



SERUM GAMMA GLUTAMYL TRANSFERASE (GGT) LEVEL IN NON-ST ELEVATION ACUTE CORONARY SYNDROME (NSTEMI-ACS) AND ITS CORRELATION WITH ANGIOGRAPHIC SEVERITY AND CARDIAC EVENTS

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ABSTRACT

Background: GGT has shown to be involved in the development of cardiovascular disease. It is considered to play a central role in the formation of the fibrous cap, apoptosis of cellular elements of the lesion, plaque erosion and rupture, enhanced platelet aggregation and thrombosis leading to myocardial damage. The progress and prognosis of cardiovascular disease may be predicted by increasing GGT levels, a tool preferable to other biochemical indicators. **Objective:** To study the relationship between serum gamma glutamyl transferase (GGT) level in non-ST Elevation Acute Coronary Syndrome (NSTEMI-ACS) and its correlation with Angiographic severity and cardiac events. **Materials and Methods:** A total of 108 Non-ST Elevation Acute Coronary Syndrome patients were enrolled in this prospective cohort study. Patients whomever got admitted and fulfilled the inclusion/exclusion criteria were evaluated by history, physical examination, Complete Blood investigations including Serum Gamma Glutamyl Transferase level, Chest X-ray, electrocardiogram, echocardiography, coronary angiography at the time of admission. Gensini score was used to calculate the severity of angiographic lesions. Non-ST Elevation Acute Coronary Syndrome and its Angiographic severity and cardiac events was studied in three groups -NSTEMI-ACS patients with Significant Stenosis, NSTEMI-ACS patients with non-significant stenosis and the control group. **Result:** Out of 108 patients, 33 were females and 75 were males. 72% patients had NSTEMI-ACS with significant angiographic stenosis, while 28% patients had NSTEMI-ACS with non-significant angiographic stenosis. In control group, 16 were females and 29 were males. The mean age of study cohort was 52.17 years with age ranging from 31 to 70 years. The mean age of the control group was 53.06 years with age ranging from 31 to 70 years. Age group of patients with NSTEMI- ACS and that of the control group were comparable. Patients with Non-ST Elevation Acute Coronary Syndrome showed significantly higher serum GGT level (33.12 U/l), in comparison to Control group (15.3 U/l) P Value 0.0045. Similarly, GGT level were significantly elevated in patients of ACS with significant angiographic stenosis (38.34 U/l) in comparison to patient of ACS with insignificant angiographic stenosis (19.5 U/l) P value 0.001. Higher GGT levels were associated with triple vessel disease (43.5 U/l), Double vessel disease (41.1 U/l), and in Single Vessel Disease (33.91 U/l) P value < 0.0001. High GGT level also corresponds with high Gensini score P value < 0.002 correlating with angiographic severity. Mean GGT values above 43 U/l were associated with adverse cardiac events. P value was insignificant 0.81. **Conclusion:** Serum gamma glutamyl transferase (GGT) levels are higher in patients with non-ST Elevation Acute Coronary Syndrome (NSTEMI-ACS). Higher GGT levels in NSTEMI-ACS patients are also associated with complex coronary anatomy, high Gensini score and adverse cardiac events.

KEY WORDS: Non-ST Elevation- Acute coronary syndrome, Gensini Score, Serum Gamma Glutamyl Transferase.

INTRODUCTION

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with

1) Acute myocardial ischemia and includes unstable angina (UA),

- 2) Non—ST-segment elevation myocardial infarction (NSTEMI),
- 3) ST-segment elevation myocardial infarction (STEMI).

ST segment elevation myocardial infarctions is usually diagnosed on the basic of triad of Chest pain, characteristic Electrocardiographic changes and elevated plasma enzyme activity. However, the diagnosis clues for NSTEMI and Unstable angina such as presentation, physical examination, ECG changes are often non-specific.

