

RESEARCH ARTICLE

The value of platelet count in evaluating the degree of liver fibrosis in patients with chronic hepatitis B

Li-Kun Zhong¹ | Guo Zhang¹ | Shuang-Yan Luo¹ | Wu Yin² | Huai-Yu Song¹ 

¹Department of Gastroenterology, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China

²Department of Pathology, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China

Correspondence

Huai-Yu Song, Department of Gastroenterology, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, China.
Email: huaiyu_song@163.com

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Abstract

Objective: To investigate the value of platelet count in evaluating the degree of liver fibrosis in patients with chronic hepatitis B (CHB).

Methods: A total of 158 CHB patients who underwent liver biopsy in our hospital were included, and the clinical characteristics of these patients were retrospectively analyzed. The diagnostic values of platelet count, aspartate aminotransferase-to-platelet ratio index (APRI), and the fibrosis index based on four factors (FIB-4) for significant fibrosis ($F \geq 2$) and early cirrhosis ($F = 4$) stages in CHB patients were assessed by the use of receiver operating characteristic (ROC) analysis.

Results: The median (F0: 221.0; F1: 210.0; F2: 188.0; F3: 171.0; and F4: 155.5) and mean rank (F0: 120.4; F1: 100.1; F2: 82.2; F3: 67.9; and F4: 49.5) of platelet count decreased along the aggravation of fibrosis (F0-F4). The areas under the ROC curve for the platelet count in diagnosis of significant fibrosis stage was 0.70, which had no significant difference with FIB-4 (0.73) and APRI (0.68) in diagnostic efficacy ($P = .428$). The areas under the ROC curve of platelet count in diagnosis of early cirrhosis were 0.72, which had no significant difference with FIB-4 (0.76) and APRI (0.68) ($P = .094$).

Conclusion: The platelet count, as a simple and non-invasive index, could evaluate the degree of liver fibrosis in CHB individuals. At the same time, the diagnostic efficiency of platelet count to evaluate the significant liver fibrosis and early cirrhosis is comparable to FIB-4 and APRI.

KEYWORDS

chronic hepatitis B, liver cirrhosis, liver fibrosis, platelet count

1 | INTRODUCTION

Chronic hepatitis B (CHB) is a major public health problem, affecting about 240 million people all over the world.¹ Chronic hepatitis B virus (HBV) is the main potentially life-threatening factor which could bring out cirrhosis and liver cancer. Patients, with HBV infection, are likely to develop into liver fibrosis, which can lead to

cirrhosis, further severe complications, and hepatocellular carcinoma (HCC).^{2,3} Therefore, the early diagnosis of liver fibrosis or cirrhosis is crucial to the prediction of HBV infection, the guidance of treatment, and the judgment of prognosis.⁴

Liver biopsy is still the gold standard in the assessment of liver fibrosis, but non-invasive methods such as serological indicators and ultrasound imaging techniques have gained its popularity

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with the character of risk-free, non-invasive, and repeatable.^{5,6} However, elastic ultrasonic equipment such as FibroScan and FibroTouch is not equipped in many primary hospitals. Biochemical markers, which are easily to inspect, calculate, and repeat, are also used to identify patients with CHB. Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and the fibrosis index based on four factors (FIB-4) are two commonly used biochemical markers which have been reported could predict hepatic fibrosis in large cohorts of patients infected with chronic hepatitis C virus (HCV).⁷⁻⁹ In addition, APRI and FIB-4 are also two biochemical markers for HBV which take AST, alanine aminotransferase (ALT), platelet count, and patient age into account.^{7,10} However, APRI and FIB-4, with the requirement for combining with other indexes, actually increase the workload. If there is simpler serological index to investigate liver fibrosis, the patients could get early detection and treatment in the primary hospital.

Platelets were firstly described and recommended as an object for further study in 1865 by Max Schultz.¹¹ Previous studies always focus on the function of platelets in mediating hemostasis. While a growing body of evidence proved platelets not only play a role in hemostasis but also served as an important factor in liver disease. Platelet could be an indicator in diagnosing liver inflammation because the reduced platelet activation reflected the progresses of chronic hepatitis and even cancer.¹² Nurden AT and Ripoche J et al^{13,14} also have identified that platelets served as an active player in liver inflammation from the studies of rodent and in vitro researches.

