**Name of journal:** ***World Journal of*** ***Gastroenterology***

**Manuscript NO: 35755**

**Manuscript Type: ORIGINAL ARTICLE**

***Retrospective Study***

**Value of the gamma-glutamyltranspeptidase-to-platelet ratio in the diagnosis of hepatic fibrosis in patients with chronic hepatitis B**

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**Supported by** Natural Science Fund Project of China, No. 81460301; Natural Fund Key Project of Ningxia, No. NZ15134; Natural Science Found Project of China, No. 81760363.

**Conflict-of-interest statement**: The authors declare that there are no conflicts of interest related to this study.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Unsolicited manuscript

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**Telephone**: +86-136-19511768

**Received:** August 5, 2017

**Peer-review started:** August 7, 2017

**First decision:** September 4, 2017

**Revised:** September 14, 2017

**Accepted:** September 29, 2017

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To investigate the value of the gamma-glutamyltraspeptidase-to-platelet ratio (GPR) in the diagnosis of hepatic fibrosis in patients with chronic hepatitis B (CHB).

***METHODS***

We obtained 390 untreated CHB patients in the study. The GPR, APRI and FIB-4 of all patients were analysed todetermine if these parameter were correlated with age, gender, medical history, liver function (TBil, ALT, AST), GGT, PLT countor hepatic fibrosis stage. The GPR, APRI and FIB-4, as well as the combination of the GPR and APRI or the, GPR and FIB-4 were assessed in different cirrhosis stages were receiver operating characteristic curve analysis to evaluate their value in diagnosing hepatic fibrosis in CHB patients.

***RESULTS***

The GPR, APRI, and FIB-4 were not correlated with CHB patients’ age, gender or disease duration (*P* > 0.05), but all of these parameters were positively correlated with serum ALT, AST, GGT and PLT counts (*P* < 0.01). Additionally, the GPR, APRI and FIB-4 were positively correlated with hepatic fibrosis (*P* < 0.01); the area under the curve values for the GPR in staged F1, F2, F3, and F4 were 0.723, 0.741, 0.826, and 0.833,respectively which were significantly higher than the respective values for the FIB-4 and APRI (F1,0.581, 0.612; F2,0.706, 0.711; F3, 0.73, 0.751; and F4, 0.799, 0.778).The respective diagnostic cutoffpoints for each periodwere 0.402, 0.448, 0.548, and 0.833.The diagnostic sensitivity and specificity were respectively 88.8% and 87.5% in F1, 72.7% and 89.7% in F2, 81.3% and 98.6% in F3, and 80% and 97.4% in F4 when the GPR and APRI were connected in parallel; 86.6% and 90.2%, 78.4% and 96%, 78.6% and 97.4%,and, 73.2% and 97.9% when the GPR and APRI were connected in series; 80.2% and 89%, 65% and 89%, 70.3%and 98.5%, and 78.8% and 96.8% when the GPR and FIB-4 were connected in parallel; and 83.6% and 87.9%, 76.8% and 96.6%, 72.7% and 98%, 74.4% and 97.7%when the GPR and FIB-4 were connected in series.

***CONCLUSION***

The GPR, as a serum diagnostic index of liver fibrosis, is more accurate, sensitive and easy to use than the FIB-4 and APRI, and the GPR can significantly improve the sensitivity and specificity of hepatic fibrosis diagnosis in CHB when combined with the FIB-4 or APRI.

**Key words:** Chronic hepatitis B; Gamma-glutamyltraspeptidase-to-platelet ratio; APRI; FIB-4; Hepatic fibrosis

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**Core tip**: Hepatic fibrosis is a precursor of cirrhosis for chronic hepatitis B patients. Severe hepatic fibrosis and cirrhosis can increase the incidence and mortality of primary liver cancer. Although liver biopsy is still the gold standard for the diagnosis of liver fibrosis it is not widely used as a routine examination because of its invasiveness, high cost and lack of repeatabilitdentification of a simple, convenient, cheap and noninvasive index to assess patients’ hepatic fibrosis level is thus urgently needed. The aim of the present study was to investigate the value of the gamma-glutamyltranspeptidase-to-platelet ratio in the diagnosis of hepatic fibrosis in patients with chronic hepatitis B.

