*Original Research Article*

# ROLE OF GAMMA GLUTAMMYL TRANSPEPTIDASE TO PLATELET RATIO(GPR) IN PREDICTING ADVANCED LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS C INFECTION


**Abstract:**

The liver biopsy is the gold standard for the diagnosis of liver fibrosis, but because of its invasiveness, high cost and lack of repeatability its use is limited.A new model widely used these days for evaluating the grade of hepatic fibrosis is the gamma-glutamyltraspeptidase (GGT)-to-Platelet ratio (GPR) and has shown great benefit in this regard. The aim was to evaluate the role of GPR as a noninvasive predictor of significant liver fibrosis in patients with chronic hepatitis C in our population

**Methods:**

All patients with chronic hepatitis C and compensated liver disease were included in the study after informed consent. Patient's baseline characteristics were recorded. Patient's baseline Complete blood count (CBC) and Liver function tests were also recorded. Patients then underwent shear wave elastography (SWE) to stratify the degree of fibrosis. These indices were used to calculate Gamma glutamyl transferase(GGT) /platelet ratio. Results were presented as means ± SD for quantitative data or as numbers with percentages for qualitative data. Continuous variables were analyzed using the Student's t-test; while categorical variables were analyzed using the Chi-square test. A p value of <0.05 was considered statistically significant.

**Results:**

A total of 91 patients were included in the study. Out of 91 patients, 56(61.5%) were males. At baseline, 57(62.6%) patients had ≥F3 fibrosis(advanced fibrosis or cirrhosis).Mean GPR was 1.5±2.1.Area under ROC was obtained for GPR in predicting advanced liver fibrosis(≥F3) was 0.8 (p-≤0.001). At a GPR cut off of ≥0.6, the sensitivity was of 94.74%, specificity of 62%, positive predictive value of 80.69%, negative predictive value was of 87.50% and diagnostic accuracy of 82.42% in predicting advanced liver fibrosis.( ≥F3) in patients with chronic hepatitis C .

**Conclusion:**

The GPR has found to be significantly associated with liver fibrosis in HCV patients presenting in our clinic.However,further studies are needed to validate the role of GPR in predicting liver fibrosis.



**Keywords:** HCV, shear wave elastography, Liver fibrosis,Platelets,GammaGlutamyl Transferase, GPR

**Introduction:**

Globally, hepatitis C is the most common causes of cirrhosis and hepatocellular carcinoma associated with increased morbidity and mortality. In order to halt the disease progression, early diagnosis and prompt treatment are the corner stones of treatment of hepatitis C resulting in decreased number of patients with advanced fibrosis,cirrhosis and HCC.[1-3] The gold standard method to assess the degree of fibrosis is liver biopsy.The use of liver biopsy is restricted due to its invasiveness,cost,complications and contraindications. [3-6] Currently, clinical practice needs non-invasive cost effective assessment tools that can easily predict liver inflammation and advanced liver fibrosis.[7]

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Recently,Shear Wave Elastography(SWE) has emerged as a reliable non-invasive tool in staging liver fibrosis which accurately assesses the liver fibrosis and has eliminated the need of liver biopsy.However,there are certain confounding factors that can alter the yield of TE and have limited its utility including severe inflammation,increased bilirubin,cholestasis, presence of ascites, cost, and lack of skilled operators.[8-9] Lately,certain serum biomarkers and bedside scores have been proposed that are useful in predicting advanced liver fibrosis and are of particular importance as they donot require skilled staff and costly equipment and these scores have the advantage of comprising only two or three laboratory investigations.[10]

Among these non-invasive tools,APRI and FIB-4 are the 2 widely used non-invasive models.[11,12] Several novel non-invasive tools to assess liver fibrosis includeneutrophil-to-lymphocyte ratio (NLR),red cell distribution width (RDW)-to-platelet ratio(RPR) andAST/alanine aminotransferase (ALT) ratio (AAR).[13]Recently, the gamma-glutamyltranspeptidase (GGT) to platelet ratio (GPR)

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had emerged as a novelmarker in the estimation of liver fibrosis .Studies in patients with HBV infection have revealed the superior accuracy of GPR as compared to the classical biomarkers APRI and FIB-4 in this regard in west African cohorts while French studies found GPR to be non-superior to APRI and FIB-4. GPR also failed to show superior accuracy in Brazilian and Chinese cohort.

