Chemistry Research Journal, 2018, 3(1):92-97

Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Correlation of gamma glutamyl transpeptidase (γGT) levels in patients with hepatitis and related chronic hepatic conditions

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Abstract Gamma glutamyl transpeptidase (abbreviated as γGT) is a notable hepatic enzyme that plays an important role in gamma-gutamyl cycle in liver. Any alterations in its concentration depict patho-physiological changes or a diseased condition in liver. The current study describes the assessment of correlation of elevated γGT levels with hepatitis stages and/or related chronic conditions such as hepatoma, to evaluate its diagnostic significance. One hundred and sixty patients (males n = 102; females n = 58) within age range of 27-76 yrs were selected retrospectively for the period Dec 2015 to Dec 2017, and when required prospectively through evaluation of laboratory information system. The evaluated clinical status of hepatitis, with progressing clinical conditions, was classified into four stages I-IV. Blood samples were analyzed for γGT, ALT (alanine aminotranferase), AST (aspartate aminotranferase), ALP (alkaline phosphatase), Bil (Total bilirubin), albumin, (ALB) Pro-thrombin time (PT) and hepatitis profile tests by standard methods. Cumulative correlation of γGT with all four hepatitis stages depicted significant correlation of R^2 = 0.958 whereas corresponding significant linearity manifested as R^2 of 0.927 in individual staging I, R^2 = 0.885 in stage II, R^2 = 0.972 in Stage III and R^2 = 0.972 in Stage IV. γGT exhibited around 3 folds ($P < 0.01$) increase at stage I, 19 folds ($P< 0.00001$) at stage IV when compared with controls, and upto 7 folds when γGT levels of stage I were compared with levels of Stage IV ($P < 0.0001$) of the same. The significance of γGT was further strengthen when γGT levels were compared with other hepatic parameters including ALT, AST, ALP, Bil, ALB and PT with intensifying degree of elevation at initial and various progressing stages of hepatitis. The results showed that γGT is the most significantly independent hepatic parameter that exhibited significant elevation at all hepatitis stages in comparison with other hepatic parameters. The presented data sturdily suggested substantial significance of determining γGT in hepatic infections and recommend inclusion of it in assessments of patients that were suspected of or confirmed with progressing clinical severity such as development of end stage cirrhosis and even malignancy to conclude better prognosis and adjustments of treatment regiments.

Keywords Gamma glutamyl transpeptidase, γGT, hepatitis, Hepatic parameters

1. Introduction

Gamma glutamyl transferase or gamma glutamyl transpeptidase (abbreviated as γGT) is a notable hepatic enzyme bearing the nomenclature of EC 2.3.2.2 and involved in transfer of gamma-glutamyl functional groups [1]. Since it

plays an important role in gamma-gutamyl cycle in liver, which is the main metabolic pathway for glutathione, in addition to drugs detoxications cycles, any alterations in its concentration depicts patho-physiological changes or a diseased condition in liver [1,2]. In most of hepatic diseases, including hepatitis and cirrhosis, elevation of γGT was often reported, that depicted parenchymal damages and eventual poor response to therapy [3-6]. In recent years, γGT has also been indicated as a biomarker for evaluation of chronic hepatic conditions, such as hepatitis C and B infections and in some cases, HCC [2,4, 7-9]. The current study describes the assessment of correlation of elevated γGT levels with hepatitis stages and/or related chronic conditions such as hepatoma, to evaluate its diagnostic significance for prognosis and treatments.

2. Material and Methods

2.1 Research protocols and patients selection: The current research study covers the period of Dec 2015 to Dec 2017. Patients were selected through retrospective, and when required prospective evaluation of laboratory information system, counseling of patients attending lab and out-door services and data review. It was ensured that only those patients' data were included that were assigned with hepatitis anomalies. All data gathered, inclusive of hepatic profiles, hepatitis status and laboratory findings were grouped accordingly as per protocols described earlier [10]. Initial assessments of data was carried out in 520 patients, that were further merited through evaluation and investigations into final number of 160 patients (males n = 102; females n = 58) within age range of 27-76 yrs. To determine and establish proper correlation between γGT and hepatitis status, the clinical conditions were classified into four stages I-IV as per description detailed in a recent study [10]. Inclusion and exclusion criteria were also established accordingly, keeping in view related co-morbid and interfering components. Patients were grouped according to their stages as Stage I, n = 31; Stage II, n = 35; Stage III, n = 55 and Stage IV, n = 39.