Hu YC, Liu H, Liu XY, Ma LN, Guan YH, Luo X, Ding XC. Value of the gamma-glutamyltranspeptidase-to-platelet ratio in the diagnosis of hepatic fibrosis in patients with chronic hepatitis B. *World J Gastroenterol* 2017; In press

**INTRODUCTION**

Hepatic fibrosis is a precursor of cirrhosis in patients with chronic hepatitis B (CHB), the main cause of CHB[1]. Severe hepatic fibrosis and cirrhosis can increase the incidence and mortality of primary liver cancer[2]. Although liver biopsy is still the gold standard for the diagnosis of liver fibrosis, it is not widely used as a routine examination because of its invasiveness, high cost and lack of repeatability. The APRI and FIB-4 are commonly used in the clinic as two noninvasiveserum models; but their complicated calculation, poor sensitivity and requirement for combination with other indexes for comprehensive evaluation of the degree of hepatic fibrosis actually increase the workload. As an alternative, Transient elastography Fibroscan by imaging is considered to be a good tool for the diagnosis of hepatic fibrosis, but its performance is restricted by several factors, such as diet, obesity, ascites, and rib gap width. In recent years, researchers have tried to identify a simple, convenient, cheap and noninvasive index to assess patients’ hepatic fibrosis level, which could assist in early diagnosis to achieve timely treatment, delay cirrhosis or liver cancer incidence, improve patients’ quality of life, and prolong patients’ survival time.

The gamma-glutamyltraspeptidase-to-platelet ratio (GPR) is a newly reported model for evaluating the grade of hepatic fibrosis, which is of great value in predicting hepaticfibrosis[3-11]. In June 2015, Maud Lemoine *et al*[3] first reported that the GPR could be widely used as an independent predictor to assess hepatic fibrosis in CHB patients in West Africa, and that the sensitivity of the GPR is higher than that of the APRI and FIB-4. In November 2015, Boyd *et al*[9] showed that in patients with HBV and HIV superinfection in France,the GPR can predict the level of significant hepatic fibrosis. In November 2016, Li *et al*[11]repoetedthat GPR was better than other noninvasive serum models in assessing hepatic fibrosis in CHB patients high HBV DNA (≥ 5 log10 copies/mL) and normal or mildly elevated alanine transaminase (ALT) (≤ 2 times upper limit of normal (ULN) in a Chinese population. Moreover, Wang *et al*[4] and Pang *et al*[5] each reported that the GPR could be used as an independent factor in the preoperative evaluation of patients with primary liver cancer caused by CHB. However, likely due to the small sample size, they did not carry out an in-depth stratified pathological study of hepatic fibrosis. Based on these findings, to further explore the value of the GPR in the diagnosis of hepatic fibrosis, We retrospectively analyzed a total of 652 outpatients and inpatients diagnosed with CHB at the General Hospital of Ningxia Medical University from May 2010 to January 2016, among which 390 cases of newly diagnosed CHB patients with complete data without previous therapy were examined with correlation analysis and receiver operating characteristic curve (ROC) analysis. The correlation among patient’s general information, medical history and laboratory examination results were determined.

**MATERIALS AND METHODS**

***Case selection***

There were 652 outpatients and inpatients diagnosed with CHB at the General Hospital of Ningxia Medical University from May 2010 to January 2017. Patients with severe heart, brain or kidney disease; severe infection; super infection with hepatitis A virus, hepatitis C virus, hepatitis D virus, or hepatitis E virus or autoimmune liver disease; heavy drinking; or pregnancy were excluded. The remaining 390 newly diagnosed CHB patients, who did not undergo hepatoprotective, anti-hepatic fibrosis drug or antiviral drug treatments, were selected for the study, which included 283 males and 107 females. All CHB patients in the study had a complete history; data on, HBV serum markers, serum HBV DNA and, liver function; and liver biopsy results. According to the clinical diagnostic criteria in the Guidelines for prevention and treatment of chronic hepatitis B published in 2001, all of the CHB patients were classified and analysedbased on liver function and liver fibrosis.

***Clinical indexes***

The clinical characteristics of the CHB patients in this study, including their medical history HBV serum markers, liver function, blood platelets, serum GGT, hepatic fibrosis indexes (APRI, FIB-4, GPR) and pathological grade of hepatic fibrosis, were statistically analysed.

**HBV serum markers detection:** Chemiluminescence detection was used to assess HBV serum markers.The equipment and reagents were provided by Abbott Company (United States).

**Liver function and GGT detection:** A kinetic method was used to assess liver function and GGT. ACX9 automatic biochemical analyser (Beckman) Company, United States was employed for this purpose.The biochemical test kit was also from Beckman.r-GT normal range was 10-60U/L.

**Platelet detection:** An automatic blood cell analyser was used for platelet detection.The normal range was÷10-30 × 10/L.