Non-ST-elevation myocardial infarction (NSTEMI) is an acute ischemic event causing myocyte necrosis. The initial ECG may show ischemic changes such as ST depressions, T-wave inversions, or transient ST elevations; however, it can also be normal or show nonspecific changes. So, ECG has to be repeated at a predetermined interval or if the symptoms return. Therefore, the diagnosis of NSTEMI depends on the detection of elevated troponin levels^[1] which can distinguish it from an unstable angina. Thus, Unstable angina and NSTEMI are closely related clinical scenarios whose pathogenetic mechanisms and clinical presentations are similar but vary in severity.

Gamma glutamyl transferase GGT, also called as Gamma Glutamyl Transpeptidase GGTP is a unique enzyme in glutathione (GSH) metabolism which was originally found to be an indicator of liver or biliary tract diseases and alcohol consumption. Recently, catalytically active GGT has been found within atherosclerotic coronary plaques from autopsy studies and surgical endarterectomies. It is believed that serum GGT which have been partially adsorbed onto LDL lipoproteins carryout GGT activity inside the plaque. GGT-mediated reactions catalyse the oxidation of LDL lipoproteins, likely contributing to oxidative events influencing plaque formation and rupture. It also plays an important part in the progressive development of atherosclerotic plaque and also in instable nature, apoptosis, erosion and rupture, increased platelet aggregation, and thrombosis. The current study sought to evaluate the diagnostic and prognostic role of measurement of serum GGT level in NSTEMI-ACS patient. This was done through a single sampling process done upon first medical contact, exploring the correlation with cardiac biochemical markers, coronary angiographic features and adverse events.

METHOD

Following approval from the Ethical Committee of SRM medical college, this study was carried out on patients admitted to the ICCU of SRM Hospital, Tamil Nadu, Chennai, between March 2017 and NOV 2018, because of sudden-onset chest pain.

Patients with 1. Recent Myocardial Infarction 2. Known Hepatic Disease 3. Alcohol Consumption 4. Decompensated Heart Failure 5. Renal Dysfunction 6.

Documented Cancer 7. History of Cerebrovascular Events 8. Patients who had Percutaneous Trans luminal Coronary Angioplasty (PTCA) Or CABG Within 6 Months 9. Patients who did not consent to be included in the study are excluded from the study. Before inclusion, informed written consent was obtained after explanation of the study protocol, which was approved by our local institutional human research committee according to international guidelines.

A standard study form and an acknowledged patient approval form were completed for all patients with sudden-onset chest pain, who were being diagnosed and treated for the condition.

Patients were subjected to thorough history taking, clinical examination, 12 lead ECG, chest x ray, echocardiography (including assessment of segmental wall motion abnormalities (SWMA), left ventricle (LV) dimensions, and LV ejection fraction (LVEF%) by Simpson's method), recording of serum levels of cardiac Troponin T, and CK-MB, recording of serum level GGT on admission, and in addition to coronary angiography in a timely tailored fashion according to established diagnosis of each patient.

They were classified into patients with UA, ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and effort angina according to chest pain analysis, electrocardiogram (ECG) findings & serum conventional cardiac biochemical markers' levels cardiac Troponin T, creatine kinase (CK-MB).

Those presenting with chest pain and diagnosed as having NSTEMI - ACS were identified as the patient group; those diagnosed with patients of effort angina were identified as the control group. Patients in whom the test results were negative were also included in the control group. Acute coronary syndrome encompasses USAP, non-ST elevated MI (NSTEMI) and ST elevated MI (STEMI). Patients with typical resting chest pain lasting > 20 min, in whom chest pain had started as a new symptom within the previous 2 months and in whom the intensity of the pain had increased, together with no increase in myocardial enzymes, were defined as the USAP subgroup. Those patients with typical chest pain lasting > 30 min, in whom cardiac enzyme increases accompanied ST segment depression and T-wave negativity, were included in the NSTEMI subgroup.

