



## Role of Gamma glutamyl transferase as an early indicator of hepatic involvement in Carcinoma Gall bladder.

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### ABSTRACT:

Gamma Glutamyl Transferase (GGT) is a liver enzyme that play much role in many reactions of hepatic metabolism. Although used as biochemical indicator of chronic alcoholism, it is ironically the most neglected parameter of LFT. In this study, GGT had been studied as an early screening test in carcinoma GB to evaluate hepatic metastasis. Also, its efficacy had been studied as a tumor maker of hepatic involvement in Carcinoma GB, which can help in further management and prognosis. Also, the correlation of stage and level of GGT is been studied in order to assess if higher level of GGT is associated with higher stage (stage wise progression of GGT level.)

**KEYWORDS:** GGT, Hepatic metastasis, tumor marker, stagewise progression.

Received 16 Feb, 2021; Revised: 28 Feb, 2021; Accepted 02 Mar © The author(s) 2021.

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### I. INTRODUCTION:

GGT is a transferase that catalyses many reactions in hepatic cell, and thus are used as a part of Liver Function Test since decades. Its physiological function is to facilitate amino acid transport across cell membrane and in Glutathione metabolism<sup>[1]</sup>. It is found in cell membrane of many tissues like hepatocytes, biliary tract, spleen, brain, seminal vesicle; kidneys and Pancreas (highest conc<sup>[2]</sup>). The GGT found in serum is mostly derived from hepatobiliary tree, and hence the increased level usually indicates hepatobiliary dysfunction like hepatitis, obstructive jaundice, and liver metastasis. Its association with alcohol and drug induced hepatic damage are well established<sup>[3]</sup>. It can also be elevated in conditions like pregnancy, cardiovascular disease, epilepsy and Brain tumours, renal disease, DM and cervical carcinoma etc<sup>[4]</sup>. From various reports in the literature, it appears that in icteric and an-icteric patients with metastatic carcinoma to the liver, increased GGT activity is the most sensitive indicator of liver involvement<sup>[5]</sup>. Apart from elevated other liver enzymes specially Alkaline Phosphatase, GGT is one of the earliest marker to rise in any case of Obstructive Jaundice. With raised ALP, a raised GGT is one of the sensitive marker for biliary obstruction. Isolated GGT elevation in a healthy person is always clinically linked to Chronic alcoholism. Also it is well known that abnormally high level of GGT is strongly suggestive of secondary hepatic metastasis or primary tumor like intrahepatic Cholangiocarcinoma<sup>[6]</sup>. Due to reasons, GGT had been always underestimated as a diagnostic test in hepatobiliary malignancies. This may be due to its ectopic elevation in many other non hepatic diseases, false positive elevation in healthy alcoholic individuals, overuse of the test as a part of LFT and unawareness of lab technicians regarding its value. Apart from these factors, level of GGT varies according to age, sex & body weight<sup>[7]</sup>. The normal range of serum GGT is 15-85 IU/L for men, and 5-55 IU/L for women<sup>[8]</sup>.

### II. MATERIAL AND METHOD:

*Source of data:* Patients of Carcinoma GB admitted in Department of General Surgery at RIMS, Ranchi.

*Type of study:* Observational study using unpaired groups.

*Period of study:* One year (March 2019 to March 2020)

*Place of study:* Indoor patients in the Department of Surgery at RIMS, Ranchi.

*Sample size(n):* 50 patients of GB mass.

**Inclusion criteria:** Patients admitted with the diagnosis of GB mass (USG/CECT) of both genders of 18-70 years; Patients having no history of Chronic alcoholism and patients having no other hepatic comorbidities like cirrhosis or hepatitis (viral or drug induced); or any other non-hepatic comorbidities.

**Exclusion criteria:** Patient of Chronic alcoholism; patient of advanced disease/ having Extra-hepatic metastasis and patients having other comorbidities either hepatic or non-hepatic which can cause rise in GGT.

**Plan for analysing data:** 50 patients of GB mass were enrolled after thorough history and clinical examination. Blood Sample was sent for routine examination including LFT and tumor markers (CEA, CA 19-9). All the samples were tested by IFCC Kinetic technique at RIMS Ranchi and results were recorded. Additionally, further definitive imaging (CECT) of all patients were done and groups were made on the basis of hepatic involvement.

**Evaluation of Result-** Patients were divided into two groups:

**Group A-** Those having no hepatic involvement ie; 12 patients(n=12)

**Group B-** Those having radiologically proven hepatic involvement ie; 38 patients(n=38)

Level of GGT including other parameters in both groups were collected and compared according to hepatic involvement. Also, level of CEA and CA19-9 were collected and compared with parallel elevation of the GGT level in both the groups; and a correlative association between 'level of GGT' and 'hepatic involvement' was made by 'Unpaired t-test' using a computer based statistic application ie; 'Analystat app'.