In addition, platelets play a role in the liver fibrosis and cirrhosis. Hepatocyte growth factor released by platelets contributed to alleviate the fibrotic process, and platelet transfusion improved residual liver function in patients with cirrhosis.¹⁵ Besides, reduced platelets due to portal hypertension and hypersplenism could be recognized in patients with cirrhosis.¹⁶ Therefore, platelets might suppress fibrogenesis and drive hepatic mitogenesis during the process of liver fibrosis, but also could diminish hepatocyte regeneration and exacerbate fibrosis under certain conditions.¹⁷

In the present study, we collected the data about liver biopsy in patients with CHB to evaluate whether platelets have a diagnosis value for liver fibrosis. At the same time, the collected data were compared with serological index APRI and FIB-4 to evaluate the predictive value of platelet count.

2 | PARTICIPANTS AND METHODS

2.1 | Participants

A total of 158 patients with CHB who underwent percutaneous liver biopsy at the People's Hospital of Guangxi Zhuang Autonomous Region from October 2012 to October 2018 were collected and studied. The diagnostic criteria of CHB were based on the Chronic Hepatitis B Prevention Guide issued in 2010 by Chinese Medical Association. The research was approved by the ethics committee

of People's Hospital of Guangxi Zhuang Autonomous Region (NO. KYLC-2016-02). Signed informed consent was obtained from all individual participants. Inclusion criteria for patients were as follows: (a) with HBsAg positive for more than 6 months; (b) aged from 18 to 70 years old; and (c) without a history of critical illness. Exclusion criteria for patients were as follows: (a) with other hepatitis virus infection; (b) with alcoholic liver disease; (c) with any disease related to fibrosis (such as connective tissue diseases, chronic obstructive pulmonary disease, kidney failure, tumors, and so on); (d) have received any anti-fibrosis therapy; and (e) pregnancy.

2.2 | Laboratory examinations

The common laboratory examinations were taken, including blood routine examination, liver function, HBV markers, HBV-DNA, and coagulation function. The platelet count was showed in the blood routine examination.

2.3 | Non-invasive serological indicators for liver fibrosis

Aspartate aminotransferase-to-platelet ratio index was calculated based on the ratio of AST and platelet, and the formulae were presented as $(AST (U/L)/ ULN) \times 100/ \text{platelet} (10^9/L)$.⁷ FIB-4 was calculated based on ALT, AST, platelet count, and age, and the formulae were presented as $(\text{age (years)} \times AST (U/L))/ (\text{platelets} (10^9/L) \times ALT (10^9/L)^{1/2})$.¹⁰

2.4 | Pathological examination of hepatic tissue

The pathological results of hepatic tissue were considered as the gold standard of hepatic fibrosis stage.⁶ Liver biopsy was taken by the guidance of B-ultrasound. Percutaneous liver biopsy was performed by 18 G biopsy needle, and two tissue samples with the length of about 2 cm were taken and then fixed by 10% formalin. The stages of liver fibrosis were classified according to the Metavir scoring system as following: F0, no fibrosis; F1, mild fibrosis in portal area without septum; F2, moderate fibrosis in portal area with a few septa; F3, severe fibrosis with numerous septa without cirrhosis; and F4, cirrhosis.^{18,19}

2.5 | Statistical analysis

Frequency and percentage were used to represent categorical variable. Mean and standard deviation or median and interquartile range were used to signify continuous variable. Analysis of variance was adopted to compare mean, which would be tested by Kruskal-Wallis test when it did not satisfy the test of normality and homogeneity of variance. Non-parametric statistical methods were used to test the

trend at different average stages. Area under the receiver operating characteristic (ROC) curve of each index was used to compare the diagnostic efficacy of each diagnostic method. All analyses were performed using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15; StataCorp LLC), and statistical significance was defined as $P < .05$.

3 | RESULTS

3.1 | Study population

A total of 158 patients, who infected with CHB and underwent percutaneous liver biopsy from October 2012 to October 2018 in our hospital, were enrolled in the study. Table 1 showed the characteristics of all patients including age, gender, pathological fibrosis, ALT, AST, platelets, and APRI.