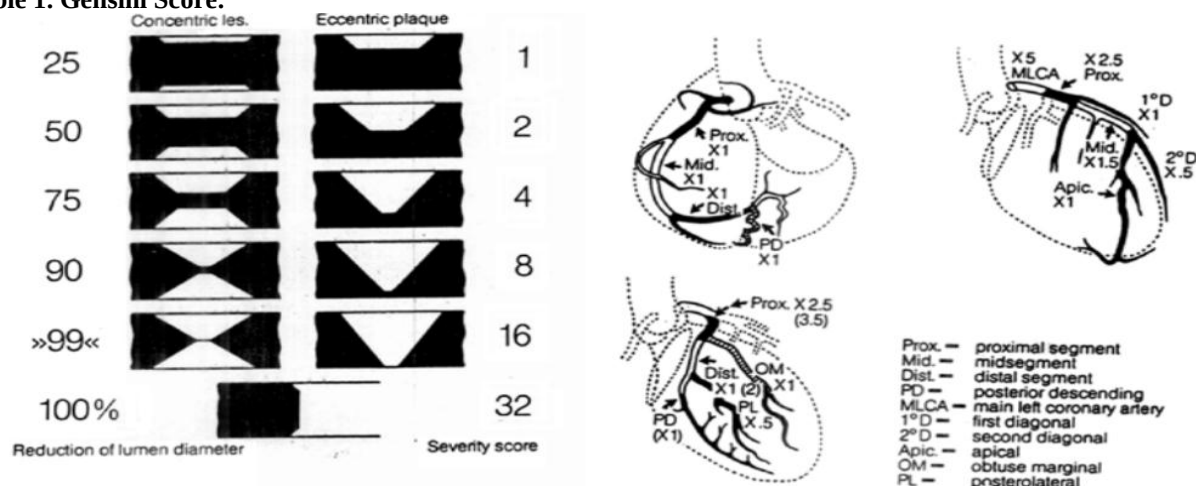
Coronary Angiography

Coronary angiography was done within the first six hours after initial blood sampling for Troponin T, CK-MB, and GGT. Blood sampling was done upon ICCU admission, through a peripheral venous access. Time window between first medical contact & coronary angiography varied among the included patients, owing to different natures of clinical presentations. Patients presented with STEMI (evidenced by ECG findings) and

underwent coronary angiography within 2 hours of ICCU admission, while patients with UA & NSTEMI had a relatively wider time window before undergoing coronary angiography. Vascular access was obtained through femoral artery puncture using Seldinger's technique. Standard angiographic views were obtained,

which included an average six left coronary artery and two right coronary artery injections, yielding sufficient data for quantitative angiography. The Gensini score was used to calculate the severity of angiographic lesions as shown in the table 1.

Table 1. Gensini Score.



Serum Gamma glutamyl transferase levels

Blood samples are taken from all subjects in the patient and control groups from the ante cubital vein and stored in a 2 ml of non-heparinized blood collector under strict aseptic condition and refrigerated. This sample was sent to the laboratory where it was centrifuged to separate the serum. Serum enzyme Gamma Glutamyl Transferase GGT was measured by calorimetric method using autoanalyzer.

Statistical analysis

For statistical analysis, one-way analysis of analysis of Variance (ANOVA) was used, followed by the Newman-Keuls Multiple Comparison test.

RESULTS

PATIENTS

This study was carried out on 153 patients admitted to the ICCU because of sudden-onset chest pain. Of these,

70.5% (n = 108) formed the patient group and 29.5% (n = 45) formed the control group. In the overall study population, 67.9% (n = 104) were male and 32.02% (n = 49) were female. The median age was 51-60 (range 31 – 70 years). Of the control group, 64.44% (n = 29) were male and 35.56% (n = 16) were female, with a median age of 51-60. Of the patient group, 69.44% (n = 75) were male and 30.55% (n = 33) were female, with a median age of 51 - 60. No significant differences were identified between the control and patient groups in terms of mean age and sex distribution. When the patient group was classified according to the NSTEMI-ACS subtypes, 72.22% (n = 78) were included in the NSTEMI-ACS with significant stenosis subgroup, 27.77% (n = 30) in the NSTEMI-ACS with non-significant stenosis subgroup.

