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GAMMA GLUTAMYL TRANSFERASE IN PREDICTION OF EARLY VIROLOGICAL RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH PEGYLATED INTERFERON AND RIBAVIRIN COMBINATION THERAPY

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Keywords:
early virological response; gamma glutamyl transferase; HCV; predictor.

Abstract

Background: γ-glutamyl transferase (GGT) has been taken into account in the evaluation of patients with chronic hepatitis C (CHC). **Aim of the work:** is to evaluate GGT in prediction of early virological response (EVR) in patients with chronic HCV treated with pegylated Interferon (PEG INF) and ribavirin combination therapy. **Patients and methods:** the study included 100 treatment naive patients with chronic HCV started PEG/INF + ribavirin combination therapy. Laboratory investigations including full hepatic profile, GGT, quantitative HCVRNA were done before the start of treatment with their follow up at 4 and 12 weeks of the treatment. Baseline liver biopsy and abdominal ultrasound were done for all patients. **Results:** GGT levels decreased significantly from week 4 to week 12. Significant positive correlations between GGT and AST at week 0, and between GGT and AST and ALT at week 12 were found. Patients with EVR showed significant lower GGT levels at weeks 0, 4 and 12 than those without. A cutoff value of baseline GGT < 55 mg/dl was the best to predict EVR, with sensitivity of 77.8%, specificity of 87.8%. **Conclusion:** GGT can be used as a predictor of EVR to PEG INF/Ribavirin combination therapy in patients with chronic HCV.

Introduction

Hepatitis C virus (HCV) is a globally prevalent pathogen and a leading cause of death and morbidity. The most recent estimates of disease burden show an increase in sero-prevalence over the last 15 years to 2.8%, equating to >185 million infections worldwide ***(1)***.

Egypt has the highest prevalence rate of HCV in the world. Nosocomial transmission has been, and probably still is, the most common route for new infections. In particular, widespread parenteral treatment of schistosomiasis in earlier decades resulted in high levels of HCV transmission ***(2)***. Genotype 4 HCV is the most common HCV in Middle East and Egypt ***(3).*** Accepted standards for treatment -till December 2014- indicate that persons infected with genotypes 1 and 4 are treated with PEG-IFN/RBV for 48–72 weeks ***(4)***.

There are multiple host and viral factors which have been shown to impact the progression of disease in chronic HCV. These factors include individual characteristics (age, sex, race, genetics), viral characteristics (genotype), behavioral (smoking, alcohol), metabolic factors (insulin resistance, obesity), and co-infection (Hepatitis B and HIV) ***(5)***.
Increased γ-glutamyl transeferase (GGT) was found to be associated with liver injury and with chronic hepatitis C (HCV) outcomes. Increasing GGT during antiviral treatment was found to be strongly associated with diminished sustained virological response. GGT was suggested to be associated with clinical outcomes and an independent predictor of virological response among patients with liver disease due to HCV ***(6).***

This study was designed to evaluate GGT in prediction of EVR in patients with chronic HCV treated with PEG/INF and ribavirin combination therapy.

Patients and Methods

The present study was conducted on 100 treatment naive patients with chronic HCV, who received PEG INF/Ribavirin combination therapy, and followed in the Hepatology outpatient clinic in Ain Shams University Hospitals during the period from June 2013 to April 2014.

The patients were included in the study according to the following criteria:
Inclusion criteria: patients with positive HCV antibodies using a third generation ELISA test and detectable HCV RNA by PCR, aged 20 to 60 years, with liver fibrosis stages (F1-F4) according to METAVIR score, body mass index < 30, hemoglobin>10g/dl, platelets>100000/mm^3, Neutrophil count >1.500/ mm^3, leukocyte count >3500/mm^3, INR (≤ 1.5), total serum bilirubin <1.5 g/dL, serum albumin > 3.5gm/dl, serum creatinine within normal (0.6-1.5 mg/dL), TSH within normal (0.4-4.2IU/mL), ANA< 1: 16 and if female: negative pregnancy test.
Exclusion criteria: patients ineligible to interferon therapy such as decompensated liver disease, psychological disorders, thyroid dysfunction, autoimmune diseases, uncontrolled diabetes or patients who developed significant side effects in relation to PEG INF/Ribavirin antiviral therapy were excluded from the study. Patients with other liver diseases rather than hepatitis C such as hepatitis B, combined viral hepatitis, autoimmune hepatitis, alcoholic liver diseases, metabolic liver disease, drug induced liver disease, hepatocellular carcinoma and Wilson disease were also excluded from the study.
All the patients in this study were subjected to the following:

