevated in patients who suffered from major adverse cardiovascular events. Patients with significantly elevated GGT values may, in future, be referred for early invasive revascularization procedures like PCI/ CABG.

In conclusion, as concerns ischemic heart disease, GGT assay seems to have the features of a good prognostic marker with optimal sensitivity of the diagnostic assay and it helps improve our ability to predict adverse events in CAD. Further its prognostic impact can be utilized in risk stratification and the need for urgent therapeutic intervention.

Limitations of the study

The sample size of the study (75) was relatively small. A larger number would have strengthened our understanding of the correlation between the studied parameters. There is no way to know whether some subjects already had elevated GGT values or if the rise was linked to the ischemic event. Only further long term prospective studies will clearly elucidate this cause and effect.

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