Table 2. Sex distribution between NSTEMI-ACS and Control group.

Sex Groups	ACS Significant Stenosis	%	ACS Non Significant Stenosis	%	Control	%
Male	55	70.51	20	66.67	29	64.44
Female	23	29.49	10	33.33	16	35.56
Total	78	100	30	100	45	100

DESCRIPTIVE DATA

Descriptive data analysis showed that; 67 (38%) in patient group were diabetic compared to 10 (22%) in control group, 43 (40%) in patient group were

hypertensive compared to 11 (24.44%) in control group, 41 (38%) in patient group were dyslipidaemia compared to 12 (26.67%) in control group, 44 (40.74%) in patient group were smokers compared to 12 (26.67%)

in control group. Upon ICCU admission, mean serum Cardiac Troponin level value in ACS significant stenosis group was 0.18 ng/ml, NTSE-ACS insignificant stenosis group was 0.01ng/ml. Mean serum CK-MB level value in NTSE-ACS significant stenosis group was 29.5 u/l, NTSE-ACS insignificant stenosis group was 23.76 u/l and in Control group was 16u/l. Median Ejection fraction value in NTSE-ACS significant stenosis group was 51%, NTSE-ACS insignificant stenosis group was 55% and in Control group was 60.7%. Mean serum GGT level value in NTSE-ACS significant stenosis group was 38.34 U/l, NTSE-ACS insignificant stenosis group was 19.5 U/l and in Control group was 15.3 U/l. Concerning number of coronary arteries showing significant stenosis, it was found that 37(34.25%)patients had single vessel affection, 20 (18.5%) patients had two vessels affection,

and 21 (19.44%) patients had more than two vessels affection.

SERUM GAMMA GLUTAMYL TRANSFERASE AND NTSE-ACS

Median serum GGT level among patients with NSTE-ACS was recorded to be 33.12 U/l, while it was 38.34 U/l among patients with NSTE-ACS significant angiographic stenosis & 19.5 U/l among NSTE-ACS patients with insignificant angiographic stenosis. There was a statistically significant correlation between the final diagnoses of the included patients and serum GGT levels ($P < 0.001$), being higher among patients with NSTE-ACS. From the study, we can conclude that if the median level of GGT is more than 30 U/l, we can diagnose NSTE-ACS patients with significant stenosis, almost with an 85% sensitivity & specificity.

Table 3. GGT levels in NSTE -ACS patients compared with Control group.

Gamma Glutamyl transpeptidase (U/L)	ACS significant Stenosis	%	ACS Non Significant Stenosis	%	Control	%
<25	1	1.28	28	93.33	45	100.00
26-35	27	34.62	2	6.67	0	0.00
>35	50	64.10	0	0.00	0	0.00
Total	78	100.00	30	100.00	45	100.00

Groups	Count	Sum	Average	Variance
ACS Significant Stenosis	78	2991	38.34615	47.86563
ACS Non Significant Stenosis	30	586	19.53333	14.74023
Control	45	688	15.28889	9.528283

ANOVA

Source of variation	SS	Df	MS	F	P-Value	F-crit
Between Groups	17768.28	2	8884.138	294.02	0.0045	3.056
Within Groups	4532.365	150	30.21577			
Total	22300.64	152				

Gamma Glutamyl Transferase (GGT) AND Vessel Grades

Median serum GGT level among patients with single vessel affection was recorded to be 33.91U/l, while it was 41.1U/l among patients with two vessels affection & 43.5U/l among patients with more than two vessels affection. Results showed statistically significant correlation between serum GGT level & number of coronary vessels showing significant stenosis P value < 0.0001.

Table 4. Comparison between GGT levels and Vessel Grades.