1. Full history taking and complete clinical examination
2. **Laboratory investigations including:** complete liver biochemical profile (ALT, AST, ALP, total and direct bilirubin); complete blood count (CBC); prothrombin concentration and INR; random blood sugar; renal functions (urea and creatinine) by standard laboratory tests. HCV antibody by third generation ELISA, quantitative HCV RNA by PCR, serum ANA by ELISA,TSH by hormonal assay.
   Serum levels of GGT were determined after the blood sample was centrifuged and the serum was taken to automated chemistry set (Beckman Coulter) using GGT Human kit.
3. Fundus examination.
4. Abdominal U/S: Equipment used: Hitachi, EUB-5500. Measurements were performed after overnight fasting and the patient in supine position with emphasis on: Liver size (measuring the span of the right lobe in the mid clavicular line on oblique view and classified as shrunken <11 cm, average= 11-15 cm or enlarged >15 cm), liver echogenicity (bright or coarse echo pattern), splenic bi-polar diameter (longest axis) in cm (measured in a coronal plane, from the upper to the lower pole of the spleen which normally measures up to 12-13 cm). Portal vein diameter (mm) and patency were also determined. The normal PV is up to 13mm in diameter. It was measured from the inner to the outer wall during suspended respiration (**Figure 1a, 1b**).
5. Liver biopsies and histopathological examination: ultrasound guided liver biopsies were performed under conscious sedation using a 16-gauge Klatskin needle. The length of the histological specimens was no less than 2.5 cm. All biopsy specimens were placed in 10% neutral buffered formalin solution for fixation and embedded in paraffin blocks. Serial

sections (sectioned at 4-µm intervals) were concurrently stained with Hematoxylin-Eosin and Masson's trichrome. An experienced pathologist blinded to the clinical data scored the liver biopsies according to the METAVIR score ***(7).***

6. Medications received: the patients were treated with weight-based dosing of pegylated interferon-alpha 2b (PEG-INTRON, 1.5 µg/kg per week, MSD comp.) given by subcutaneous (SC) injection once / week plus ribavirin (**Rebetol** 200 mg, Merck Sharp & Dome, a subsidary of Merck & Co., Inc.) in the dose of 1000–1200 mg/day for body weight <75 or ≥75 kg, respectively) for a total period of 48 weeks.
7. Follow up of patients: complete liver biochemical profile (ALT, AST, ALP, total and direct bilirubin), prothrombin concentration, INR, complete blood count (CBC), serum GGT and quantitative HCV RNA by PCR were re-evaluated at week 4 and week 12. EVR was defined as undetectable hepatitis C virus (HCV)-ribonucleic acid (RNA) or ≥ 2 log HCV-RNA decrease after 12 wk of treatment.
8. Statistical analysis: IBM SPSS statistics (V. 20.0, IBM Corp., USA, 2011) was used for analysis of the obtained data. Data were expressed as Mean ± SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data. The following Statistical tests were done: **Student *t - test*** for comparison between two independent mean groups for parametric data. Linear Correlation coefficient was used for detection of correlation between two quantitative variables in one group. ***Wilcoxon signed rank test (z)*** for comparison between two independent groups for non-parametric data, repeated measures, or "before" and "after" measures. ***Ranked Spearman correlation test (r)*** to study the possible association between each two variables among each group for non-parameteric data. ***Chi-square test (X^2)*** to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error < 0.05 was considered significant. The **ROC** was constructed to obtain the most sensitive and specific cut-off for each technique. To evaluate the most discriminating markers between the compared groups, **AUC** was also calculated. The obtained results are shown in tables 1, 2, 3 and figures 2, 3, 4.

   Informed written consents were obtained from all patients and the study was approved by the ethical committee of Ain Shams University.

Results

This study was conducted on 100 chronic HCV infected patients. Patients were of mean age 42.94 and of mean body mass index of 26.69. 78 of them were males (78%) and 22 of them were females (22%). 50% of patients had stage of fibrosis F1, 42% of patients had stage of fibrosis F2 and 8% of patients had stage of fibrosis F3. 82% of patients had activity of inflammation of A1 and 18% of patients had activity of inflammation of A2.

82% of patients had negative PCR at week 12 of treatment (EVR), while 18% showed positive PCR or decreasing PCR log less than two logs (non responders) at week 12 of treatment **(Figure 2)** .

