

# Association of Raised Gamma Glutamyl Transferase (GGT) Levels in Patients with Acute Coronary Syndrome and Their in Hospital Outcome

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## ABSTRACT

**Objective:** To determine the frequency of raised serum GGT levels in patients with acute coronary syndrome and their in-hospital outcome.

**Study design:** Case descriptive.

**Subjects and methods:** 120 patients hospitalized in CCU of Services Hospital, Lahore with the diagnosis of Acute Coronary Syndrome (ACS) were included in study. All had baseline serum GGT level determined and outcome in terms of Major Adverse Cardiac Event (MACE), which included mortality from cardiac cause and recurrent MI, was studied within 4 days of hospital stay.

**Results:** Among all participants 36 (30.0%) patients had raised GGT (>40U/L). In STEMI 35.4% NSTEMI 19.4% and unstable angina 20.0% had raised GGT levels. In CCU 23 (19.2%) patients suffered MACE (7 died). 60.9% of patients with MACE had raised GGT levels.

**Conclusion:** Raised serum GGT activity was found to be a strong predictor of the development of MACE in the patients with ACS during CCU. And significant association of GGT with diabetes mellitus and obesity may account, at least in part, for the prognostic role of GGT.

**Key words:** Gamma Glutamyl Transferase (GGT), Acute Coronary Syndrome (ACS),

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## INTRODUCTION

The term acute coronary syndrome comprises unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment myocardial infarction (STEMI). ACS is often the first presentation of coronary artery disease (CAD), the leading cause of mortality and morbidity in many parts of the world. The underlying cause of ACS is a sudden rupture of a pre-existing atherosclerotic plaque. Patients who survive the acute phase of myocardial infarction remain at risk of recurrent cardiac events, including sudden death. Risk stratification is critical in managing patients with ACS. Risk prediction models identify high-risk patients who would benefit from early revascularisation therapy<sup>1</sup>.

Inflammation is implicated in arterial plaque formation, plaque rupture and clot formation during subclinical and symptomatic coronary events<sup>2</sup>.

Certain inflammatory markers have been identified to be associated with increased incidence of cardiovascular complications and death in patients with ACS. Among these biomarkers some have emerged to be potentially useful in early risk assessment of patients with ACS, such as CRP, interleukin 6, hepatic enzymes, B type natriuretic peptide and troponin. Despite the potential prognostic importance of these novel biochemical markers,

many of them are not routinely available<sup>3</sup>.

Gamma-glutamyltransferase (GGT), catalyses the first step in the degradation of extracellular glutathione (GSH), allowing for the precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis. Thus in this way, GGT activity favours the cellular supply of GSH, the most important non-protein antioxidant of the cell. However, there is also clear evidence that the degradation of GSH can play a pro-oxidant role in selected conditions; low density lipoprotein (LDL) oxidation through GSH/GGT-dependent iron reduction has been suggested as a potential mechanism in atherosclerosis.<sup>4,5</sup>

Serum GGT has been proposed as a marker of oxidative stress<sup>6</sup>. GGT contributes to oxidative stress pathways in several organs systems, localizes to atheromatous plaques containing oxidized LDL, and is pro-inflammatory, further implicating this protein in atherogenesis<sup>7</sup>.

Elevation in serum GGT activity predicts outcomes in unselected population and in patient with ascertained ischemic heart disease, independently of myocardial damage, thus adding to prognostic information provided by traditional risk factors<sup>8</sup>. GGT is a unique biomarker in the continuum of cardiovascular disease risk. GGT is thus a potentially valuable addition to the growing list of clinically available tests useful in initially stratifying patient risk associated with well-known cardiovascular conditions

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and should be considered in assessing appropriate aggressiveness of treatment<sup>9</sup>.

Although the relationship between GGT and coronary artery disease has been reported, there are limited data exploring the changes of GGT in acute coronary syndromes<sup>10</sup>.

There is no local published literature available on this topic. So this study is aimed to determine the frequency of raised GGT level in acute coronary syndrome and its prognostic value in patients with ACS in Pakistani population. The results of my study will be quoted as a reference for the health care professionals for early detection and better management in patients of ACS with raised GGT and that way will also help the patients by reducing their mortality and morbidity.