GGT levels Vs Vessel Grades	Normal	SVD	DVD	TVD
< 25	28	1	0	0
26-35	2	24	3	0
>35	0	12	17	21
Total	30	37	20	21

GGT levels Vs Vessel Grades	Count	Sum	Average	Variance
Normal	30	586	19.53	14.74023
SVD	37	1255	33.9189	41.68769
DVD	20	822	41.1	27.46316
TVD	21	914	43.52381	11.1619

ANOVA

Source of Variation	Ss	df	MS	F	P-value	F-crit
Between groups	9108.174	3	3036.058	118.14	0.0001	2.691979
Within Groups	2673.262	104	25.70			
Total	11781.44	107				

Gamma Glutamyl Transferase (GGT) and Gensini Scores

Median serum GGT level among patients with Gensini score between 51 -100 was recorded to be 35 U/l while it was between 26-25U/l among patients with a score

between 26-50 & <25 U/l among patients with Gensini score <25. There was a statistically significant positive correlation between Gensini score and serum GGT level ($P < 0.002$), correlating with the angiographic severity.

Table 5. Comparison between GGT levels and Gensini score.

GGT levels Vs Gensini	<25	26-50	51-100
<25	1	17	8
26-35	0	8	13
>35	1	27	50

GGT levels Vs Gensini	Count	Sum	Average	Variance
<25	1	12	12	0
26-50	27	682	25.25926	426.7373
51-100	50	2919	58.38	768.3629

ANOVA

Source of variation	SS	df	MS	F	P-value	F-crit
Between Groups	20426.02	2	10213.01	15.71395	0.002	3.118642
Within Groups	48744.97	75	649.9329			
Total	69170.99	77				

Gamma Glutamyl Transferase (GGT) And Adverse Events

Twenty patients (18.5%) from the NSTEMI-ACS patient group had adverse event; 3 were cardiogenic shock, 7 were arrhythmias, 7 were heart failure and 1 death. Mean

GGT values were above 43 U/l in adverse events subgroup. P value was insignificant 0.8. Hence there is no significant correlation between adverse cardiac event and serum GGT level according to our study.

Table 6. Adverse Events in Patients with NSTEMI-ACS.

Adverse Events	ACS Significant Stenosis		ACS Non significant Stenosis	
	count	mean GGT Levels (U/L)	count	mean GGT Levels (U/L)
Cardiac Shock	3	44.67	0	0
Arrhythmia	6	44.33	1	20
Heart failure	6	43.67	1	22
Death	3	44.67	0	0
Chi Square Statistic	0.952			
Degree of Freedom	3			
P value	0.813			

So, it was found that there was a statistically significant correlation between serum GGT level (measured upon CCU admission) and each of the following: NSTEMI-ACS, VESSEL GRADE and with Gensini score correlating with angiographic severity.

DISCUSSION

Coronary Artery Disease is one of the leading causes of mortality and morbidity all over the world and has reached epidemic proportions both in Developed as well as Developing Countries. Coronary artery disease account for about approximately 9.4% of total deaths (2.5 million) in developing countries and 16.3% (1.3 million) of all deaths in developed countries.^[1]

Acute Coronary Syndrome (ACS) is a major part of chronic inflammatory atherosclerotic coronary artery disease. The structure of the atherosclerotic plaque consists of I) the core of lipid II) Inflammatory mediators III) cap of thin fibrous tissues.

Since we know that the serum GGT is partially adsorbed onto LDL lipoproteins, it carries out its enzyme activity in the plaque (in proportion to serum GGT levels), where free iron is also present. GGT-mediated reactions catalyse the oxidation of LDL lipoproteins, and a considered to play an important role in the formation of the fibrous cap, apoptosis of cellular elements of the lesion, plaque erosion and rupture, enhanced platelet aggregation and thrombosis.^[2]

Hence, it can be said that increased level of serum GGT can lead to formation of enhanced plaque and rupture, ultimately resulting in ACS. These findings have been supported by many large epidemiologic studies.^[3]

GGT levels in NSTEMI-ACS

In our study population, the mean GGT levels (33.12 U/l) were elevated in patients who were diagnosed to have NSTEMI-ACS, when compared to the control group (15.3U/l). From above findings, we can conclude that, there might be an influence of GGT in plaque formation and its rupture leading to NSTEMI - ACS.