Liver enzymes AST and ALT showed significant decrease between Week 0 - Week 4 and between week 0- week 12. GGT showed significant decrease in its level between week 4 and week 12 as shown in **table 1**.

There was significant positive correlation between GGT and AST at week 0, and between GGT and AST and ALT at week 12. There was significant correlation between GGT and the hemoglobin at week 0. On the other hand, there was no significant correlation between grade of inflammation or stage of liver fibrosis and GGT or between GGT and PCR **table 2**. There was significant difference between the patients with EVR and those without EVR as regard GGT with lower levels of GGT in the group with EVR at weeks 0, 4 and 12. Also there was significant difference between the group with EVR and those without EVR regarding the baseline AST as shown in **table 3**.

Using ROC analysis in this study, a cutoff value of baseline GGT < 55 mg/dl was the best to discriminate between patients with EVR and patients without, with sensitivity of 77.8%, specificity of 87.8%, positive predictive value 58.3 and negative predictive value 94.7, as shown in **figure 3.**

On constructing a ROC curve to evaluate GGT as a non invasive serum biomarker to predict the stage of liver fibrosis, a cutoff value of baseline GGT < 47 mg/dl was the best to discriminate between insignificant fibrosis (F1) and significant fibrosis (≥ F2) with sensitivity of 56%, specificity of 64%, positive predictive value 60.9 and negative predictive value 59.3 as shown in **figure 4**.

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Discussion

The objective of HCV antiviral therapy is to obtain a sustained virologic response (SVR) ***(8).*** The factors that determine the likelihood of achieving SVR are called predictors of response. They can be classified as viral or host related, or as pre or on treatment depending on the time point of evaluation ***(9)***.

Recently, γ-glutamyl transpeptidase (GGT) has been taken into account in the evaluation of patients with chronic hepatitis C (CHC) ***(10)***. It is uncertain why GGT is associated with poorer prognosis with chronic hepatitis C, as well as greater severity of other liver diseases and with a number of diverse conditions, such as cardiovascular disease, type 2 diabetes, various malignancies, and overall mortality ***(6)***. In a number of studies, low baseline GGT level was shown to be an independent predictor of a SVR ***(11)***.

The current study aimed to prove whether GGT can be used as a predictor of early virological response to PEG INF/Ribavirin therapy of chronic HCV in Egyptian patients.

The current study was conducted on 100 patients whose ages ranged from 22-59 years. Such wide age range in the present work can be explained by the widespread parenteral treatment of schistosomiasis in earlier decades which resulted in high levels of HCV transmission ***(2)***. The reuse of syringes during a schistosomiasis eradication program in the 1960s and 1970s is the supposed cause of the widespread introduction and spread of HCV in Egypt. However, Egypt is experiencing continued HCV transmission associated with unsafe injection practices which result in up to 500 000 new infections annually ***(2)***.Tattooing is associated with two to three fold increased risk of hepatitis C ***(12)***, also personal-care items such as razors, toothbrushes, and use of medical and dental unsterile equipment. Sharing such items can potentially lead to exposure to HCV ***(13)***.

Patients included in the present study were of mean BMI of 26.7. High BMI inversely correlated with SVR, and a lower baseline body weight was significantly associated with SVR across all genotypes in the era of PEG-IFN/RBV combination therapy**,** while obesity was found to affect response to antiviral therapy adversely ***(14)(15)***.

The current study shows male predominance (78%), which is in agreement with ***Singh et al.***, who found that the highest frequency of Hepatitis C infection was found in the middle aged (41-60 years) patients with male predominance ***(16)***.
This study shows statistically significant decrease in AST, ALT levels from week 0 to week 12, which is in agreement with ***Everheart and Wright,*** who found that changes in AST and ALT is strongly associated with early virological response ***(6)***.
In the current study, 82% of patients showed EVR with significant decrease in GGT levels from week 0 to week12 and lower baseline and week 12 levels of GGT in patients with EVR. This is in agreement with the results of ***Everheart and Wright,*** who found that increasing GGT was strongly associated with diminished week 20 response, end of treatment response, and sustained virological response ***(6)***. This also goes with the results of **García-Samaniego et al,** who found that patients who failed to achieve EVR in their study had higher GGT levels ***(17)***.