**MATERIALS AND METHODS**

Acute coronary syndromes (ACS) are the main reasons for cardiovascular mortality and morbidity. It has been shown that oxidative and inflammatory events have very important roles in the pathophysiology of ACS. It has been demonstrated that GGT participates in oxidative events associated with atheroma plaque formation. The relationship between GGT and coronary artery disease has been reported, however there is limited data exploring the changes of GGT in acute coronary syndrome and its prognostic value on the development of major adverse cardiac event (MACE) in the patients with ACS.

All those male and female patients under 25 years age presenting with acute coronary syndrome (as per operational definition) were included in the study. Patient with history of alcoholism, hepatobiliary disease, with Alanine transaminase (ALT) >40 U/L (Normal reference range 0-40 U/L), coarse liver echotexture, taking barbiturates or phenytoin (history and medical record) were excluded from this study.

One hundred and twenty patients of either sex with acute coronary syndrome presenting to Cardiac Care Unit fulfilling the inclusion criteria were enrolled in the study. Blood samples were collected according to standardized technique to determine the serum GGT. Patients were followed for in-hospital outcome for four days. In-hospital outcome was taken in terms of MACE (as per operational definition).

SPSS Windows software (version 13.0) was used for data analysis. Qualitative data e.g. type of acute coronary syndromes (unstable angina, NSTEMI and STEMI) and raised GGT levels and in-hospital outcome i.e., MACE is presented in form of frequency and percentage. The level of significance were set at p<0.05.

**RESULTS**

Total 120 patients were included in study. Range of Serum Gamma Glutamyl transferase (GGT) in study population was 14-57U/L with a mean of 34.23±12.293. Among all participants 36 (30.0%) patients had raised Serum GGT levels (>40 U/L). Regarding the types of Acute Coronary Syndromes, 79(65.8%) patients presented with ST-Segment Elevation MI (STEMI), 36 (30.0%) presented with non-ST-Segment Elevation MI (NSTEMI), 5(4.2%) had Unstable Angina(UA). In patients who presented with STEMI, 35.4% had raised serum GGT levels. Percentage of raised GGT in unstable angina was 20.0% and in NSTEMI was 19.4% (Table-1)

On follow-up in CCU 23 (19.2%) patients suffered Major Adverse Coronary Events (MACE). Among the patients who suffered MACE 16(13.3%) had Recurrent MI and 7(5.8%) died. 14(60.9%) of patients suffering MACE had raised serum GGT levels (Table 2).

Table-2: Correlation of Raised GGT Levels with MACE in Patients of ACS

Raised Gamma GT Levels		Major Adverse Coronary Events (MACE)	
		Yes	No
Yes	Count	14	22
	% within raised GGT	38.9%	61.1%
	% within MACE	60.9%	22.7%
No	Count	9	75
	% within raised GGT	10.7%	89.3%
	% within MACE	39.1%	77.3%

P-Value: 0.000 (<0.001)

Table 1: Relationship of Raised GGT Levels with the Type of Acute Coronary Syndrome

Raised Gamma GT		Types of Acute Coronary Syndromes (ACS)		
		Unstable Angina	NSTEMI	STEMI
Yes	Count	1	7	28
	% within raised GGT	2.8%	19.4%	77.8%
	% within types of ACS	20.0%	19.4%	35.4%
No	Count	4	29	51
	% within raised GGT	4.8%	34.5%	60.7%
	% within Types of ACS	80.0%	80.6%	64.6%

P-Value: 0.1 (>0.05)

## DISCUSSION

In recent years emerging evidence has shown that serum GGT is more than a mere marker of alcohol consumption or hepatobiliary dysfunction. Baseline serum GGT concentration appears to be an independent risk factor for development of cardiovascular disease.

Risk stratification is critical in managing patients with ACS. The timely reperfusion of the occluded coronary artery is of the utmost importance in the management of ACS as the patients who survive the acute phase of myocardial infarction remain at risk of recurrent cardiac events, including sudden death.