Our study concurs with that of Dogan et al^[3] study, whose findings reveals a median GGT level of 32U/l in ACS vs 16U/l in effort angina group of patient and median GGT level of 37 in significant stenosis subset versus 22 U/l insignificant stenosis subset on NSTEMI-Acute Coronary Syndrome population. Our study finding are also supported by study by Emiroglu^[9] et al, Demircan et al^[10] and Ulus^[11] et al.

GGT and Vessel Grade

From our study we found a significant association that exist between increased GGT level and the vessel grade P value <0.0001.

Our study can be correlated with that of by Aksakal^[7] et al. which states that there is an association between the GGT serum level and the complexity of the coronary lesions and including the reason for the mortality overall in patients with stable angina pectoris for a lifelong follow up.

But, the study by Demircan et al^[10] has said that there is no relation between the level of GGT and the number of affected coronary vessels.

GGT and Gensini score correlation

In our study the association between the median GGT level and Gensini score were significant. (P value 0.002). The gensini score were 51-100, 26-50, < 25 in people

who were having GGTP values >35, 26-35, GGT values <25 U/l respectively.

Our findings and GGT & Gensini correlation were also similar to Açikel et al^[12] study as Gensini score which is used angiographic evaluation of CAD severity has found to be related with the level of GGT for atherosclerosis burden evaluation with fatty liver correlation study. Recently, Baktir AO et al^[8] have evaluated GGTP activity and the CAD burden by SYNTAX score correlation in patients with STEMI. Although they found significant positive association between SYNTAX score and major adverse cardiac events, the study has failed to show any correlation between serum GGT levels and Coronary lesion complexity and severity by SYNTAX scores.

GGT and Adverse events

We followed up the patients for intra hospital outcome for NSTEMI-ACS, the results were a greater number of adverse events totals of 20 in NSTEMI-ACS subgroup in patient having a mean GGT values above 43 U/l.

Our study also correlates with recently conducted study in which over 600 ST Elevation Myocardial Infarction patients who were undergoing primary PCI were evaluated by Gul et al^[4] for correlation of serum GGTP on admission and in hospital cardiovascular adverse events and mortality. They found that patients who were having high serum GGT more than 37 had a higher risk of mortality and adverse cardiovascular events.

Our study is also supported by GGT and major adverse cardiac events MACE studies done by Dogan et al^[3], Apkek et al^[7], Gul et al^[4], Brietling et al^[6] and Lazzeri et al⁵ in various groups of ACS. They concluded that elevated serum GGTP level is an independent CV risk factor which predicts CV events, non-fatal Myocardial Infarction and mortality due to cardiac cause in unselected populations, in patients with history of MI, and in patients with ACS after adjusting for other CAD risk factors.

Even though, there are no proper studies conducted to demonstrate the correlation between increased level of GGT and adverse cardiovascular event. From our study it can be found that there is relation between elevated GGT level and adverse cardiac event. Hence in CAD population, there might be a relation between the of level of GGT and prognosis of a patients excluding other risk factors.

CONCLUSION

Serum GGT levels appear to be useful for diagnosing NSTEMI-ACS and assists in the prediction of angiographic severity and adverse events, in patients presenting at the ICCU with NSTEMI-ACS. Hence it can be used along with other parameters to determine the diagnosis and prognosis of patients with NSTEMI-ACS.

Limitations of the Study

This is a single-centre study with a small sample size of the cohort. Large scale studies are still needed to confirm the obtained results. Serial serum GGT level sampling was not included in the study protocol. Furthermore, C Reactive Protein, TIMI & GRACE score and their relation with the level of GGT were also not included in the study. These items were outside the scope of the present study, which aimed at evaluating the value of serum GGT (single measurement) in NSTEMI-ACS patients & their relation with angiographic severity and adverse events. Further studies with wider scope are needed for evaluation of long-term impact of high serum GGT in NSTEMI-ACS patients.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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