2.2. Sample collection and chemical analysis: Blood samples were collected for analysis of γGT, ALT (alanine aminotranferase), AST (aspartate aminotranferase), ALP (alkaline phosphatase), Bil (Total bilirubin), albumin, (ALB) Pro-thrombin time (PT), hepatitis profile tests by standard methods ALT (alanine aminotranferase) and hepatitis profile tests. Hepatic profile testing was performed on Axsym (Abbott, USA) whereas γGT, ALT AST, ALP, Bil and albumin were analyzed by IFCC (international federation of clinical chemists) recommended method on Cobas 6000 c501 (Roche Diagnostics, Basil), where as PT was analyzed on CA-1500 (Sysmex). During initial analysis and data collection, it was observed that there were no significant difference or variation among above mentioned hepatic parameters in both hepatitis B or C patients and even males and females, thus data were combined together as a single entity for broader balanced assessment. Normal reference range for ALT is less than 40 IU/L, γGT = 32- 49 IU/L, AST = 35-50 IU/L, ALP = 104-129 IU/L, Bil = less than 1.0 mg/dl, Alb = 3.4-4.8 gm/dl and PT = 8-12 seconds.

Hepatitis staging I t IV, Inclusion and Exclusion criteria: The stages were designated according to clinical and lab profile data. Stage I = Hepatitis C or B reactive + fatty liver seen, stage II = hepatitis C or B reactive + cirrhosis [non-invasive]; stage III = hepatitis C or B highly reactive + with CT/X ray described cirrhosis progression; stage IV = Hepatitis C or B highly reactive + highly progressive/ proliferative cirrhosis or/and hepatoma. Patients with previous history of surgery, immuno-compromised, known alcoholics, steroidal therapies, below 20 years and above 80 yrs were excluded from the study.

Statistical analysis: Data were statistically analyzed by Pearson's correlation, multivariate analysis with level of significance $P< 0.05$ and regression R2 analysis by SPSS version 13 (USA).

3. Results

A total of 160 patients (males = 102 and females 58) were assessed for correlation of their γGT levels in four stages of progression of hepatitis. Results are summarized in Fig 1 to Fig 5 and Table 1. During preliminary analysis of collected data, it was observed that there were no significant difference among all tested hepatic parameters such as gGT, AST, ALT, ALP, Bil, Alb and PT in both hepatitis B or C patients of both genders, thus data were pooled together as a single entity for broader-based assessment. γGT levels considerably corresponded to the stage of hepatitis from I to IV, which depicted moderate infection level (Stage I) to significantly morbid/critical stage of

hepatitis (Stage IV). Regression association analysis suggested linear correlation of γGT levels and its corresponding relation to the hepatitis criticality. Cumulative correlation of γGT with all hepatitis stages depicted significant correlation of $R^2 = 0.958$ (Fig 1) whereas corresponding significant linearity manifested as R^2 of 0.927 in individual staging I (Fig 2), $R^2 = 0.885$ (Fig 3) in stage II, $R^2 = 0.972$ (Fig 4) in Stage III and $R^2 = 0.972$ (Fig 5) in Stage IV. To further strengthen the resulting significant correlation of γGT at various clinical stages of hepatitis, other hepatic parameters, such as ALT, AST, ALP, Bil, albumin and PT were included in the study and statistically analyzed with corresponding levels of γGT (Table 1). The data suggested correlated significance of γGT with other hepatic parameters, most significantly at Stage I levels of it with Alb, Bil and PT ($P < 0.001$) and stage II value with ALT, AST and ALP levels at stage IV ($P< 0.0001$). The elevation of γGT was noted to be profound, a significant 3 folds ($P < 0.001$) at Stage I as compared control reference and 2 folds higher than other hepatic parametric elevations. Similarly, in comparison to control reference, a staggering 19 fold elevation ($P < 0.00001$) of γGT level was noted in stage IV, a highly significant 7 fold ($P < 0.0001$) increase when stage IV levels were compared with stage I levels and 3 folds ($P < 0.001$) when stage I was compared with control reference values. Furthermore, when γGT value of Stage IV was compared with ALT and AST of same staging, γGT value were noted to 5-9 fold ($P< 0.0001$) higher than that of both hepatic enzymes (Table 1).