The rupture of an atherosclerotic plaque is the cause of acute coronary syndrome<sup>11</sup>. Inflammation plays a key role in the development of atherosclerosis and acute coronary syndromes<sup>12</sup>. GGT was found to play a role in the pathogenesis of atherosclerosis because it was detected in atheromatous plaques of carotid and coronary arteries triggering the oxidation of LDLs. There are high-volume studies showing the relationship of GGT with coronary artery disease and cardiovascular mortality. This study was aimed to determine the frequency of raised GGT in patients with acute coronary syndrome and to observe the prognostic relevance of raised GGT levels for non-fatal re-infarction and cardiac death. Few data are so far available on the prognostic role of GGT in patients with acute coronary syndromes<sup>13</sup>.

In my study 120 patients were admitted. On follow up in CCU 36(30.0%) patients had raised Serum GGT levels (>40 U/L), 23(19.2%) patients suffered Major Adverse Coronary Events (MACE) in which 7(5.8%) died. 14(60.9%) of patients suffering MACE had raised serum GGT levels (P-Value <0.001). Where as in Ulus T *et al.* 20(17.09%) of 117 patients had raised GGT levels, 17 (14.5%) patients suffered MACE among them 2 died. Serum GGT activity was significantly higher in the patients with MACE than those free of MACE (P=0.001). High incidence mortality in my study can be attributed to the lack of interventional facilities in our setup, however the results suggests a strong association between raised GGT levels and cardiac morbidity and mortality.

In one study conducted on the importance of gamma-glutamyltransferase activity in patients with coronary artery disease by Demircan S *et al.*<sup>15</sup> serum GGT levels of patients with ACS were higher when compared to the patients with stable Coronary artery disease (40.2±32.5 U/L versus 29.1±18.3 U/L, p<0.002). Although there was no control group in my study but the results are comparable to this study.

A recent study conducted in Italy by Lazzeri C *et al.*<sup>13</sup>. On the prognostic role of gamma-glutamyltransferase activity in 337 non-diabetics with ST-elevation myocardial infarction GGT values are independent predictor for early mortality. In my study STEMI was the most common presentation of ACS (65.8%), among these patients 35.4% had raised serum GGT levels.

Increase in GGT was more significant in NSTEMI and STEMI groups and thus proposed a relationship between gamma glutamyl transferase and severity of acute coronary syndromes. No difference was found between UA and control groups. And the difference between NSTEMI and STEMI was not significant as well. In my study 35.4% STEMI, had raised serum GGT levels. Percentage of raised GGT in unstable angina was 20.0% and in NSTEMI was 19.4%.

As for ischemic cerebral and heart disease, GGT serum assay seems to have all of the main features of a true prognostic marker: the diagnostic assay has optimal sensitivity-specificity, epidemiological evidence of its presence before the event in apparently healthy people and patients with clinical overt disease increases our ability to predict it. It has additive and independent predictive value in comparison with established risk factors<sup>17</sup>.

The prooxidant effects of serum GGT and its link with the evolution of atherosclerotic plaque is further proved by the fact that both cutaneous and surgical revascularization are able to abolish the GGT prognostic value.

The findings depicted above raise the issue about whether cardiovascular risk associated with increased GGT is modifiable. Avoidance of alcohol consumption and hepatotoxic drugs, a number of other variables, such as coffee consumption, weight loss, smoking cessation, and changes in nutrition have been described to be beneficial in reduction of serum GGT and cardiovascular risk<sup>18</sup>.

Several investigations have shown that some drugs e.g. fibrate, are effective in decreasing both serum lipids and GGT and concomitantly the incidence of subsequent cardiovascular events; large scale randomized trials are required to explore this impact directly<sup>11</sup>.

## CONCLUSION

The results of this study suggest that increased GGT activity is a marker of poor prognostic for adverse cardiac event development in ACS patients. In the future, serum GGT might be used in the risk stratification of ACS patients and might help to determine the cases in which more intensive therapeutic strategies are required. To better clarify

this issue, additional studies with increased number of ACS patients are needed.

This study also showed association of raised GGT activity with obesity and diabetes. Other studies have also showed its relation with metabolic syndrome. If such associations are confirmed in future studies in diverse populations, higher level of this relatively inexpensive marker could serve as a predictor and risk stratification tool for cardiovascular disease and diabetes mellitus.

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