**APRI and FIB-4 calculation formulas:** The formulas for calculating the APRI and FIB-4 indexes were as follows: APRI = (AST/ULN) × 100/PLT count (10/L) and FIB-4 = (age × AST)/(PLT count × ALT square root). TBIL normal range was 3.4-17.1 umol/L. AST normal range was 15-40U/L. ALT normal range was 9-50U/L.

**Hepatic tissue pathological fibrosis analysis:** The degree of fibrosis was grade from F1 to F4 according to the guidelines CHB published in 2015.

**Statistical method:** A database of all data was established in Excel2000 and statistically analysed using SPSS17.0 software; the data are expressed as the mean ± SD. Normal distributed data were compared by *t*-test, and non-normally distributed data were compared using the χ2 test. In addition, correlations were determined by Pearson correlation analysis; *P* < 0.05 indicated that the difference was statistically significant. ROC curves were drawn for the GPR, APRI and FIB-4; and the area under the curve (AUC) values were calculated to determine the optimal cut-off points on the ROC curves corresponding to the greatest sum of the sensitivity and specificity and to calculate the rate of diagnostic accuracy. ROC curve, is a graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied. The ROC curve is created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various threshold settings. The true-positive rate is also known as sensitivity, recall or probability of detection in machine learning. The false-positive rate is also known as the fall-out or probability of false alarm and can be calculated as (1 − specificity). The ROC curve is thus the sensitivity as a function of fall-out. In general, if the probability distributions for both detection and false alarm are known, the ROC curve can be generated by plotting the cumulative distribution function of the detection probability in the Y-axis versus the cumulative distribution function of the false-alarm probability on the x-axis.

The value of the GPR, APRI, and FIB-4, as well as the combination of the GPRand APRI or the GPR and FIB-4, in the diagnosis of CHB associated liver fibrosis was evaluated according to the test results. A difference was statistically significant at *P* < 0.05.

**RESULTS**

***Correlation analysis of GPR, APRI and FIB-4 and clinical data***

A total of 390 patients with CHB were enrolled in this study, including 283 males and 107 females, with a mean age of 38.94 ± 11.39 years. Pearson correlation analysis showed that the GPR, APRI and FIB-4 were not associated with the CHB patients’ age, genderor the dieasecourse but were associated with TBil, AST, ALT, GGT, and PLT counts(*P* < 0.01; Table 1).

***Correlation analysis of GPR, APRI and FIB-4 and CHB liver function classification***

To investigate the relationships between the GPR, APRI and FIB-4 and CHB disease, the CHB patients were divided into three groups according to the patients’ condition: 244 mild cases, 57 moderate cases and 80 severe cases.Spearman correlation analysis showed that the GPR, APRI and FIB-4 were positively related to the grade of the CHB patients’ liver function (*P* < 0.01; Table 2).

***Correlation analysis of GPR, APRI and FIB-4 and hepatic fibrosis stages of CHB***

According to the liver biopsy results, the degrees of hepatic fibrosis was divided into F1 to F4, and the Spearman rank correlation analysis showed that theGPR, APRI and FIB-4 were positively correlated with the stage of hepatic fibrosis (*P* < 0.01; Table 3).

***ROC analysis of GPR, APRI and FIB-4 in diagnosis of hepatic fibrosis in CHB***

The AUC values for the GPR in F1, F2, F3, and F4 were 0.723, 0.741, 0.826, and 0.833, respectively which were significantly higher than of the values for the FIB-4 and APRI (F1, 0.581 and 0.612; F2, 0.706 and 0.711; F3, 0.73 and 0.751; and F4, 0.799 and 0.778).The diagnostic cut-off points for each period were respectively 0.402, 0.448, 0.548, and 0.833.The diagnostic sensitivity and specificity had a gradually increasing trendwith the aggravation of hepatic fibrosis. In particular,the diagnostic sensitivity and specificity were 88.8% and 87.5% in F1, 72.7% and 89.7% in F2, 81.3% and 98.6% in F3,and 80% and 97.4% in F4 when GPR andAPRI were connected in parallel;86.6% and 90.2 %, 78.4% and 96%, 78.6% and 97.4%, and 73.2% and 97.9%,respectively, when GPR and APRI were connected in series; 80.2%, 89%, 65%, 89%, 70.3%, 98.5%, 78.8%, 96.8% when GPR and APRI were connected in parallel; and 83.6% and 87.9%, 76.8% and 96.6%, 72.7% and 98%, and 74.4% and 97.7%, respectively, when GPR and APRI were connected in series (Table 4).