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The aim our study was to evaluate the diagnostic accuracy of GPR in predicting advanced liver fibrosis in patients with chronic HCV infection in our population.There is little work done in this regard as GPR has not been studied in chronic HCV infection for the prediction of advanced liver fibrosis specifically in our population

**Aim:**

The aim our study was to evaluate the diagnostic accuracy of GPR in predicting advanced liver fibrosis in patients with chronic HCV infection in our population

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**Material and methods:**

This was a cross-sectional prospective study which was carried out in the department of hepato-gastroenterology,Sindh institute of urology and Transplantation from January 2019 to June 2019.All patient with age >18 years and chronic HCV infection were enrolled in the study. The patients with conditions other than chronic HCV infection that can result in enhanced liver injury and inflammation and liver fibrosis such as chronic HBV and HDV co-infection, metabolic conditions such as Non-alcoholic liver disease, Wilson disease, hemochromatosis and patients with hepatocellular carcinoma were excluded from the study. An informed consent was taken from all the patients before enrollment in the study.

All the patients then underwent history taking and physical examination followed by non-invasive laboratory investigations such as complete blood count and liver function tests. These patients then underwentimaging studies including ultrasound abdomen for features of chronic liver disease and Shear Wave Elastography(SWE) to assess fibrosis.

**GPR was calculated using the formula:**

$$GPR = \frac{GGT(/ULN)}{PLT\ count\ (10^9/L)}$$

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**Assessment of Fibrosis staging by SWE:**[14]

Two-dimensional SWE was performed using a LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA) and a convex probe (1–6 MHz) by experienced radiologist with expertise in SWE and have already performed 200 SWE. After the visualization of the right liver lobe through an intercostal space, and a region of interest (ROI) was marked at less than 5 cm below the liver capsule and avoided major vessels. Measurements were taken 10–15 times while the patients held their breath for 5–10 seconds. The result was considered reliable when 10 successful shots and an IQR/median ratio should be less than 30%.

**SWE fibrosis grading:**[14]

Normal-mild fibrosis (F0-F1) -<5.4 kPa

Significant fibrosis (F2)- 5.4-9.9kPa

Advanced fibrosis (F3)- 9.9-12.9kPa

Cirrhosis(F4)- >12.9 kPa

**Statistical analysis:**

The data was entered and analyzed using SPSS.v20.The baseline characteristics of all the patient were recorded. Continuous variables were expressed as Mean ±SD, while categorical variables were expressed as frequency and percentages. Categorical variables were analyzed using Chi square test while student t test was used to analyze continuous variables. GPR was calculated and area under the ROC(AUROC) was obtained to evaluate the diagnostic performance of GPR in predicting advanced fibrosis. A p-value of ≤0.05 was considered statistically significant.

**Results:**

A total of 91 patients were included in the study. Out of 91 patients, 56(61.5%) were males.Mean age was 43.51±12.5 years.The baseline characteristics of the patients are shown in **Table 1** and **2**.Child Pugh Class(CTP) A was noted in 60(65.9%) at the time of presentation while CTP B was noted in 31(64.1%) patients. Most of the patients did not have any comorbidities.At baseline,52(54%) patients had F4 fibrosis as measured by SWE, while 24(37.4%) patients had F2 fibrosis,10(11%) patients had F1 fibrosis and 5(5.5%) had F3 fibrosis. 57(62.6%) patients had ≥F3 fibrosis(advanced fibrosis or cirrhosis).Mean platelet count was 85±47($x10^9$/L).Mean Gamma glutamyl Trans-peptidase was 74±59(IU/L) .Mean GPR was 1.5±2.1.