### III. OBSERVATION AND RESULT :

In patients of Ca GB with no hepatic involvement (*Group A*), level of GGT was found to be within normal limit except a mild rise (<2 fold) only in 1 case ie, 8.3%. Other parameters of LFT was also found normal in most of the patients, except for the mild elevation of ALP in 5/12 patients ie, 41.6% cases.

Level of CEA was within normal limit in Group A cases except elevation (25 ng/ml) only in 1/12 case ie, 8.33%. CA 19-9 was mildly elevated (<50 U/ml) in 2/12 case ie, 16.66%.

In patients of Ca GB with hepatic involvement (*Group B*), level of GGT was consistently elevated (>2-4 fold rise) in all 38/38 patients ie, 100% cases. The level of all three parameters ie, AST, ALT and ALP was elevated in 17/38 patients ie, 44.7% cases.

Isolated AST elevation is seen in 21/38 ie, 55.5% cases; while isolated ALT elevation is seen in 18/38 ie, 47.5% cases. Isolated ALP is seen in 29/38 ie, 76.3% cases.

Level of CEA was elevated (>20 ng/ml) in 18/38 ie, 47.5% cases; while the level of CA 19-9 was elevated (>850 U/ml) in 32/38 ie, 84.2% cases.

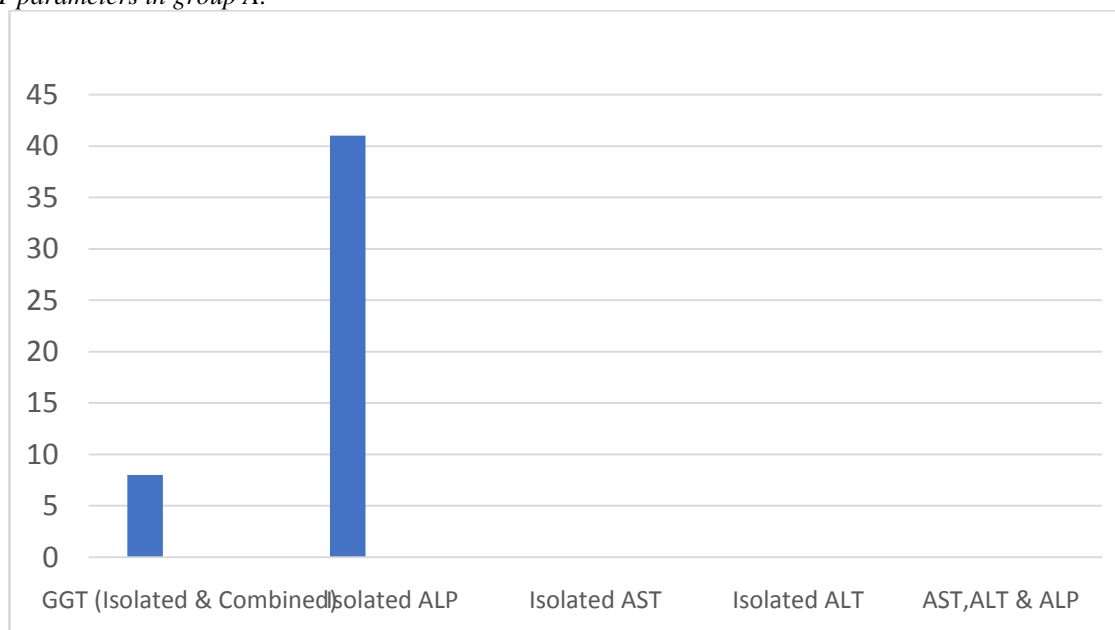
None of the parameters of LFT except GGT shows such consistent elevation in all the cases (100%) of Ca GB with hepatic involvement in Group B.

GGT is found more consistently elevated in all cases (100%) in comparison to the elevation of tumour markers CEA and CA 19-9 in Group B cases.