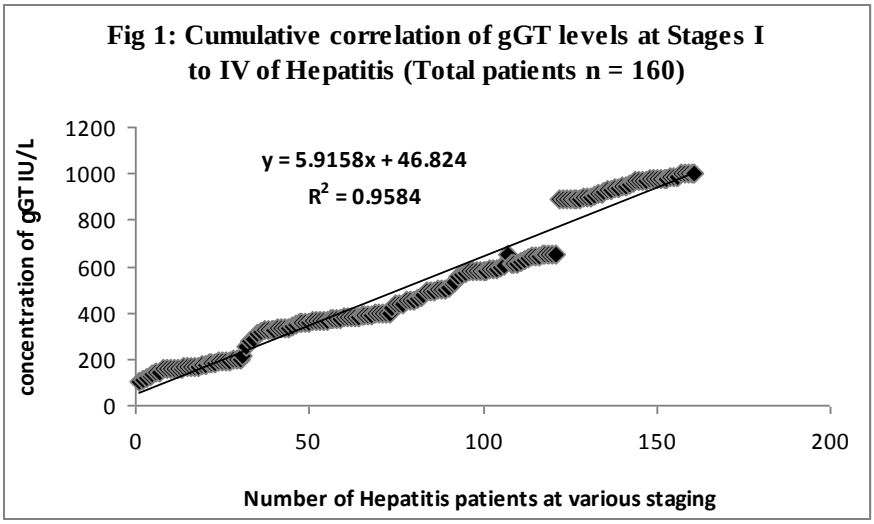
Table 1: γ-Glutamyl transpeptidase and other Hepatic parameters in patients of various Hepatitis stage

	Hepatitis stages				
Hepatic parameters	**I**	**II**	**III**	**IV**	**Control reference ranges**
γGT IU/L	159.63 ± 10.50[b]	348.54 ± 30.25[c]	542.58 ± 50.15	967.41 ± 62.35[d]	32-49[b,c,d]
ALT IU/L	54.54 ± 5.60[a]	235.75 ± 25.70	368.62 ± 36.52	575.14 ± 50.20[c]	< 40 [a,c]
AST IU/L	52.46 ± 5.90	213.80 ± 16.70[a]	396.75 ± 32.65	490.29 ± 48.25[c]	35-50[a,c]
ALP IU/L	168.25 ± 15.20[a]	259.46 ± 26.15	401.25 ± 35.60	509.30 ± 51.35[c]	104-129[a,c]
Bil mg/dl	2.26 ± 0.95[a]	5.20 ± 1.10	4.29 ± 0.98	4.90 ± 1.10 [b]	< 1.0[b]
Alb gm/dl	3.90 ± 0.86	3.50 ± 0.60	3.00 ± 0.50	2.90 ± 0.40[b]	3.4-4.8[b]
PT sec	12.40 ± 1.25	13.26 ± 2.40	15.29 ± 3.50	16.31 ± 4.60[b]	8-12[b]

Results are expressed as mean ± SD

γGT (γ-Glutamyl transpeptidase), ALT (alanine aminotranferase), AST (aspartate aminotranferase), ALP (alkaline phosphatase), Bil (Total bilirubin), albumin, (ALB) Pro-thrombin time (PT).