Comparison of continuous and categorical variables in terms of advanced fibrosis.(**Table 2 and 3**).Area under ROC was obtained for GPR in predicting advanced liver fibrosis(≥F3) was 0.8 (p-≤0.001).(**Figure 1,2**)At a GPR cut off of ≥0.6,the sensitivity was of 94.74%,specificity of 62%,positive predictive value of 80.69%,negative predictive value was of 87.50% and diagnostic accuracy of 82.42% in predicting advanced liver fibrosis.( ≥F3) in patients with chronic hepatitis C .( **Table 4**)

**Discussion:**

Chronicity of liver disease can result in liver fibrosis and cirrhosis due to continued inflammation and non-avoidance of the etiological factor.In order to prevent disease progression, accurate and timely evaluation of degree of liver fibrosis is required. The goal standard test for this purpose is liver parenchymal biopsy but due to its invasiveness and technical expertise it is less often performed.Currently, non-invasive imaging methods such as fibroscan,SWE and TE are used to document the degree of liver fibrosis.However, high cost, the lack of availability of these techniques everywhere, presence of certain confounding factors along with lack of skilled operators can alter the interpretation of these imaging techniques.Currently, non-invasive tool are utilized for assessment of liver fibrosis in addition to these imaging techniques.

**Lemoine et al.**proposed a model of gamma-glutamyltranspeptidase-toplatelet ratio (GPR), as bedside available test useful in predicting the levels of liver fibrosis in chronic hepatitis B(CHB) patients in African populations.[15]Ding R et al. further validated this model in Chinese population.[16]In our study, we have used the GPR ratio in predicting liver fibrosis in chronic HCV population using shear wave elastography to evaluate the degree of fibrosis.

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Our study population included those patients who had chronic HCV infection and who were either under treatment for it with direct acting antivirals(Sofosbuvir/Daclatasvir) or already treated for it with the same regimen.

We categorized the patients into advanced fibrosis(≥F3) and non-advanced fibrosis(≤F2).The application of GPR in the two groups revealed the association of High GPR with advanced fibrosis(p-value≤0.001). Similar results were seen in the previous studies done by Vardar et al in a Turkish cohort,lemoine et al in an African cohort and Ding R et al in a Chinese cohort in CHB patients.[15-17] *Lui et al.* used the GPR cutoff values suggested by lemoine at al in both HBsAg positive and HbsAg negative population in evaluating the degree of fibrosis and found lower sensitivity and specificity of GPR in both the groups.[18]Previously,Nada *et al.*have shown the association of high GPR of ≥0.31 with advanced fibrosis in chronic hepatitis C patients in an Egyptian population with a sensitivity of 92%,specificity of 88%,PPV of 86% and NPV of 91% .[19]In our study,GPR cut off of ≥0.6 was obtained using AUROC. The sensitivity of GPR was 91%, which was comparable to that of the previous studies.However, when compared to the previous studies, the specificity, PPV and NPV of GPR was lower in our studied population with a good diagnostic accuracy of 80% in predicting advanced liver fibrosis(≥F3) in patients with chronic hepatitis C.

There were certain limitations to our study. First of all the small sample size has affected the specificity of the GPR in our population. Secondly, for the assessment of liver fibrosis,SWE was used instead of liver biopsy which is the gold standard due to its invasiveness and high cost.

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The strength of the study lies in the fact that this is the pioneer study from this region which has evaluated the role of GPR in HCV patients.

**Conclusion:**

The diagnostic accuracy of GPR in predicting advanced fibrosis in our population was effective in 82.42% patients.However, studies comprising larger sample size are needed to validate this score before using it as an important non-invasive assessment tool in predicting advanced fibrosis.



**Table 1-Baseline characteristics of the population included in the study(n-91)**

| Study population | n-91(%) |
|---|---|
| Mean age(years±S.D) | 43.5±12.5 |

| | | |
|---|---|---|
| **Gender** | **Male** | 56(61.5) |
| | **Female** | 35(38.5) |
| **Hemoglobin(g/dL)** | | 10.8±2.1 |
| **Total Leucocyte Count(x$10^9$/L)** | | 4.5±2.4 |
| **Platelet Count(x$10^9$/L)** | | 80±52 |
| **Total Bilirubin(mg/dl)** | | 1.3±0.75 |
| **Alkaline Phosphatase(IU/L)** | | 190±187 |
| **Aspartate Transaminase(AST)(IU/L)** | | 59±52 |
| **Alanine Transaminase(ALT)(IU/L)** | | 45±34 |
| **Gamma GlutamylTranspeptidase(GGT)(IU/L)** | | 74±59 |
| **Child Turcotte Pugh Score** | **A** | 60(65.9) |
| | **B** | 31(34.1) |
| **MELD score** | | 10.9±3.4 |
| **Shear wave Elastography(SWE)** | | |
| **F1 Fibrosis** | | 10(11%) |
| **F2 Fibrosis** | | 24(37.4%) |
| **F3 Fibrosis** | | 5(5.5%) |
| **F4 Fibrosis** | | 52(54%) |
| **Esophageal varices** | **Present** | 50(55) |
| | **Absent** | 41(45) |
| **Liver Fibrosis** | **Present** | 57(62.6) |
| | **Absent** | 34(37.4) |
| **GPR(Gamma GlutamylTranspeptidase to Platelet Ratio)** | | 1.5±2.1 |