3.2 | The average of platelet count, APRI, and FIB-4 in different pathological stages

The Kruskal-Wallis test was used to test the average of platelet, APRI, and FIB-4, because platelet did not meet the normality test, neither APRI nor FIB-4 meet the homogeneity test of variance and normality test. Meanwhile, the non-parametric statistical method was used to test the trend of the above indicators in different stages of fibrosis. As shown in Table 2, the average of platelet count, APRI,

TABLE 1 The characteristics of patients (n = 158)

Variables	Patients with CHB (n = 158)
Gender	
Male	118 (74.7%)
Female	40 (25.3%)
Age, mean (SD)	39.22 (9.50)
Pathological fibrosis	
F0	5 (3.2%)
F1	37 (23.4%)
F2	55 (34.8%)
F3	39 (24.7%)
F4	22 (13.9%)
ALT (U/L), median (IQR)	49.00 (28.00, 83.00)
AST (U/L), median (IQR)	37.00 (28.00, 53.00)
Platelets ($10^9/L$), median (IQR)	181.00 (152.00, 222.00)
APRI, median (IQR)	0.51 (0.35, 0.92)
FIB-4, median (IQR)	1.24 (0.81, 1.82)

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; CHB, chronic hepatitis B; FIB-4, fibrosis index based on four factors; IQR, interquartile range; SD, standard deviation.

TABLE 2 The differences of platelet count, APRI, and FIB-4 based on different pathological stages of liver fiber

Index	F0 (n = 5)	F1 (n = 37)	F2 (n = 55)	F3 (n = 39)	F4 (n = 22)	P value ^a	P for trend ^b
Platelet ($10^9/L$), median (IQR)	221.0 (206.0-228.0)	210.0 (171.0-272.0)	188.0 (149.0-240.0)	171.0 (144.0-195.0)	155.5 (131.0-173.0)	<.001	<.001
Mean rank	120.4	100.1	82.2	67.9	49.5		
APRI, median (IQR)	0.51 (0.26-0.57)	0.41 (0.27-0.63)	0.50 (0.36-0.91)	0.60 (0.41-1.32)	0.76 (0.51-2.24)	.002	<.001
Mean rank	62.5	58.3	77.8	90.2	104.3		
FIB-4, median (IQR)	0.63 (0.61-0.81)	0.92 (0.66-1.25)	1.26 (0.87-1.56)	1.63 (0.85-2.08)	2.17 (1.25-3.44)	<.001	<.001
Mean rank	28.4	56.4	77.4	91.4	114.2		

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis index based on the 4 factors; IQR, interquartile range.

^aKruskal-Wallis test.

^bTrend test.

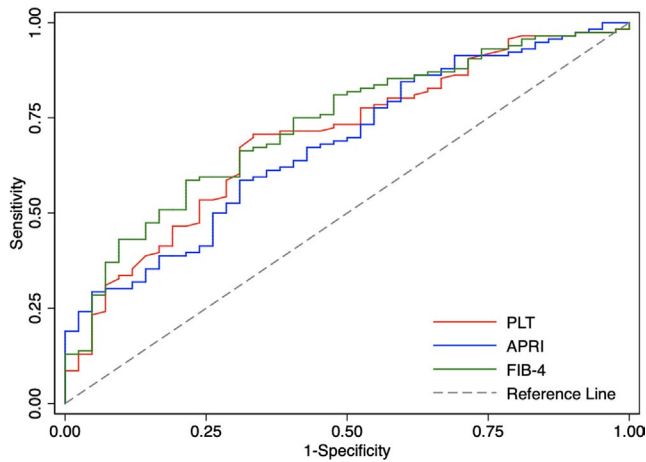


FIGURE 1 Area under ROC curves of PLT, APRI, and FIB-4 for the diagnosis of hepatic fibrosis ($F \geq 2$; $n = 158$). APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, the fibrosis index based on four factors; PLT, platelet count

and FIB-4 at different stages of liver fibrosis (F0-F4) was analyzed using the non-parametric Kruskal-Wallis test. From F0 to F4 stages, the median and average rank of platelet (P for trend $<.001$) showed a downtrend, while APRI and FIB-4 (P for trend $<.001$) showed an up-trend. The result showed that the degree of fibrosis would be higher with the lower platelet and the higher APRI and FIB-4.

