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GAMMA-GLUTAMYL TRANSFERASE AS PREDICTOR OF EARLY VIROLOGIC RESPONSE IN SOFOSBUVIR TREATED CHRONIC HEPATITIS C GENOTYPE 3 PATIENTS

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Abstract:

Objective: *Analyze the baseline Gamma-glutamyl transferase (GGT) as predictor of Early Virologic Response (EVR) in Sofosbuvir treated chronic hepatitis C genotype 3 patients.*

Study Design: *Cross sectional study*

Study setting & Duration: *Department of Medicine, Liaquat University Hospital Jamshoro/Hyderabad from August 2017 to March 2018.*

Subjects and Methods: *A sample of 100 HCV- PCR positive; comprising of 63 male and 37 female was studied. Anti HCV-antibodies were detected by 3rd generation ELISA assay kit. Viral load HCV- RNA was detected by RT- PCR method on Cobas Amplicor (Roche Diagnostic Inc.). Hemoglobin, platelets, serum bilirubin, albumin, Prothrombin time (PT), alanine transaminase (ALT) and gamma glutamyl transferase (GGT) were detected. Data was analyzed on SPSS ver 22.0 by Student`s t-test and Chi- square test at 95% confidence interval (CI) (P < 0.05).*

Results: *Age (mean ± SD) of male and female was noted as 43.93±7.95 and 43.45±4.54 years respectively (P=0.032). Of 100 sample, 63% were male and 37% were female (P=0.940). Hemoglobin, Prothrombin time and serum GGT shows significant differences between groups. Logistic regression analysis model for GGT as predictor of EVR shows 0.912 (91.2%) Area under curve (P=0.0001).*

Conclusion: *The present study concludes low serum GGT level positively predicts an early virological response (EVR) in chronic hepatitis C patients.*

Key words: *Gamma Glutamyl transferase, Chronic Hepatitis C, Early Virological Response*

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INTRODUCTION:

Globally hepatitis C viral (HCV) infection has emerged as a serious health problem. World incidence of HCV is estimated as 200 million (3.3%).[1] Approximately 3-4 million people are infected by HCV throughout the World. Reported incidence of HCV ranges 0.2 – 40% and varies in different geography areas of World.[2] An annual burden of 10 million chronic viral hepatitis C (CHC) has been reported in the Pakistan.[3,4] Amongst highest HCV infection countries, the Pakistan ranks second with an approximate incident rate of 4.5% to 8%.[1,5] HCV is a hepatotropic virus that disturbs the hepatocyte enzymes. Alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) are liver enzymes of clinical significance.[6] GGT has emerged as a biological indicator of viral response to drug therapy. GGT is expressed on the cell membranes of renal tubules, brain capillaries and biliary epithelium. GGT is a cell-surface heterodimeric glycoprotein that catalyzes the glutathione metabolism.[7] GGT is used a clinical biomarker of hepatobiliary disorders, drug intake and alcohol consumption, etc. However, its diagnostic and prognostic worth is debatable.[8] Few recent studies[1,7,8] have highlighted its predictive, prognostic and diagnostic value. Raised GGT is reported as indicator of mortality in chronic liver disease, diabetes mellitus and neoplastic disorders.[9] Serum GGT levels are raised in CHC patients.[6-9] Previous studies have reported low baseline GGT level is a strong predictor of sustained virologic response (SVR) to anti viral drug therapy such as interferon.[1,6-9] Serum GGT levels are reported to be predictor of hepatocellular carcinoma (HCC) in CHC patients. Its predictive value for the HCC development has been in non- cirrhotic CHC patients even after successful eradication of HCV.[10-13] Whether serum GGT levels are associated or not with development of CHC are not well understood. A study from China reported serum GGT levels during various phases of CHC. This study reported GGT as a potential predictive clinical biomarker for hepatitis C in response to sofosbuvir therapy. The present prospective study analyzed the baseline Gamma-glutamyl transferase (GGT) as predictor of Early Virologic Response (EVR) in Sofosbuvir treated chronic hepatitis C patients in patients reporting at our tertiary care hospital

SUBJECTS AND METHODS:

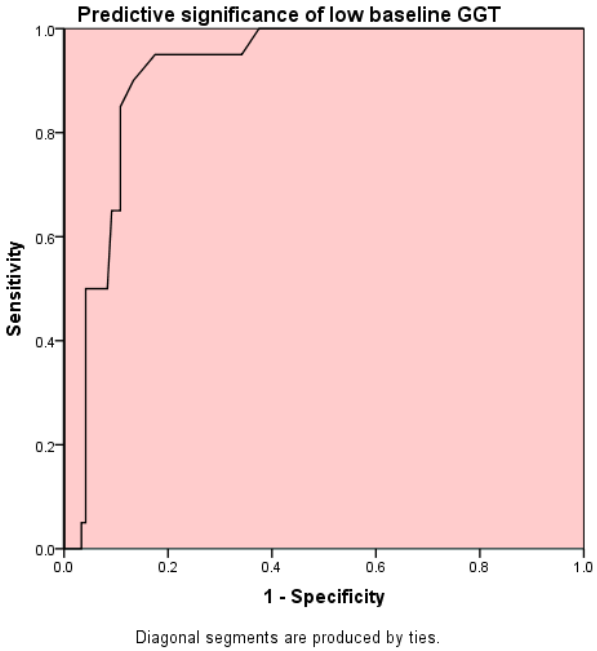
A cross sectional study was conducted at the Department of Medicine, Liaquat University Hospital Jamshoro/Hyderabad from August 2017 to March 2018. A sample of 100 HCV- PCR positive; comprising of 63 male and 37 female were selected according to inclusion criteria. Age 40- 50 years, HCV- RNA PCR positive, genotype 3, drug naïve, without signs of liver fibrosis of both gender were included. Chronic hepatitis cases of relapse/recurrence with previous anti HCV therapy were excluded. Sofosbuvir 400mg daily and ribavirin (1000mg daily for body weight <75 kg and 1200mg for body weight >75 kg) were prescribed.[6] Ribavirin was given in 2 doses. Anti HCV- antibodies were detected by 3rd generation ELISA assay kit. Viral load HCV- RNA was detected by reverse transcriptase polymerase chain reaction (RT- PCR) method. Cobas Amplicor (Roche Diagnostic Inc.) was used for RT- PCR analysis. HCV genotyping was performed by hybridization method. Lower limit of detection was 20 IU/ml. Serum HCV- RNA was detected as baseline and at 4 weeks, 12 weeks and at the end of therapy period. Rapid virological response (RVR), early virological response (EVR) and Sustained virological response (SVR) were defined as undetectable serum HCV-RNA at week 4, week 12 week and 24 weeks respectively.[6] Study protocol was in accordance to the Helsinki`s declaration. Inclusion and exclusion were strictly exercised. They were informed that the information will not be shared to none and there will be no harm to them. Volunteers were interviewed to gain their confidence. Volunteers were requested for blood sampling for laboratory testing purpose. Volunteers were informed that they may withdraw at any time and this will not affect their medical therapy. Volunteers were asked to sign the consent form. Volunteers were examined clinically. Age, gender and blood pressure were noted. Venous blood was collected under strict aseptic conditions from prominent vein in the cubital fossa. Blood sample (2 ml) for hemoglobin and platelet estimation was collected in the EDTA tubes. 3 ml blood was centrifuged at x12, 000 g for ten minutes to separate the sera. Hemoglobin, platelets, serum bilirubin, albumin, Prothrombin time (PT), alanine transaminase (ALT) and gamma glutamyl transferase (GGT) were detected by standard laboratory methods. A proforma was designed for data collection. Confidentiality of patient's data was secured. Study was approved by the institution`s ethical review committee (ERC). Data was analyzed on SPSS ver 22.0 by Student`s t-test and Chi- square test. Student`s t-test analyzed the continuous variables and results presented as mean +/- SD. Chi- square test was used for analysis of categorical variables and outcome presented as frequency and %. Data was analyzed at 95% confidence interval (CI) ($P < 0.05$).

RESULTS:

Age (mean ± SD) of male and female was noted as 43.93±7.95 and 43.45±4.54 years respectively (P=0.032). Of 100 sample, 63% were male and 37% were female (P=0.940) (Table I). Baseline hemoglobin, platelets, serum bilirubin, albumin, Prothrombin time (PT), alanine transaminase (ALT) and gamma glutamyl transferase (GGT) are shown in table I. Results of present study reports 100% results of EVR in CHC genotype 3 patients and there was no response difference between male and female patients. Logistic regression analysis model for GGT as predictor of EVR shows AUC of 0.912 (91.2%) (P=0.0001) (Graph 1 and Table II).