Statistical analysis = $P < 0.05$ level of significance. **a** = 0.01, **b** = 0.001, **c** = 0.0001, **d** = 0.00001



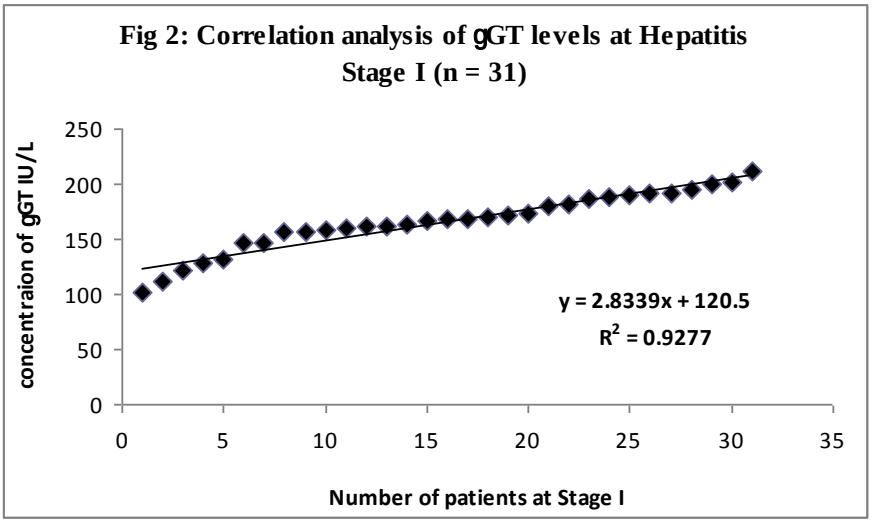


Fig 2: Correlation analysis of gGT levels at Hepatitis Stage I (n = 31)
concentraion of gGT IU/L
250
200
150
100
50
0
0
5
10
15
20
25
30
35
y = 2.8339x + 120.5
R2 = 0.9277
Number of patients at Stage I

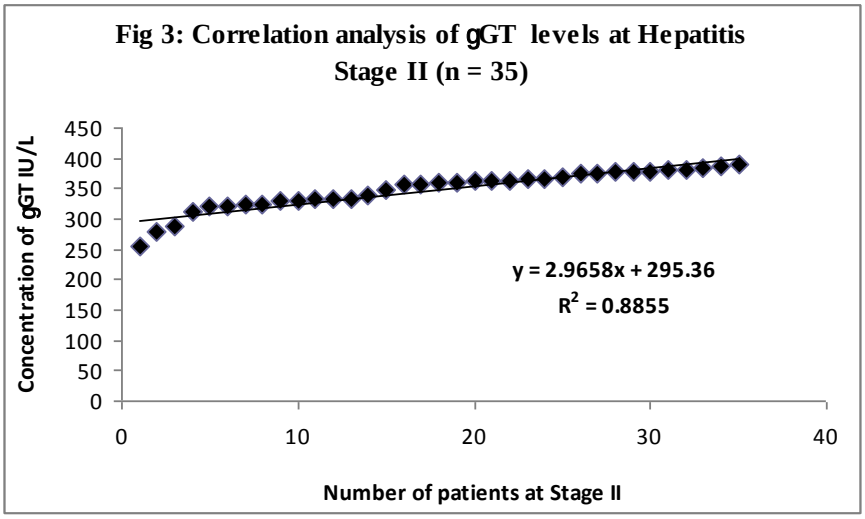


Fig 3: Correlation analysis of gGT levels at Hepatitis Stage II (n = 35)
Concentration of gGT IU/L
450
400
350
300
250
200
150
100
50
0
0
10
20
30
40
y = 2.9658x + 295.36
R2 = 0.8855
Number of patients at Stage II

