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Estimation of gamma-glutamyl transferase with acute coronary syndrome

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Abstract
Introduction: Cardiovascular diseases (CVDs) are the leading cause of mortality in India attributing to a quarter of all mortality. Despite spectacular progress in disease prevention, detection and treatment over the last three decades; more CV deaths are caused by ischemic cardiac events. Considering the early mortality rate from acute myocardial infarction (AMI) (30-day), still, death from CVD Carries a higher burden. In several patients, the progressive phenomena of cardiac failure leading to ischemic cardiomyopathy reflects the burden of underlying coronary artery disease. Thus, identification of at risk patients who may be prone for future heart failure after the first myocardial infarction and detection of the extent of future heart failure is the cornerstone of secondary prevention strategies. This might help in prospective treatment in decreasing morbidity and mortality from heart failure following AMI.
Aim & Objective: To study the correlation between the rise in GGT levels and different subsets of Acute Coronary Syndrome. To study the correlation between GGT and the Risk of Major Adverse Cardiovascular Events (MACE).
Materials and Methods: This is a cross-sectional study conducted at Rajah Muthiah Medical College and Hospital. After obtaining clearance from institutional research and ethical committee, informed consent was obtained and patients of ACS in our CCU were selected. Using a standardized method GGT levels were measured and patients were followed up for five days in the hospital for adverse events. This study was done for some time between November 2019 to October 2021 and 75 patients with diagonized ACS were included.
Results and Observations: In this study, there is a significant correlation between the presence of LV dysfunction and high GGT values. Serum levels of GGT were significantly higher in both the ST-elevation-MI and Non-ST-elevation-MI patients but not in unstable angina patients. The patients who suffered complications has a mean GGT Value of 90.22. (IU)/L (SI units). The mean value for patients without MACE is significantly less than 46.44 (IU)/L (SI units).
Conclusion: Gamma-glutamyl transferase levels were significantly elevated above normal in cases of acute coronary syndrome. GGT levels were independently correlated with STEMI and NSTEMI but it did not correlate with unstable angina. There is a significant correlation between GGT levels and the incidence of left ventricular systolic LV dysfunction. The mean value of GGT was significantly higher in patients who suffered from major cardiovascular complications.

Keywords: Gamma Glutamyl Transferase, Acute Coronary Syndrome, LDL oxidation, atherosclerotic plaque, MACE.

Introduction
Acute coronary syndrome (ACS) means a spectrum of clinical presentations ranging from ST-segment elevation myocardial infarction (STEMI) to presentations found in non–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina [1]. ACS is almost related with rupture of an atheromatous plaque and partial or complete thrombosis of the infarct-related artery [2]. 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 some form of myocardial infarction, after further workup only 15% to 25% of such patients have MI. The important diagnostic challenge is to differentiate patients with ACS or other life-threatening conditions from patients with noncardiovascular, benign causes of chest pain [3]. The workup and detection of myocardial infarction 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 pathology of all three subsets of acute coronary syndrome is in the formation of a thrombus overlying a plaque [4]. The treatment for all the three subsets is

almost similar but with certain unique features based on the type of acute coronary syndrome. Numerous recent advances have shown better accuracy and efficacy in the workup of cases with acute chest pain, mainly owing to better biomarkers of cardiac injury. GGT shows promise as a new tool in the risk stratification of various types of acute myocardial infarction.[5] In some cases, the cells do not die, but damage due to an inadequate supply of oxygen results in heart muscles that do not work correctly or efficiently. The problem may be temporary or permanent. Unstable angina is the term used to describe the condition when acute coronary syndrome does not lead to cell death. The location of the blockage, the length of time that the blood flow is blocked and the amount of damage that occurs determine the type of acute coronary syndrome [6, 7].

Materials and Methods

This is a cross-sectional study conducted at Rajah Muthiah Medical College and Hospital. After obtaining clearance from institutional research and ethical committee, informed consent was obtained and cases of Acute Coronary Syndrome in our CCU were selected. Using a standardized method serum levels of GGT were measured and all the cases were followed for five days in the hospital for any cardiac complications. This study was done for some time between November 2019 to October 2021 and 75 patients with diagonized ACS were included. All patients presenting with the acute coronary syndrome were included in the study excluding alcoholics and hepatobiliary disease patients. Gamma-glutamyltransferase levels were measured in all cases using a standardized photometric method with normal value ranging from 0-45 IU/L. Blood samples are collected in a similar manner since six hours from the time of presentation. Cases were divided into three subsets based on electrocardiographic and Troponin T measurement.