**DISCUSSION**

CHB is an inevitable stage for patients with HBV infection, developing from hepatic fibrosis to cirrhosis and leading to chronic liver failure and HBV-related hepatocellular carcinoma. Assessment of the degree of hepatic fibrosis and the progression of CHB is important in determining the treatment strategy for and prognosis of CHB patients[12,13]. Currently, liver biopsy is still the gold standard for evaluating the degree of hepatic fibrosis in certain high-risk liver cirrhosis and liver cancer patients and is an indicator for clinicians to guide patients, and especially CHB patients with mildly elevated AIT, to start antiviral therapy in a timely fashion. However, as an invasive examination, liver biopsy can cause serious complications[14-18]; thus ,it is not preferred, by most CHB patients in the clinic. Given this situation, strategies for avoiding and reducing the frequency of liver biopsy and obtaining reliable liver pathological data are urgently needed[19-21].The APRI and FIB-4 were developed as serum models in recent years and have been widely used in the assessment of hepatic fibrosis classification[22-26]. However, for patients with severe liver inflammation, the hepatic fibrosis results yielded by the APRI and FIB-4 are variable. Therefore, these indexes are predominantly used for hepatic fibrosis evaluation in patients with mildly abnormal liver function before treatment.Recently, Maud Lemoine *et al*[3] analysed combination of GGT and PLT counts and found that the GPR was significantly better than the FIB-4 and APRI in predicting significant liver fibrosis. However, due to the sample size, the depth of the study was limited. To further explore the value of applying the GPR, a correlation analysis of 390 newly diagnosed CHB patients who were not treated with hepatoprotective therapy, anti-liver fibrosis drugs or antiviral drugs to assess the correlation of the GPR, APRI and FIB-4 with age, gender, medical history, liver function (TBil, ALT, AST), GGT, PLT count and liver tissue fibrosis stage. The results showed that the serum GPR, APRI and FIB-4 had no correlation with the CHB patients’ age, gender or duration, but were correlated with TBil, AST, ALT, GGT, and PLT count.Furthermore,the GPR, APRI and FIB-4 were positively associated with liver function and liver tissue pathological grade (*P* < 0.01).These results indicate that the GPR, as well as the APRI and FIB-4, cannot only can be used as an index to judge the severity of acute liver injury, but also has potential value in evaluating the degree of hepatic fibrosis in patients with CHB.

To further analyse the value of the GPR for the diagnosis of hepatic fibrosis, we performed ROC analysis of the GPR, APRI and FIB-4 according to the stage of liver fibrosis. The results showed that the AUC values for GPR in F1, F2, F3, and F4 were 0.723, 0.741, 0.826 and 0.833, respectively, which were significantly better than the values for the APRI and FIB-4 (F1, 0.581 and 0.612; F2, 0.706 and 0.711; F3, 0.73 and 0.751; and F4, 0.799 and 0.778). The diagnostic cutoff points for each period were respectively 0.402, 0.448, 0.548, and 0.833.The diagnostic sensitivity and specificity showed a gradually increasing trend with aggravation of liver fibrosis. Thus, the combined detection of the GPR and FIB-4 or the GPR and APRI could improve the sensitivity and specificity the diagnosis of CHB-associated hepatic fibrosis in each stage. These results indicate that the GPR can accurately differentiate the stages of hepatic fibrosis in CHB patients, and that the diagnostic value of the GPR is superior to those of the APRI and FIB-4.Thus, the combined detection of the GPR and FIB-4 or the GPR and APRI can significantly improve the diagnostic sensitivity and specificity of hepatic fibrosis diagnosis in CHB. However, serum GGT levels may increase slightly to moderately in acute hepatitis, chronic active hepatitis, decompensated cirrhosis, obstructive jaundice, alcoholism and hepatocellular carcinoma cases[16,27-28], which may lead to variation of the GPR. Due to the sample size in this study, we did not further stratify the cohort by liver function. The value of the GPR in evaluating the degree of hepatic fibrosis in CHB patients with different levels of liver function is thus still unknown, so further research involving stratified analyses and verification of our results with increased sample sizes is needed.

**ARTICLE HIGHLIGHTS**

***Research background***

Hepatic fibrosis is a precursor of cirrhosis in patients with chronic hepatitis B (CHB), the main cause of CHB. Severe hepatic fibrosis and cirrhosis can increase the incidence and mortality of primary liver cancer. Hepatic fibrosis is a precursor of cirrhosis for chronic hepatitis B patients. Looking for a non-invasive, simple, easy to operate, cheap way to assess liver fibrosis is very important.

Liver biopsy is still the gold standard for the diagnosis of liver fibrosis, its invasiveness, high cost and lack of repeatability. As an alternative, Transient elastography Fibroscan by imaging is considered to be a good tool for the diagnosis of hepatic fibrosis, but its performance is restricted by several factors.