**Table 2- Comparison of continuous variables in terms of advanced liver fibrosis**

| Variable | No Fibrosis(≤F2) (n-34) Mean ± SD | Advanced Fibrosis(≥F3)(n-57) Mean ± SD | p-value |
|---|---|---|---|
| **Age** | 43.3 ± 10.75 | 43.65 ± 13.5 | **0.889** |
| **Hemoglobin(g/dL)** | 10.6 ±2.5 | 10.9 ± 1.75 | 0.334 |
| **Total Leucocyte Count(x$10^9$/L)** | 5.3± 2.6 | 4.1 ±2.6 | **0.024** |
| **Platelet Count(x$10^9$/L)** | 108.7 ± 66.6 | 62.9 ± 29.5 | **≤0.001** |
| **Total Bilirubin(mg/dl)** | 0.95± 0.62 | 14.5 ±0.75 | **≤0.001** |
| **Alkaline Phosphatase(IU/L)** | 119±44 | 224± 29 | **0.005** |
| **Aspartate Transaminase(AST)(IU/L)** | 35±`19 | 73±60 | **0.001** |
| **Alanine Transaminase(ALT)(IU/L)** | 26±13 | 57±37 | **≤0.001** |
| **Gamma GlutamylTranspeptidase(GGT)(IU/L)** | 48±21 | 90±69 | **0.001** |
| **CTP score** | 5.7± 1.2 | 6.4 ± 1.3 | **0.015** |
| **MELD Score** | 10.2±4.3 | 11.3 ±3.6 | 0.208 |
| **GPR** | 1.0± 2 | 1.8± 2 | **0.04** |

**Table 3- Comparison of categorical variables in terms of advanced liver fibrosis**

| Variable | | Liver fibrosis (≥F3)(n-57) n(%) | No Fibrosis(≤F2)(n-34) n(%) | p-value |
|---|---|---|---|---|
| **Gender** | **Male** | 39(68.4) | 17(50) | 0.08 |
| | **Female** | 18(31.6) | 17(50) | |
| **Esophageal varices** | **Yes** | 43(75.4) | 23(67.6) | 0.421 |
| | **No** | 14(24.6) | 11(32.4) | |
| **CTP score** | **A** | 32(56.1) | 28(82.4) | **0.01** |
| | **B** | 28(43.9) | 6(17.6) | |
| **GPR** | **<0.6** | 54(94.7) | 13(38.2) | **≤0.001** |
| | **≥0.6** | 3(5.3) | 21(61.8) | |

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**Figure 1-*:Area under ROC curve for GPR is 0.8(p-value-≤0.001)***