At week 12, the current study showed significant correlation between GGT and both AST and ALT which is also in agreement with results of ***Everheart and Wright*** who found changes in GGT were positively correlated with changes in AST and ALT ***(6)***. Liver enzymes have been used as a marker for hepatic regeneration after the destruction of hepatocytes in viral hepatitis ***(10)***. They are considered as indicators of hepatocellular injury ***(17)***. They are elevated in several diseases, such as chronic viral hepatitis, non-alcoholic fatty liver disease, autoimmune hepatitis, hemochromatosis, and alcoholic liver disease. These enzymes assist in diagnosis, in patient follow-up and as markers of response to treatment because they reflect inflammatory activity in the parenchyma of the liver ***(18)***.

Baseline GGT also correlated with AST levels, as both are liver enzymes and they increase when the liver is inflamed or damaged ***(19)***(***20)***. Experimentally, GGT may have a pro-oxidant activity by promoting the generation of free radical species in presence of free metal ions such as iron (***21)***.

A cutoff value of baseline GGT < 55 IU/mL was the best to predict EVR in the present study. This is in some similarity with ***García-Samaniego et al,*** who found that GGT < 85 IU/mL together with other factors were identified as independent predictors for EVR ***(17)***.

On constructing ROC curve, a cutoff value of baseline GGT of 47 mg/dl was the best to discriminate between insignificant fibrosis and significant fibrosis with sensitivity of 56% and specificity of 64% where positive predictive value was 60.9 and negative predictive value of 59.3.

Conclusion

GGT can be used as a predictor of early virological response to the combination antiviral treatment (PEG/INF and ribavirin) in chronic HCV infected Egyptian patients.

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Table 1: Changes in liver enzymes, serum albumin and GGT over the follow up period

					Difference			
		Mean	**±**	**SD**	**Comp.**	**Mean**	**SD**	**t**	**P-value**
Albumin (g/dl)	**W0**	4.341	±	0.451	**W0-W4**	0.134	0.144	6.461	<0.001*
	W4	4.206	±	0.458	**W0-W12**	0.349	0.205	11.799	<0.001*
	W12	3.991	±	0.365	**W4-W12**	0.215	0.238	6.267	<0.001*
AST (u/l)	**W0**	64.520	±	40.153	**W0-W4**	34.440	42.775	5.693	<0.001*
	W4	30.080	±	14.408	**W0-W12**	34.310	42.955	5.648	<0.001*
	W12	30.210	±	14.319	**W4-W12**	-0.130	15.365	-0.060	0.953
ALT (u/l)	**W0**	73.900	±	49.209	**W0-W4**	41.940	53.659	5.527	<0.001*
	W4	31.960	±	20.460	**W0-W12**	43.846	49.086	6.316	<0.001*
	W12	30.054	±	15.408	**W4-W12**	1.906	22.449	0.600	0.551
GGT (IU/ml)	**W0**	56.474	±	38.350	**W0-W4**	2.012	22.849	0.623	0.536
	W4	54.462	±	29.541	**W0-W12**	4.426	23.124	1.353	0.182
	W12	52.048	±	30.842	**W4-W12**	2.414	7.168	2.381	0.021*

W0: week 0/ baseline values W4: value at week 4 of treatment
W12: value at week 12 of treatment

AST: Aspartate Aminotranseferase
ALT: Alanine Aminotranseferase
GGT: Gamma glutamyl transeferase

Table 2: Correlation between GGT and all other parameters at Weeks 0, 4 and 12:

The parameter	GGT0		GGT4		GGT 12	
	r	P-value	r	P-value	r	P-value
Age	0.265	0.063	0.235	0.101	0.223	0.119
PCR	0.198	0.609	0.649	0.059	-0.040	0.918
Glucose	0.018	0.904	-0.136	0.378	-0.186	0.232
Creatinine	0.197	0.171	0.066	0.653	-0.012	0.933
Albumin	0.138	0.340	0.099	0.505	0.098	0.508
AST	0.330	0.019*	0.093	0.523	0.298	0.036*
ALT	0.029	0.842	0.274	0.055	0.288	0.043*
WBCs	-0.086	0.554	-0.004	0.978	0.267	0.061
ANC	-0.058	0.690	0.054	0.709	0.213	0.142
Hbg	0.453	0.001*	0.041	0.776	0.149	0.301
Platelets	-0.143	0.323	-0.043	0.765	-0.085	0.561
BMI	0.005	0.974	0.108	0.454	0.098	0.499
Activity	1.158	0.252				
Fibrosis	-1.085	0.283				

ANC: absolute neutrophils count
BMI: body mass index
Hbg: hemoglobin
WBCs: white blood cells
0: baseline values
4: values at week 4 of treatment
12: values at week 12 of treatment

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Table 3: Comparison between patients with and without EVR regarding all parameters.