Researchers have tried to identify a simple, convenient, cheap and noninvasive index to assess patients’ hepatic fibrosis level, which could assist in early diagnosis to achieve timely treatment, delay cirrhosis or liver cancer incidence, improve patients’ quality of life, and prolong patients’ survival time.

***Research motivation***

At present, liver biopsy is still the gold standard for the diagnosis of liver fibrosis, liver biopsy can cause serious complications; thus, it is not preferred, by most CHB patients in the clinic. Though our research to identify a simple, convenient, cheap and noninvasive index to assess patients’ hepatic fibrosis level. In the future, patients can save money and avoid pain, meanwhile, accurate assessment hepatic fibrosis level.

***Research objectives***

Though our research to identify a simple, convenient, cheap and noninvasive index to assess patients’ hepatic fibrosis level. In the future, in our clinical work, assessing the level of liver fibrosis in patients is faster and easier, effectively reducing the liver biopsy caused by a series of complications.

***Research methods***

There were 652 outpatients and inpatients diagnosed with CHB at the General Hospital of Ningxia Medical University. Patients with severe heart, brain or kidney disease; severe infection; superinfectionwith hepatitis A virus, hepatitis C virus, hepatitis D virus, or hepatitis E virus or autoimmune liver disease; heavy drinking; or pregnancy were excluded. The remaining 390 newly diagnosed CHB patients, who did not undergo hepatoprotective, anti-hepatic fibrosis drug or antiviral drug treatments, were selected for the study. We chose multiple noninvasive indicators for comparison, to illustrate that GPR is an optimal noninvasive index. Meanwhile, the sample size is large to enhance persuasiveness. Statistically analysed using SPSS17.0 software; the data are expressed as the mean ± SD. Normal distributed data were compared by t-test, and non-normally distributed data were compared using the Chi-square test.In addition, correlations were determined by Pearson correlation analysis; *P* < 0.05 indicated that the difference was statistically significant.

***Research results***

The research findings GPR is a simple, convenient, cheap and noninvasive index to assess patients’ hepatic fibrosis level, and the GPR can significantly improve the sensitivity and specificity of hepatic fibrosis diagnosis in CHB when combined with the FIB-4 or APRI. This study concludes the history of invasive method of assessing the liver fibrosis.

***Research conclusions***

The gamma-glutamyltraspeptidase-to-platelet ratio (GPR) is a newly reported model for evaluating the grade of hepatic fibrosis, which is of great value in predicting hepatic fibrosis. In June 2015, Maud Lemoine et al. first reported that the GPR could be widely used as an independent predictor to assess hepatic fibrosis in CHB patients in West Africa, and that the sensitivity of the GPR is higher than that of the APRI and FIB-4. GPR is a simple, convenient, cheap and noninvasive index to assess patients’ hepatic fibrosis level, and the GPR can significantly improve the sensitivity and specificity of hepatic fibrosis diagnosis in CHB when combined with the FIB-4 or APRI. In the future, in our clinical work, assessing the level of liver fibrosis in patients is faster and easier, effectively reducing the liver biopsy caused by a series of complications.

***Research perspectives***

In the daily work, it is required looking for more noninvasive, convenient and efficient methods to assess the level of liver fibrosis in patients with chronic hepatitis B.

**REFERENCES**

1 **Liang P**, Zu J, Yin J, Li H, Gao L, Cui F, Wang F, Liang X, Zhuang G. The independent impact of newborn hepatitis B vaccination on reducing HBV prevalence in China, 1992-2006: A mathematical model analysis. *J Theor Biol* 2015; **386**: 115-121 [PMID: 26375372 DOI: 10.1016/j.jtbi.2015.08.030]

2 **Wu JF**, Chang MH. Natural history of chronic hepatitis B virus infection from infancy to adult life - the mechanism of inflammation triggering and long-term impacts. *J Biomed Sci* 2015; **22**: 92 [PMID: 26487087 DOI: 10.1186/s12929-015-0199-y]

3 **Lemoine M**, Shimakawa Y, Nayagam S, Khalil M, Suso P, Lloyd J, Goldin R, Njai HF, Ndow G, Taal M, Cooke G, D'Alessandro U, Vray M, Mbaye PS, Njie R, Mallet V, Thursz M. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut* 2016; **65**: 1369-1376 [PMID: 26109530 DOI: 10.1136/gutjnl-2015-309260]