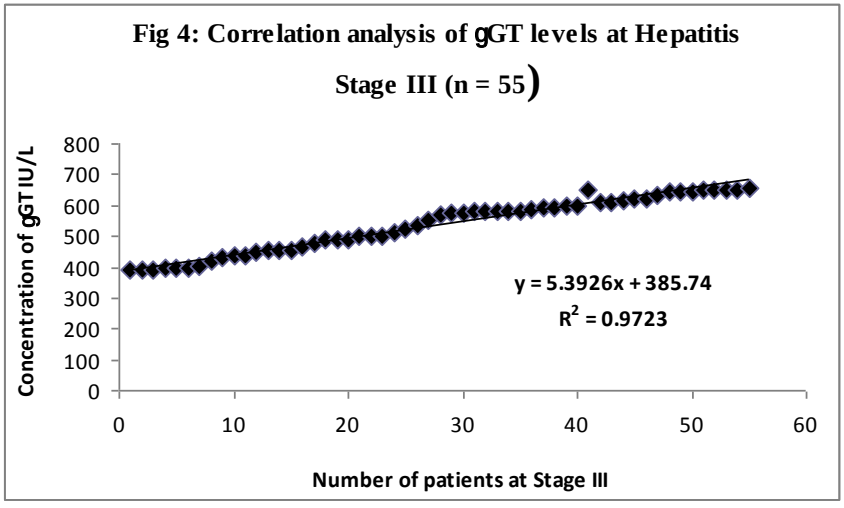
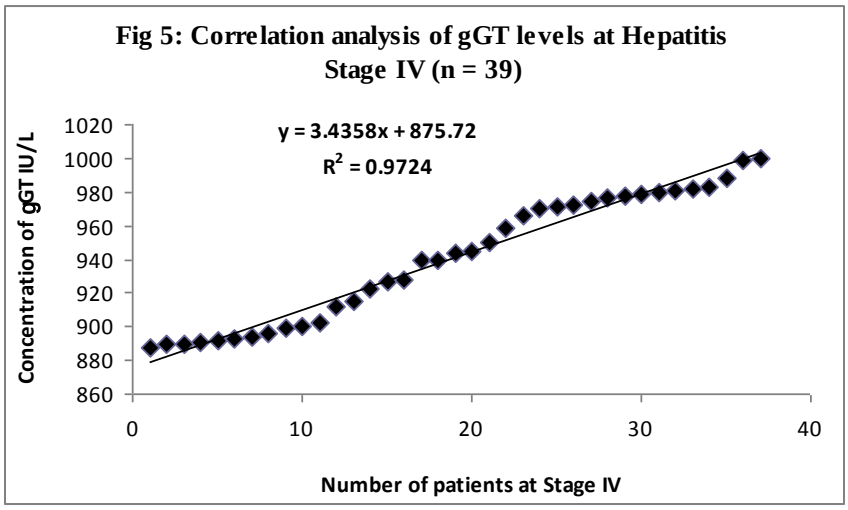


Fig 4: Correlation analysis of gGT levels at Hepatitis Stage III (n = 55)
Concentration of gGT IU/L
800
700
600
500
400
300
200
100
0
0
10
20
30
40
50
60
y = 5.3926x + 385.74
R2 = 0.9723
Number of patients at Stage III



4. Discussion

Previous and recent past studies have reported significant elevation of γGT in HCV-infected patients and in some cases HCC [2-4,7-9,11,12]. In our study considerable correlation was depicted by γGT with various stages of hepatitis from R^2 = 0.885 to R^2 = 0.972 with cumulative R^2 of 0.95. Similarly when γGT was compared with other hepatic parameters, significant correlation was noted regarding intensity of γGT elevation at various hepatitis stages and levels of significance with ALT, AST, ALP, Alb and PT. Association of elevated γGT levels and various advanced stages of hepatic fibrosis 3 and 4 was reported earlier [10,11,13]. It was argued that chronic infections of B and C origin and subsequent histological damage may represent corresponding elevation of γGT and ALT levels [5-7,14,15]. More recent studies suggested a positive role of γGT, along with alpha-fetoprotein (AFP) and interleukin 18 in evaluation of HCC [3]. Furthermore, not only hepatic disorders, diabetes mellitus, when remained untreated, were also noted as one of the co-morbid for instigating γGT elevation, suggesting stressing of hepatic metabolic functions [9]. Previous studies by several clinicians also considered γGT as a significant and independent marker in patients with hepatitis B and C infections [5,16-18], advocating our study, that depicted high level of γGT in patients with hepatitis C infections and progressing cirrhotic or malignant conditions.

5. Conclusion

The present study described determination of γGT levels in patients of various mild and chronic stages of hepatitis infections. γGT significantly correlated with different progressing clinical stages of I to IV of hepatitis with regression correlation generation of R^2 0.885 to 0.972. The data strongly suggested considerable significance of estimation of γGT in hepatic infections and in progressing clinical severity of chronic cirrhosis and development of malignancy such as HCC for recommending better prognosis and adjustments of treatment regiments.

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