	Patients with EVR			Without EVR			T-Test	
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	**t**	**P-value**
Glucose 0	97.683	±	28.784	103.778	±	28.560	-0.576	0.567
Glucose 12	94.923	±	16.391	81.250	±	8.382	1.634	0.110
Creatinine 0	0.855	±	0.197	0.868	±	0.249	-0.165	0.869
Creatinine 12	0.867	±	0.239	0.796	±	0.145	0.802	0.427
Albumin 0	4.348	±	0.472	4.311	±	0.362	0.218	0.829
Albumin 12	3.992	±	0.374	3.988	±	0.344	0.031	0.975
AST 0	57.878	±	29.990	94.778	±	64.204	-2.645	0.011*
AST 12	28.793	±	15.039	36.667	±	8.231	-1.513	0.137
ALT 0	68.951	±	45.710	96.444	±	60.723	-1.539	0.130
ALT 12	28.407	±	15.846	37.556	±	11.024	-1.641	0.107
WBCs 0	6.220	±	1.700	5.778	±	0.764	0.758	0.452
WBCs 12	3.448	±	0.818	4.544	±	1.810	-2.835	0.007*
ANC 0	2.956	±	1.167	2.778	±	0.446	0.448	0.656
ANC 12	1.762	±	0.814	2.163	±	1.238	-1.207	0.234
Hbg 0	14.120	±	1.352	14.267	±	1.651	-0.284	0.777
Hbg 12	11.463	±	1.402	12.200	±	1.862	-1.344	0.185
Platelets 0	222.359	±	48.054	191.000	±	40.672	1.816	0.076
Platelets 12	164.625	±	50.579	150.200	±	40.708	0.797	0.429
GGT 0	48.700	±	27.536	91.889	±	59.128	-3.367	**0.002***
GGT 12	43.376	±	20.207	91.556	±	40.537	-5.281	**<0.001***
BMI	26.549	±	3.517	27.333	±	3.157	-0.616	0.541
Age	41.951	±	9.762	47.444	±	7.618	-1.581	0.120

0: baseline values 12: values at week 12 of treatment

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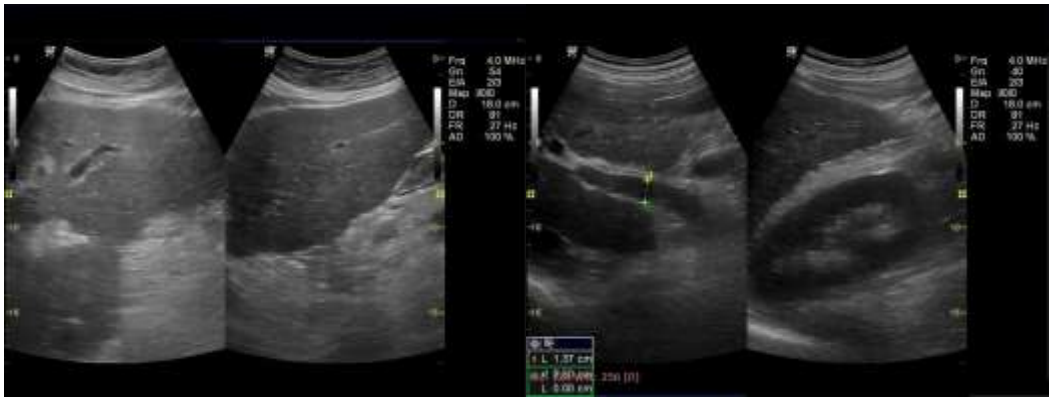