3.3 | Efficiency comparison of platelet count, APRI, and FIB-4 in diagnosing significant fibrosis ($F \geq 2$) and early cirrhosis ($F = 4$) by ROC analysis

The ROC curves of platelet count, APRI, and FIB-4 for significant fibrosis ($F \geq 2$) and early cirrhosis ($F = 4$) were drawn, and the diagnostic thresholds were obtained according to Youden index. The diagnostic efficiency of platelet count, APRI, and FIB-4 were compared through the areas under the ROC curve. The areas under the ROC curve of platelet count, APRI, and FIB-4 for the diagnosis of significant fibrosis were 0.70, 0.68, and 0.73 with no statistical difference among them ($P = .428$, Figure 1, Table 3), which might indicate the diagnostic efficiency of platelet count in diagnosing significant fibrosis was similar to that of APRI and FIB-4. Meanwhile, the areas under the ROC curve of platelet count, APRI, and FIB-4 for the diagnosis of early cirrhosis were 0.72, 0.68, and 0.76 with no statistical difference ($P = .094$, Figure 2, Table 4), which might indicate the

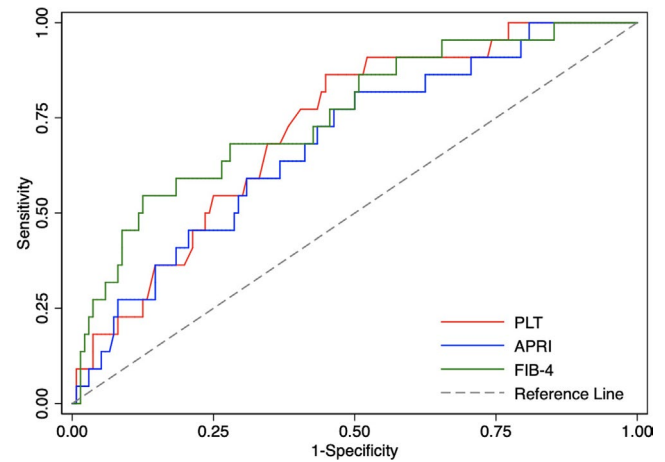


FIGURE 2 Area under ROC curves of PLT, APRI, and FIB-4 for the diagnosis of liver cirrhosis ($F = 4$; $n = 158$). APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, the fibrosis index based on four factors; PLT, platelet count

diagnostic efficiency of platelet count in diagnosing early cirrhosis was similar to that of APRI and FIB-4.

4 | DISCUSSION

The high prevalence of CHB in the world is an important public health problem. The hepatic fibrosis is a common pathological process in CHB patients. Assessment of the degree of hepatic fibrosis and the progression of CHB is essential for evaluation and treatment for the patients with CHB.^{20,21} Liver biopsy remains the gold standard for the diagnosis of liver fibrosis.⁶ However, liver biopsy with the drawbacks of invasiveness, complications, and sampling errors might be not appropriate to perform dynamic monitoring of liver pathology for multiple times.²²⁻²⁴ Safe, non-invasive, and reproducible strategies seem to be very meaningful. Elastographic methods have become a promising imaging modality without invasiveness.^{25,26} However, the obstacle to the widespread use of this technology machine is the high cost in primary or community hospitals. Hence, serologic tests gained its popularity with the features of cheaper and more accessible than the elastography in these hospitals. APRI and FIB-4 are two commonly used serum models to evaluate the degree of liver fibrosis.^{4,27,28} However, the variable hepatic fibrosis results and complex calculation are the biggest defect for APRI and FIB-4 when assessing the severe liver inflammation.

TABLE 3 Efficiency comparison of platelet count, APRI, and FIB-4 in diagnosing hepatic fibrosis ($F \geq 2$; $n = 158$)

	Threshold	Sensitivity	Specificity	PPV	NPV	Youden index	AUROC ^a (95% CI)
Platelet	196.5	0.71	0.67	0.85	0.45	0.374	0.70 (0.61-0.79)
APRI	0.511	0.59	0.69	0.84	0.38	0.277	0.68 (0.59-0.77)
FIB-4	1.256	0.59	0.79	0.88	0.41	0.360	0.73 (0.64-0.81)

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; AUROC, areas under the receiver operating characteristic curve; FIB-4, fibrosis index based on the 4 factors; NPV, negative predictive value; PPV, positive predictive value.

^a $\chi^2 = 1.70$, $P = .428$ (comparison of three indicators).

TABLE 4 Efficiency comparison of platelet count, APRI, and FIB-4 in diagnosing liver cirrhosis ($F = 4$; $n = 158$)

	Threshold	Sensitivity	Specificity	PPV	NPV	Youden index	AUROC ^a (95% CI)
Platelet	184.5	0.86	0.55	0.24	0.96	0.415	0.72 (0.62-0.82)
APRI	0.485	0.82	0.50	0.21	0.94	0.318	0.68 (0.57-0.80)
FIB-4	2.118	0.55	0.88	1.00	0.10	0.420	0.76 (0.64-0.87)

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; AUROC, areas under the receiver operating characteristic curve; FIB-4, fibrosis index based on the 4 factors; NPV, negative predictive value; PPV, positive predictive value.