Table 1. Demography and biochemical findings of study subjects (n= 100)

	Male	Female	P-value
Gender	63%	37%	0.0001
Age (years)	43.93±7.95	43.45±4.54	0.940
Systolic BP (mmHg)	128.57±16.81	141.21±19.05	0.0001
Diastolic BP (mmHg)	72.76±9.62	78.35±13.47	0.001
Hemoglobin (g/dl)	13.37±2.27	11.90±4.26	0.027
Platelet ($x10^6$)	296.36±77.54	281.27±85.91	0.369
Bilirubin (mg/dl)	1.90±0.66	1.67±0.69	0.109
Albumin (g/dl)	3.83±0.97	3.65±0.76	0.345
PT (seconds)	20.68±6.96	13.81±5.15	0.0001
ALT (U/L)	82.79±18.98	90.40±28.32	0.345
GGT (U/L)	28.32±6.27	32.83±9.48	0.005



Graph 1. Logistic regression analysis model shows the area under curve of GGT as predictor of EVR

Table II. Area Under the Curve

Test Result Variable(s): Predicted probability

Area	Std. Error[a]	P-value.[b]	Asymptotic 95% CI	
			Lower Bound	Upper Bound
0.912	0.026	0.0001	0.863	0.959

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.50

DISCUSSION:

The present cross sectional study is the first time reporting on the baseline GGT as predictor of early virological response (EVR) in sofosbuvir treated chronic hepatitis C genotype 3 patients. Age (mean ± SD) of male and female was noted as 43.93±7.95 and 43.45±4.54 years respectively (P=0.032). Of 100 sample, 63% were male and 37% were female (P=0.940). These findings are in agreement with previous studies.[1,14-15] Tahir et al[14] reported age of 30- 59 years that is in agreement with present study. However, they reported increased incidence among female subjects that contradicts to the present study. In present study, male outnumbered to female that is in agreement to Sirhindi et al[15] as they found increased among male patients. Siddique[16] reported the mean age of 46 years that is in agreement to the present study with male dominancy. The present study included genotype 3 CHC patients that are in agreement to above studies. Pakistan has high prevalence of genotype 3 hepatic C virus. The prevalence is reported as 4.5-8.2%.[1,14-16] Sofosbuvir is a newer oral anti viral drug that has yielded dramatic cure rates against chronic hepatitis C. Sofosbuvir specifically inhibits the NS5B polymerase enzyme of all genotypes of HCV. Hence sofosbuvir is pan-genotype nucleotide analogue effective against HCV.[17,18] Genotype 3 HCV is predominantly found in the country and prevalence has been reported as around 78% in Pakistan.[19,20] In present study, the logistic regression analysis model for GGT as predictor of EVR shows AUC of 0.912 (91.2%) (P=0.0001). Zebreska et al [21] reported poor response of genotype 3 HCV infection with elevated baseline GGT and low platelet counts treated with Pegylated interferon-α and ribavirin. The finding supports the observations of the presents study. They further added that the achieving a rapid (RVR) and early virological response (EVR) are associated with higher likelihood of a sustained virological response (SVR).[21] Siddique et al[16] treated 201 patients with sofosbuvir and ribavirin and reported excellent RVR and EVR at first month of therapy. The findings corroborate the present study. In present study, the success rate was 100% EVR with sofosbuvir and low baseline GGT positively predicted the EVR. Lawaitz et al[17] treated chronic HCV patients with moderate hepatic dysfunction with sofosbuvir and reported positive response of declining HCV RNA within 7 days of therapy. Mansoor et al[22] studied 153 cases of chronic hepatitis C patients and reported Sofosbuvir was highly successful in eradication of HCV- RNA and achieved EVR irrespective of genotypes. They reported genotype 3 being the most common that supports the present study. There was no difference of sofosbuvir in achieving the EVR between male and female that is in agreement to above study.[22] Sarwar et al[23] found 83.1% of CHC patients achieving SVR with sofosbuvir/ribavirin therapy. The results of present study reports 100% results of EVR in CHC genotype 3 patients. The limitations of present study include a small sample size; however, the low baseline GGT as predictive marker of EVR is being reported for the first time.

CONCLUSION:

The present study concludes low serum GGT level positively predicts an early virological response (EVR) in chronic hepatitis C genotype 3 patients. The results of present study reports 100% results of EVR in CHC genotype 3 patients with sofosbuvir and ribavirin.

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