Figure 1(a) *Figure 1(b)*

Figure 1a and 1b: Ultrasound pictures of liver cirrhosis

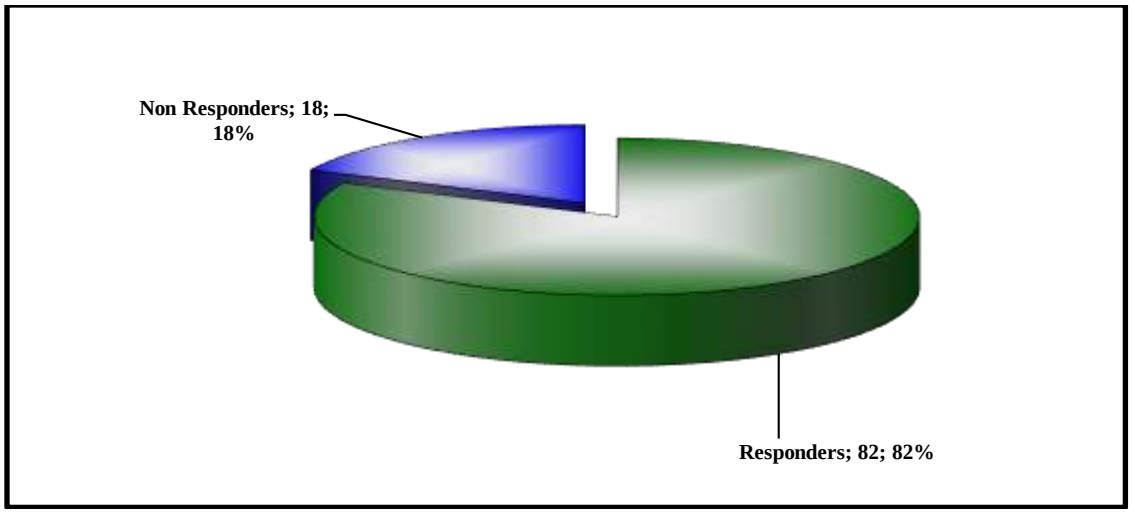

Figure 2: Number and percentage of patients achieved early virological response (EVR).

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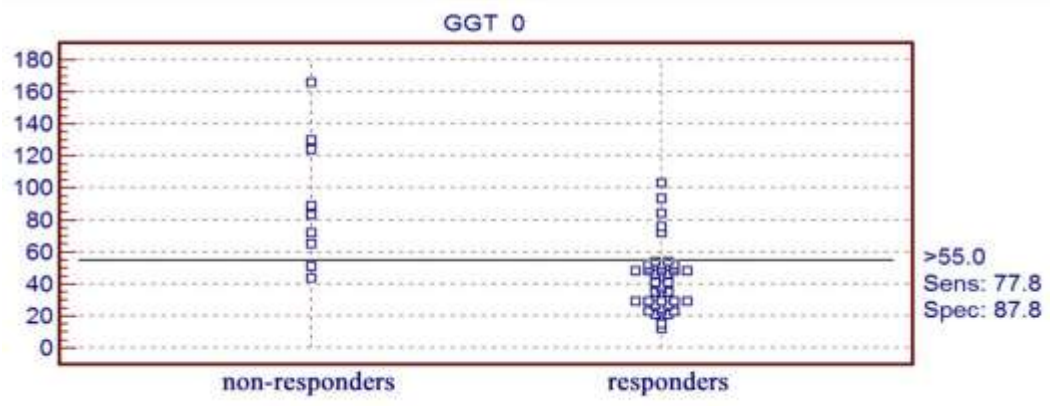

Figure 3: Baseline GGT as a predictor of EVR

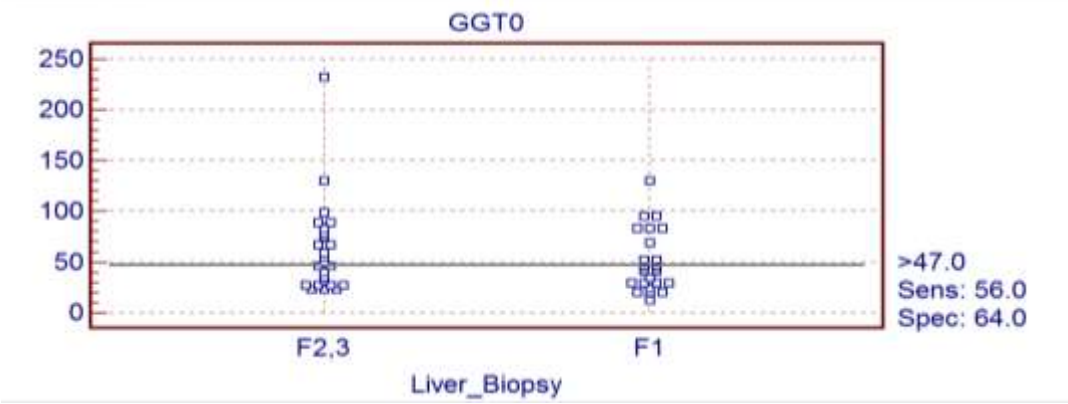

Figure 4: Baseline GGT as a non invasive predictor of stage of liver fibrosis.