^a $\chi^2 = 4.73$, $P = .094$ (comparison of three indicators).

Platelet count, with easily detected result, is a simple test. Unlike APRI and FIB-4, the platelet count has not been used alone to evaluate hepatic fibrosis. However, platelets have significant change in patients with liver fibrosis, and platelets as an indicator are involved in many conventional combination models of liver fibrosis.¹⁷ Previous study suggested that platelets could decrease the expression of TGF- β which is a principal fibrogenic cytokine and increase expression of matrix metalloproteinases in the process of hepatic fibrosis.²⁹ Platelet count might be a useful diagnostic biomarker for detection of liver hepatic fibrosis in patients with CHB. Therefore, our study aimed to evaluate the diagnostic effect of platelet count on hepatic fibrosis when applied alone. The results showed that the median (F0: 221.0; F1: 210.0; F2: 188.0; F3: 171.0; and F4: 155.5) and mean rank (F0: 120.4; F1: 100.1; F2: 82.2; F3: 67.9; and F4: 49.5) of platelet count decreased along the aggravation of fibrosis (F0-F4), which suggested platelet count might have a value to predict the degree of hepatic fibrosis. Animal studies have shown that increased platelets could reduce hepatic fibrosis by injecting thrombopoietin.^{30,31} Kurokawa et al proved that platelets reduced collagen production by inactivating hepatic stellate cells, thereby relieving the symptom of liver fibrosis.^{32,33} Some scholars proposed fibrosis index composed by platelet, and protein reflected the stages of fibrosis in patients with hepatitis C.³⁴

Thrombocytopenia, with the definition of lower platelet count compare with normal limit, is a common symptom during the progress of chronic liver disease.^{35,36} Lu SN and Iida H et al^{37,38} also have reported that decreased platelet count is associated with liver cirrhosis. However, platelet count served as a single index to assess the progression of hepatic fibrosis and compare with other serological indicators have not been reported. The present study compared the diagnostic efficiency of platelet count with APRI and FIB-4 for significant fibrosis ($F \geq 2$) and early cirrhosis ($F = 4$) by ROC analysis. The areas under the ROC curve of platelets count, APRI, and FIB-4 for assessing significant fibrosis were 0.70, 0.68, and 0.73. Besides, the areas under the ROC curve of platelets count, APRI, and FIB-4 for assessing early liver cirrhosis were 0.72, 0.68, and 0.76. All the results had no statistical significance which could be considered as the diagnostic efficiency of platelet count is comparable to APRI and FIB-4. According to the results, platelet count could be served as an evaluation standard in primary hospitals to assess the significant fibrosis and early liver cirrhosis.

There was noticeable variability in the recommended cutoff values for identification of significant fibrosis and liver cirrhosis among

different studies.³⁹ The possible explanations of heterogeneity included intervals between blood tests and liver biopsy, inadequate description of liver biopsy assessment, and blinding.³⁹ In our study, the selected patients had lower ALT and AST levels (Table 1) compared with most of previous studies,⁴⁰ so the cutoff values for APRI and FIB-4 scores were lower than known cutoff values in predicting significant fibrosis and early cirrhosis. Wei Yue et al also have reported that the cutoff value of APRI calculated in Chinese patients was lower than the cutoff value recommended by World Health Organization (WHO).⁴¹

This study has several limitations. Firstly, the sample size in this study is relatively small, so further study with a larger number of samples is warranted. In addition, the cutoffs between fibrosis stages are not so significant. Therefore, multicenter and larger sample investigations are required to evaluate the platelet count whether has the same diagnostic efficiency compared with other compound indicators. Despite these limitations, our study firstly determined that the platelet count is an optional index to assess hepatic fibrosis and cirrhosis.

Altogether, platelet count is a convenient, cheap, simple, and non-invasive indicator to evaluate the degree of hepatic fibrosis in patients with CHB. The correct evaluation could assist achieving timely treatment, delaying the incidence of cirrhosis or liver cancer, and eventually improving patients' quality of life. Platelet count could be an auxiliary diagnosis marker of hepatic fibrosis in the absence of pathological examination.

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ORCID

Huai-Yu Song  <https://orcid.org/0000-0002-1577-1946>

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