1. ST-elevation MI
2. Non-ST elevation MI
3. Unstable angina

Patients were observed for five days in the coronary care unit for in-hospital outcome. Major adverse cardiovascular events were recorded in the form of re-infarct, cardiogenic shock requiring ionotropes, ventricular tacyarrhythmias requiring cardioversion, pulmonary edema, and cardiac death. Changes in the serum levels of GGT in ACS and its prognostic value on MACE were also observed in this study. Blood sampling and laboratory methods: A venous blood sample of 3 ml size, was drawn from the patient at the date of admission to CCU, collected into gel tube, serum then separated by centrifugation and GGT calculated manually by enzymatic method using the Abbott Architect C16000 auto analyzer.

Statistical Analysis

Data was analyzed with help of SPSS. Baseline information about modifiable and non-modifiable risk factors was collected through a predefined and pretested questionnaire. Modifiable risk factors included addiction details such as smoking, tobacco usages. Non-modifiable risk factors included gender, age, family history, etc. The clinical profile of all these patients were documented. Complications were classified as re-infarct, pulmonary edema, arrhythmia, cardiogenic shock and the treatment modalities and outcome of admission were documented for all patients.

Results

Table 1: Correlation between GGT and gender

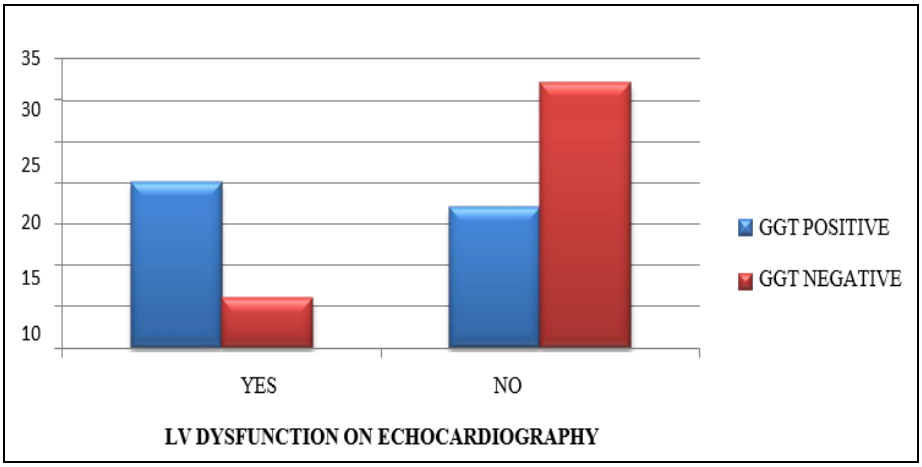
Sex		GGT		Total	P-value
		Positive	Negative		
Male	Count	20	26	46	0.201
	% within sex	43.5%	56.5%	100.0%	
Female	Count	17	12	29	
	% within sex	58.6%	41.4%	100.0%	
Total	Count	37	38	75	
	% within sex	49.3%	50.7%	100.0%	
	% within GGT	100.0%	100.0%	100.0%	

Table 1: 20 out of 46 males had a positive value for GGT (43.5%). 17 out of 29 females were positive or GGT (54.1%). The p-value was 0.201. There was no significant correlation between gender and GGT in this study.

Table 2: Distribution Of Study Subjects Based On Type Of Acute Coronary Syndrome And Correlation With Ggt Values

Type of ACS		GG		Total	P-value
		Positive	Negative		
STEM	Count	23	7	30	<0.001
	% within type of ACS	76.7%	23.3%	100.0%	
NSTEMI	Count	14	10	24	
	% within type of ACS	58.3%	41.7%	100.0%	
	% within GGT	37.8%	26.3%	32.0%	
UA	Count	0	21	21	
	% within type of ACS	0%	100.0%	100.0%	
Total	Count	37	38	75	
	% within type of ACS	49.3%	50.7%	100.0%	

Table 2: In our study of 75 patients, 30 had ST elevation in their ECGs, 24 were NSTEMI and 21 patients suffered from unstable angina.23 out of 30 cases with STEMI were positive for GGT. 14 out of 24 cases were positive for GGT while no one of unstable angina subsets had a positive GGT value. P-value is 0.001. Therefore there is a highly significant correlation between the type of ACS and GGT levels with STEMI and NSTEMI showing positive values compared to unstable angina.



Graph 1: Correlation between Lv Dysfunction and GGT

Graph 1: Out of the study population of 75, 18 subjects suffering from major adverse cardiovascular events (MACE) within their five-day in-hospital period in the form of one of the following; reinfarction, ventricular tachycardia or fibrillation requiring defibrillation, cardiogenic shock requiring inotropic support, death. All 18 patients had significantly positive GGT values. P-value is <0.001. There is a significant correlation between the incidence of MACE and GGT levels.