4 **Lemoine M**, Thursz M, Mallet V, Shimakawa Y. Diagnostic accuracy of the gamma-glutamyl transpeptidase to platelet ratio (GPR) using transient elastography as a reference. *Gut* 2017; **66**: 195-196 [PMID: 26921348 DOI: 10.1136/gutjnl-2016-311554]

5 **Park YE**, Kim BK, Park JY, Kim DY, Ahn SH, Han KH, Han S, Jeon MY, Heo JY, Song K, Kim SU. Gamma-glutamyl transpeptidase-to-platelet ratio is an independent predictor of hepatitis B virus-related liver cancer. *J Gastroenterol Hepatol*2017; **32**: 1221-1229 [PMID: 27859587 DOI: 10.1111/jgh.13653]

6 **Wang WL,** Zheng XL, Zhang ZY, Zhou Y, Hao J, Tang G, Li O, Xiang JX, Wu Z, Wang B. Preoperative g-glutamyltranspeptidase toplateletratio (GPR) is an independent prognostic factor forHBV-related hepatocellular carcinoma aftercurative hepatic resection. *Medicine* 2016; **95**: 27 (e4087) [PMID: 27399101 DOI: 10.1097/MD.0000000000004087]

7 **Pang Q**, Bi JB, Wang ZX, Xu XS, Qu K, Miao RC, Chen W, Zhou YY, Liu C. Simple models based on gamma-glutamyl transpeptidase and platelets for predicting survival in hepatitis B-associated hepatocellular carcinoma. *Onco Targets Ther* 2016; **9**: 2099-2109 [PMID: 27110127 DOI: 10.2147/OTT.S101465]

8 **Li Q**, Song J, Huang Y, Li X, Zhuo Q, Li W, Chen C, Lu C, Qi X, Chen L. The Gamma-Glutamyl-Transpeptidase to Platelet Ratio Does not Show Advantages than APRI and Fib-4 in Diagnosing Significant Fibrosis and Cirrhosis in Patients With Chronic Hepatitis B: A Retrospective Cohort Study in China. *Medicine* (Baltimore) 2016; **95**: e3372 [PMID: 27100421 DOI: 10.1097/MD.0000000000003372]

9 **Boyd A,** Bottero J, Lacombe K. Theγ-glutamyltranspeptidase-to-plateletratio as a predictor of liverfibrosisinpatients co-infectedwith HBV and HIV. Gut 2016; 65: 718-720 [DOI: 10.1136/gutjnl-2015-310607]

10 **Schiavon LL**, Narciso-Schiavon JL, Ferraz MLG, Silva AEB, Carvalho-Filho RJ. The γ-glutamyl transpeptidase to platelet ratio (GPR) in HBV patients: just adding up? *Gut* 2017; **66**: 1169-1170 [PMID: 27534672 DOI: 10.1136/gutjnl-2016-312658]

11 **Li Q**, Lu C, Li W, Huang Y, Chen L. Globulin-platelet model predicts significant fibrosis and cirrhosis in CHB patients with high HBV DNA and mildly elevated alanine transaminase levels. *Clin Exp Med* 2017; Epub ahead of print [PMID: 28884309]

12 **Trépo C**, Chan HL, Lok A. Hepatitis B virus infection. *Lancet* 2014; **384**: 2053-2063 [PMID: 24954675 DOI: 10.1016/S0140-6736(14)60220-8]

13 **Imamura H**, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makuuchi M. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 2003; **38**: 200-207 [PMID: 12547409 DOI: 10.1016/S0168-8278(02)00360-4]

14 **Sorbi D**, Boynton J, Lindor KD. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *Am J Gastroenterol* 1999; **94**: 1018-1022 [PMID: 10201476 DOI: 10.1111/j.1572-0241.1999.01006.x]

15 **McGill DB**, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology* 1990; **99**: 1396-1400 [PMID: 2101588 DOI: 10.1016/0016-5085(90)91167-5]

16 **Shukla A**, Kapileswar S, Gogtay N, Joshi A, Dhore P, Shah C, Abraham P, Bhatia S. Simple biochemical parameters and a novel score correlate with absence of fibrosis in patients with nonalcoholic fatty liver disease. *Indian J Gastroenterol*2015; **34**: 281-285 [PMID: 26341864 DOI: 10.1007/s12664-015-0580-5]

17 **Liaw YF**, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S; Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263-283 [PMID: 19669255 DOI: 10.1007/s12072-008-9080-3]

18 **Lok AS,** McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009; 50: 661-662 [DOI: 10.1002/hep.23190]

19 **Chen J**, Liu C, Chen H, Liu Q, Yang B, Ou Q. Study on noninvasive laboratory tests for fibrosis in chronic HBV infection and their evaluation. *J Clin Lab Anal* 2013; **27**: 5-11 [PMID: 23292737 DOI: 10.1002/jcla.21554]