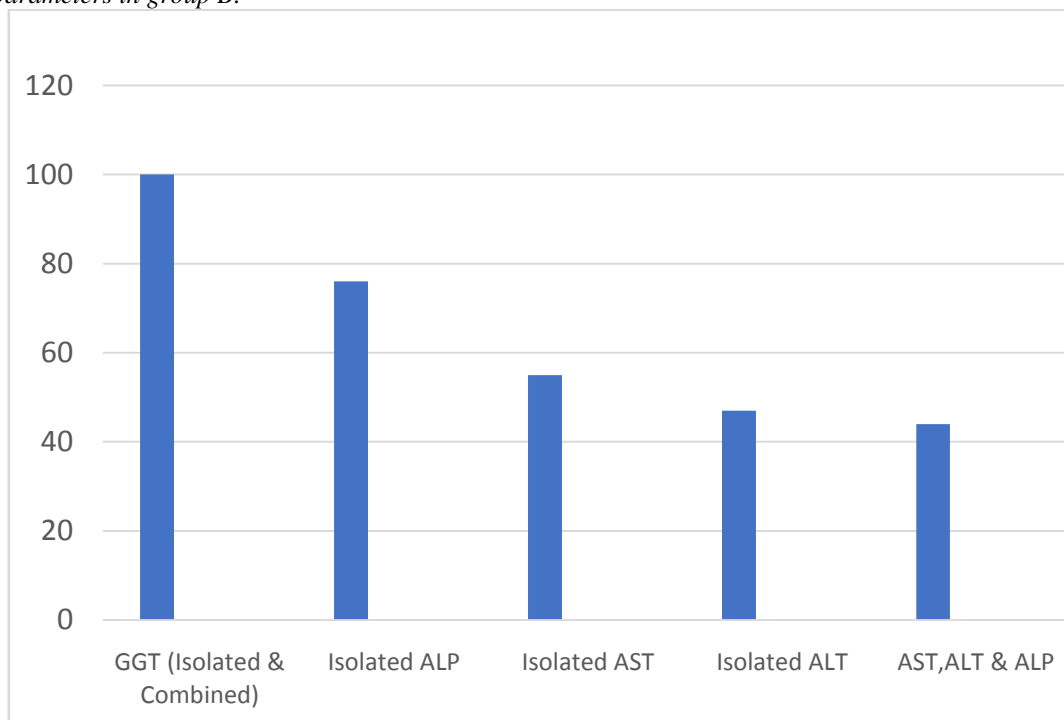
Also, the level of GGT is found to be elevated >2 fold in 'T3 disease' ie, in 30/38 cases; and it is elevated >5 fold in 'T4 disease' ie, in 8/38 cases.

*Comparison between both 'Group A' and 'Group B' in the level of parameters of LFT (in %).*