Table 3: 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 3: ANOVA test was used to look for a correlation between the three types of ACS with their respective mean GGT values. The mean GGT values for the ST-elevation-MI, Non-ST-elevation-MI and UNSTABLE ANGINA subsets were respectively 74.03, 54.88, and 34.90. The p-value was significant for this test<0.001. Therefore the difference in GGT values in the three subsets was statistically relevant. 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 ST-elevation-MI with both Non-ST-elevation -MI and UNSTABLE ANGINA. Likewise, the p-value was significant when comparing Non-ST-elevation-MI and unstable angina with the other two subsets.

Table 4: Correlation Of Other Variables With Ggt

		GGT (IU/L)
Age in years	Pearson Correlation	-0.030
	p value	0.799
Cholesterol	Pearson Correlation	0.523(**)
	p value	<0.001
LDL	Pearson Correlation	0.484(**)
	p value	<0.001
HDL	Pearson Correlation	0.155
	p-value	0.183
BMI	Pearson Correlation	0.228(*)
	p value	0.049

Table 4: There is no significant correlation between increasing age and GGT positivity in my study. The p-value is 0.799. In comparing the total cholesterol levels with GGT, the p-value is significant <0.001.so, it has a highly significant correlation between total cholesterol and GGT. In comparing LDL cholesterol levels and GGT, the p-value is <0.001. So, it also has highly significant correlation between LDL levels and GGT positivity. In comparing HDL levels and GGT, the p-value is 0.183. So, there is no significant correlation between HDL levels and GGT positivity. In comparing the BMI of the study subjects with GGT, the p-value is 0.049. Therefore there is a moderate correlation between high BMI values and GGT positivity.

Discussion

In this cross sectional study, serum levels of gamma glutamyl transferase were measured in ACS patients and we observed higher values of GGT above normal among these patients. Several studies have shown that circulating concentrations of GGT were higher in patients with ACS than in those with healthy control subjects [8]. One of the first studies that support this relation, where GGT levels were first associated with cardiovascular disease. A lesser correlation was seen between blood pressure, heart rate, and cigarette smoking. This goes against the finding of our study in that (There was no correlation with acute cardiac events) Another study that showed no correlation to acute vascular events against what our current study shows, is the cross-sectional and longitudinal study reported by Hannon TS *et al*. [9] The enzymatically active GGT identification in the plaque was done by an azo-coupling reaction using gamma-glutamyl-4-methoxy-2-naphthylamide as a substrate for GGT activity, stained with fast garnet GBC as the chromogen. They felt the pathogenic mechanism proposed for the role of GGT should be considered independent, complementary, and synergistic to conventional determinates. There is also evidence that atherosclerotic plaques contain GGT activity, revealed by many studies [10]. Where they evaluated the clinical utility of GGT activity in predicting high troponin levels in patients with the acute coronary syndrome (ACS) admitted to the emergency department with chest pain. A total of 200 troponin-positive and 203 troponin-negative patients were classified 1 and 2, respectively. γ-Glutamyl transferase activity was significantly higher in group 1 (44 ± 34 U/L) compared with group 2 (31 ± 26 U/L, P = 0.001). GGT activity cutoff >25.5

(our GGT cutoff was >30). Showed 62% sensitivity and 61% specificity. Out of the 35 diabetics in the study group, 20 cases were positive for GGT. Our study showed no significant correlation between the presence of diabetes mellitus and GGT positivity with a p-value of 0.206.24 out of the 36 hypertensives in our study were positive for GGT. It showed a positive correlation between hypertensive status and GGT with a p-value of 0.004 [11]. 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 [12]. The mean GGT value of the MACE subset was 90.22+7.818 and the 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. Comparing LDL and GGT, the p-value was <0.001 [13]. Therefore in our study, cases with higher LDL values were prone to GGT positivity. This is compatible with the recent studies which reveal GGT as playing an important role in LDL oxidation, which in turn is a hallmark of atherosclerotic heart disease [14]. A post hoc test was calculated to determine 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 [15].

Conclusion

Gamma-glutamyltransferase levels are significantly elevated above normal in cases of acute coronary syndrome. GGT levels were independently correlated with STEMI and NSTEMI but doesnt correlate with unstable angina. The correlation between serum GGT levels and the incidence of left ventricular systolic LV dysfunction is well established with significant p value. 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 Percutaneous coronary intervention/Coronary artery bypass graft. As a conclusion in ischemic heart disease, the GGT assay seems to have the elements of a good prognostic marker with optimal sensitivity of the diagnostic assay and it helps to 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

There was no control group in the study. Even though the Unstable Angina subset acted as a control group given its almost normal GGT distribution, a subset containing people with nonanginal chest pain would have given a clearer picture of the discriminatory power of GGT. 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 elucidate this cause-and-effect dilemma.

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Conflict of Interest-NONE
Ethical Committee Clearance Obtained From Institution

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