20 **Lee IC**, Chan CC, Huang YH, Huo TI, Chu CJ, Lai CR, Lee PC, Su CW, Hung HH, Wu JC, Lin HC, Lee SD. Comparative analysis of noninvasive models to predict early liver fibrosis in hepatitis B e Antigen-negative Chronic Hepatitis B. *J Clin Gastroenterol* 2011; **45**: 278-285 [PMID: 20505530 DOI: 10.1097/MCG.0b013e3181dd5357]

21 **Pinto J**, Matos H, Nobre S, Cipriano MA, Marques M, Pereira JM, Gonçalves I, Noruegas MJ. Comparison of acoustic radiation force impulse/serum noninvasive markers for fibrosis prediction in liver transplant. *J Pediatr Gastroenterol Nutr* 2014; **58**: 382-386 [PMID: 24164902 DOI: 10.1097/MPG.0000000000000226]

22 **Sebastiani G**, Halfon P, Castera L, Mangia A, Di Marco V, Pirisi M, Voiculescu M, Bourliere M, Alberti A. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. *Aliment Pharmacol Ther* 2012; **35**: 92-104 [PMID: 22035045 DOI: 10.1111/j.1365-2036.2011.04897.x]

23 **Arora A**, Sharma P. Non-invasive Diagnosis of Fibrosis in Non-alcoholic Fatty Liver Disease. *J Clin Exp Hepatol* 2012; **2**: 145-155 [PMID: 25755423 DOI: 10.1016/S0973-6883(12)60103-0]

24 **Xiao G**, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. *Hepatology* 2015; **61**: 292-302 [PMID: 25132233 DOI: 10.1002/hep.27382]

25 **Sumida Y**, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, Eguchi Y, Suzuki Y, Aoki N, Kanemasa K, Fujita K, Chayama K, Saibara T, Kawada N, Fujimoto K, Kohgo Y, Yoshikawa T, Okanoue T; Japan Study Group of Nonalcoholic Fatty Liver Disease (JSG-NAFLD). Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. *BMC Gastroenterol* 2012; **12**: 2 [PMID: 22221544 DOI: 10.1186/1471-230X-12-2]

26 **Shah AG**, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1104-1112 [PMID: 19523535 DOI: 10.1016/j.cgh.2009.05.033]

27 **Elawdi HA**, Franzini M, Paolicchi A, Emdin M, Fornaciari I, Fierabracci V, De Simone P, Carrai P, Filipponi F. Circulating gamma-glutamyltransferase fractions in cirrhosis. *Liver Int* 2014; **34**: e191-e199 [PMID: 24387676 DOI: 10.1111/liv.12455]

28 **Eminler AT**, Irak K, Ayyildiz T, Keskin M, Kiyici M, Gurel S, Gulten M, Dolar E, Nak SG. The relation between liver histopathology and GGT levels in viral hepatitis: more important in hepatitis B. *Turk J Gastroenterol* 2014; **25**: 411-415 [PMID: 25254524 DOI: 10.5152/tjg.2014.3693]

**P-Reviewer:** **Sirin G,** Jin B, He ST, Komatsu H, Koch TR, Ikura Y, Tziomalos K **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C, C

Grade D (Fair): D, D

Grade E (Poor): 0



**A**



**B**



 **C**



D

**Figure 1 ROC curves of GPR, APRI and FIB-4 for liver fibrosis.** A: F = 1; B: F = 2; F = 3; F = 4.

**Table 1 Correlation of the GPR, APRI and FIB-4 () with the baseline characteristics of the patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Factor** |  | **GPR** | **APRI FIB-4** |
| **r** | **r r P** |
| TBIL (μmol/L) | 22.70 ± 28.53 | 0.275  | 0.205 0.258 < 0.01 |
| AST (IU/L)  | 81.71 ± 146.11 | 0.183 | 0.644 0.834 < 0.01 |
| ALT (IU/L)  | 125.71 ± 246.43 | 0.113 | 0.547 0.764 < 0.01 |
| GGT (IU/L) | 225.21 ± 1008.88 | 0.779 | 0.222 0.235 < 0.01 |
| PLT count (109/L)GPR  | 160.82 ± 66.610.73 ± 1.79 | -0.285 1 | -0.285 -0.26 < 0.010.385 0.255 < 0.01 |
| APRI | 65.44 ± 140.77 | 0.385 | 1 0.847 < 0.01 |
| FIB-4 | 417.93 ± 1367.85 | 0.255 | 0.847 1 < 0.01 |

TBIL: Total bilirubin; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyltranspeptidase; PLT: Platelet; GPR: the gamma-glutamyltranspeptidase-to-platelet ratio; APRI: (AST)-to-platelet ratio index;fibrosis index based on the 4 factor.