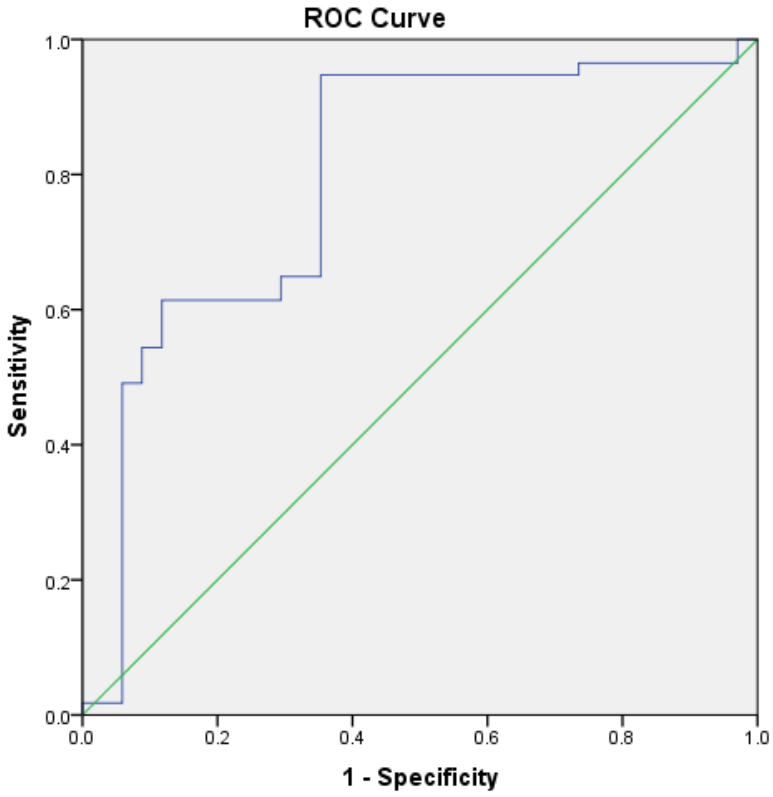


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***Figure 2-Box plot showing association of high* Gamma GlutamylTranspeptidase(GPR) *with advanced liver fibrosis***

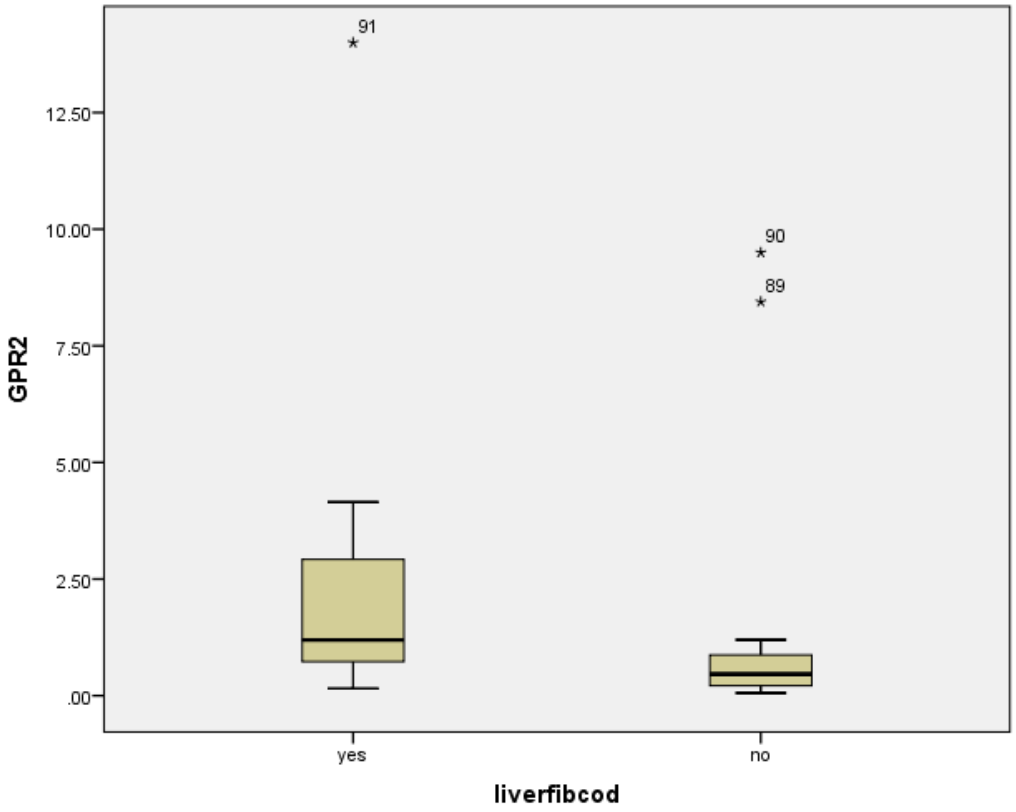


**Table 4-Diagnostic accuracy of Gamma GlutamylTranspeptidase(GPR) in predicting advancliver fibrosis**

| Statistics | Percentage |
|---|---|

| | |
|---|---|
| **Sensitivity** | 94.74% |
| **Specificity** | 62% |
| **Positive Predictive Value** | 80.60% |
| **Negative Predictive Value** | 87.50% |
| **Diagnostic Accuracy** | 82.42% |

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**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we

do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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