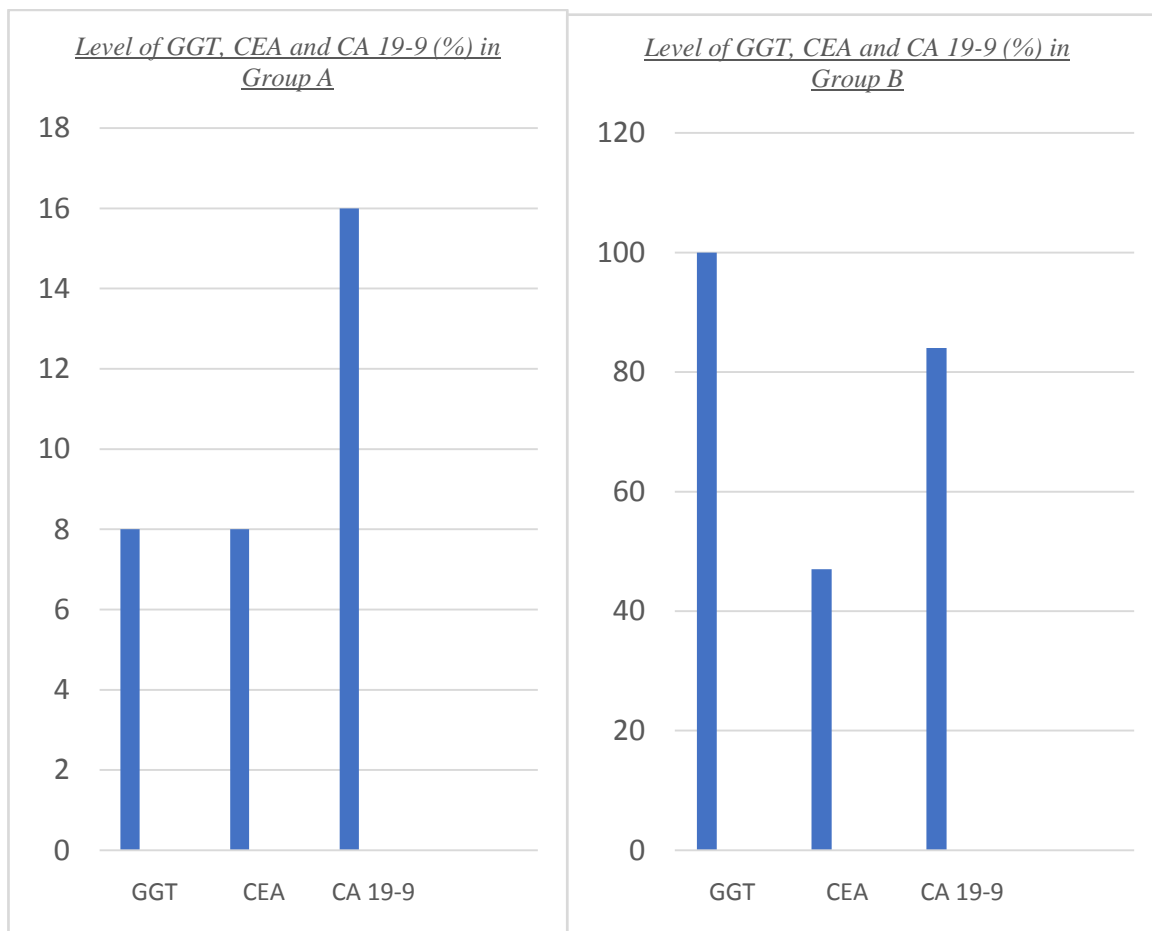
*LFT parameters in group A:*



*LFT parameters in group B:*



*Comparison between both the Group A and Group B in the level of GGT and tumour markers (CEA and CA 19-9):*



Markers elevated	Group A	Group B
GGT	8.30%	100%
CEA	8.33%	47.50%
CA 19-9	16.66%	84.20%

**Following data were evaluated on comparing both group using**

**'Unpaired t-test':-**

Biostatistics Parameters	Group A	Group B
Sample size (n)	12	38
Mean of GGT level	25.5 U/L	237.71 U/L
Standard Deviation (SD)	15.89	98.52
Standard Error of Mean (SEM)	3.06	16.79
P-value	0.001	
t-value and critical t-value	-7.016 & 2.010	

#### IV. DISCUSSION:

GGT is found within normal range or <2 fold rise in all cases of Ca GB without hepatic involvement (12/12); while the level of GGT is consistently raised >2-4 fold or even >5 fold in all (38/38) the cases of Ca GB with hepatic involvement indicating that GGT is the most sensitive indicator of hepatic metastasis in cases of Ca GB. GGT was also found consistently elevated in all (100%) cases of Group B in comparison to other parameters of LFT (AST+ALT+ALP=44.7%; AST=55.5%; ALT=47.5%; ALP=76.3%). Thus, as our previous learning says, GGT level is raised in proportion to the level of ALP, but in this study GGT rise (100%) is independent of the level of ALP (76.3%). In cases of Ca GB with hepatic involvement, GGT rise is seen in all (100%) patients; while the level of CA 19-9 is raised only in 84.2% cases. Thus it can be interpreted that GGT can be efficiently used as a tumour marker in early diagnosis of the patients of Ca GB with suspicion of hepatic involvement. In a study by Kankonker *et al* in 2013<sup>[9]</sup>, CA 19-9 was found the most sensitive tumour marker (70-87% sensitive) in patients of Ca GB with hepatic metastasis. In this study, this had been succeeded by GGT level which is found to be more sensitive (99-100%) than CA 19-9 in determining hepatic metastasis. In a study by Singh *H* in 2013<sup>[10]</sup>, it was seen that GGT is useful for evaluation of not only icteric patients in malignant biliary disease, but also for an-icteric patients harboring biliary malignancy. A study by Koenig *G et al*, GGT is found to be a predictive biomarker of antioxidant inadequacy and disease risk especially for hepatobiliary malignancy. In a very early study done by Gifford *Lum* in 1974, it was clearly observed that increased GGT activity is a good indicator of metastasis to the liver in patients of Ca GB and Pancreas. Thus, the finding of these past studies are similar to those of this study which highlights the role of GGT as an early indicator for hepatic involvement in these patients. GGT level can also be stratified according to the stage of disease. In T3 disease (79%), patients showed a rise of GGT >2 fold; while in T4 disease (21%), cases showed a raised GGT >5fold. The mean level of serum GGT in patients of Ca GB without hepatic involvement (Group A) is '25.5±15.89 U/L', while the mean level of serum GGT in patients of Ca GB with hepatic involvement (Group B) is '237.71± 98.52 U/L'; p-value being 0.001. Thus it can be clearly implicated that the serum level of GGT is raised in the cases of hepatic involvement and is strong presumptive evidence of hepatic involvement which can be used as marker for early diagnosis.

## **V. CONCLUSION:**

Level of GGT is consistently increased in all cases of Ca GB with hepatic involvement, even before and more than the rise of other LFT parameters; and hence, can be concluded that GGT can be used as a sensitive tool for early diagnosis of hepatic metastasis in cases of Ca GB. Also, GGT is raised in all cases of Ca GB with hepatic metastasis proving its accuracy and sensitivity more than that of tumour markers like CA 19-9 and CEA; thus serum GGT can be used as tumour marker for determining the prognosis of the disease with greater sensitivity and better cost effectivity than CA 19-9 or CEA. The level of GGT can also predict staging of the disease; level > 2 fold is usually seen in T3 disease, while > 5 fold in T4 disease; thus such high level of GGT may also indicate advance disease.

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