**Table 2 Correlation of the GPR, APRI and FIB-4 (mean ± SD) with the liver function severity classification**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter**  | ***n***  | **GPR** | **APRI** | **FIB-4** |
| Liver function grade mild |  244 | 0.50 ± 0.92 | 30.71 ± 76.73 | 68.39 ± 126.12 |
| r |  | 0.213 | 0.091 | 0.219 |
| *P* value |  | ＜0.01 | ＜0.01 | ＜0.01 |
| Moderate |  57 | 1.57 ± 3.59 | 101.20 ± 202.09 | 511.23 ± 1234.61 |
| r |  | 0.11 | 0.16 | 0.191 |
| P |  | ＜0.01 | ＜0.01 | ＜0.01 |
| Severe |  80 | 0.84 ± 1.74 | 145.90 ± 192.51 | 1417.54 ± 2544.58 |
| r |  | 0.016 | 0.563 | 0.720 |
| *P* value |  | ＜0.01 | ＜0.01 | ＜0.01 |

**Table 3 Correlation of the GPR, APRI and FIB-4 (mean + SD) with the fibrosis grade**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter**  | **N**  | **GPR** | **APRI** | **FIB-4** |
| Fibrosis grade |  |  |  |  |
| F1 | 122 | 0.54 ± 1.23 | 53.18 ± 134.37 | 331.04 ± 1152.78 |
| r |  | 0.077 | 0.089 | 0.077 |
| P |  | < 0.01 | < 0.01 | < 0.01 |
| F2 | 52 | 0.66 ± 2.02 | 47.55 ± 120.04 | 278.98 ± 1053.17 |
| r |  | 0.223 | 0.069 | 0.037 |
| P |  | < 0.01 | < 0.01 | < 0.01 |
| F3 | 61 | 0.60 ± 0.95 | 61.15 ± 152.26 | 406.94 ± 1580.52 |
| r |  | 0.278 | 0.226 | 0.183 |
| P |  | < 0.01 | < 0.01 | < 0.01 |
| F4 | 41 | 0.52 ± 0.85 | 49.43 ± 125.04 | 287.50 ± 1092.13 |
| r |  | 0.186 | 0.121 | 0.064 |
| p |  | < 0.01 | < 0.01 | < 0.01 |

**Table 4 GPR, APRI and FIB-4 results relative to hepatic fibrosis stage (F1, F2, F3, andF4 in CHB patients**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Parameter** | **GPR** | **APRI** | **FIB-4** | **GPR+APRI(in parallel)** | **GPR+APRI(in series)** | **GPR+FIB-4(in parallel)** | **GPR+FIB-4(in series)** |
| F1 | AUC | 0.723  | 0.581 | 0.612 | — | — | — | — |
| cutoff | 0.448 | 0.166 | 0.201 | — | — | — | — |
| sensitivity | 90.6% | 88.8% | 62.1% | 88.8% | 86.8% | 80.2% | 83.6% |
| specificity | 54.2% | 87.5% | 66.3% | 87.5% | 90.2% | 89% | 87.9% |
| F2 | AUC | 0.741 | 0.706 | 0.711 | — | — | — | — |
| cutoff | 0.402 | 0.361 | 0.4 | — | — | — | — |
| sensitivity | 57.1% | 75.8% | 47.4% | 72.7% | 78.4% | 65% | 76.8% |
| specificity | 89.5% | 92.5% | 89.3% | 89.7% | 96% | 89% | 96.6% |
| F3 | AUC | 0.826 | 0.73 | 0.751 | — | — | — | — |
| cutoff | 0.548 | 0.496 | 0.44 | — | — | — | — |
| sensitivity | 74.1% | 70.6% | 64.7% | 81.3% | 78.6% | 70.3% | 72.7% |
| specificity | 91.8% | 90.5% | 88% | 98.6% | 97.4% | 98.5% | 98% |
| F4 | AUC | 0.833 | 0.799 | 0.778 | — | — | — | — |
| cutoff | 0.591 | 0.538 | 0.503 | — | — | — | — |
| sensitivity | 83.2% | 74% | 75.4% | 80% | 73.2% | 78.8% | 74.4% |
| specificity | 96.5% | 95.4% | 94.5% | 97.4% | 97.9% | 96.8% | 97.7% |

Both parameters are met simultaneously; In series: Two parameters have a satisfaction.