

Platelet count is closely associated with the severity of liver injury in patients with chronic hepatitis B virus infection: A cross-sectional study

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Abstract. Although the platelet count may provide clues regarding the severity of liver disease, there are currently no available data supporting the utility of the platelet count to evaluate the degree of liver injury in patients with chronic hepatitis B virus (HBV) infection. The present study aimed to determine the association between the platelet count and the severity of liver injury in patients with chronic HBV infection. A total of 941 patients were included and were stratified into a Child-Turcotte-Pugh (CTP) class A group and a CTP class B/C group using the CTP scoring system. A total of 53 patients underwent liver biopsy. The pathological stage F4 was defined as cirrhosis based on the METAVIR scoring system. Compared with that in patients with CTP class A, the platelet count in patients with CTP class B/C was lower ($P < 0.001$). Similarly, for patients with normal alanine aminotransferase (ALT) levels, the platelet count was significantly different between the CTP class B/C and A groups ($P < 0.001$). The platelet count was inversely correlated with the CTP score ($r = -0.420$, $P < 0.001$) and independently associated with CTP grade B/C [odds ratio (OR), 0.994; 95% CI, 0.990-0.999; $P = 0.009$]. The area under the receiver operating characteristic curve (AUC) of the platelet count to distinguish CTP grade B/C from A was 0.712 and 0.791, respectively, in all patients with HBV infection and the subset with normal ALT levels. In addition, compared to patients with chronic hepatitis B, patients with cirrhosis had a lower platelet count and higher

aspartate transaminase-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) ($P < 0.001$). The platelet count was inversely correlated with FIB-4 ($r = -0.855$, $P < 0.001$) and APRI ($r = -0.741$, $P < 0.001$). The AUC for the platelet count to distinguish cirrhosis from chronic hepatitis B was 0.927 (sensitivity, 78.76%; specificity, 92.22%). Among patients who underwent liver biopsy, the platelet count in those with F4 was lower compared with that in patients with $\leq F3$ ($P = 0.013$). The platelet count was inversely correlated with the pathological stage ($r = -0.295$, $P = 0.032$) and was independently associated with F4 (OR, 0.978; 95% CI, 0.960-0.997; $P = 0.026$). The AUC of the platelet count to distinguish F4 from patients with $\leq F3$ was 0.761. In conclusion, the platelet count may be used as a non-invasive marker to assess the severity of liver injury and of liver fibrosis in patients with chronic HBV infection.

Introduction

Chronic hepatitis B (CHB) is a major public health concern with a global prevalence. Approximately 65,000 patients die of liver failure, liver cirrhosis and hepatocellular carcinoma caused by hepatitis B virus (HBV) infection each year (1). Significant liver fibrosis and cirrhosis cause severe liver injury in patients with CHB and are important indicators for anti-viral therapy in those patients. At present, liver biopsy is considered the gold standard for staging of the degree of liver injury, but it is not widely used due to its invasiveness and risk of complications. Even if several non-invasive tests are applied for evaluating liver injury, in general, the early diagnosis of cirrhosis still depends on liver biopsy, as these non-invasive indicators are currently not ideal.

Platelets contain numerous growth factors that are required for organ development, tissue regeneration and repair (2,3). It was reported that in chronic liver diseases, platelets participate not only in liver injury through T cell-mediated immune responses but also in tissue repair through secretion of growth factors (4,5). Although thrombocytopenia is one of the common complications in patients with chronic liver disease in the clinic, there is no available data supporting that the degree of liver injury in patients

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with chronic HBV infection or cirrhosis associated with HBV may be evaluated based on the platelet count. Only several studies have suggested that the etiology of thrombocytopenia in liver disease may be attributed to splenomegaly, hypersplenism, portal hypertension and decreased thrombopoietin production (6,7). A recent study reported that in patients with CHB with significant fibrosis receiving anti-viral therapy, the increase of platelets was associated with the improvement of liver fibrosis (8). For hepatitis C, a clinical study has suggested that the platelet count may predict significant hepatitis C-associated fibrosis (9), and recently, the platelet count was reported to be able to indicate the degree of liver steatosis and fibrosis (10,11), and may serve as a clue regarding the severity of disease in patients with non-alcoholic fatty liver disease (12).

Overall, the association between thrombocytopenia and hepatic pathogenesis remains obscure and the role of platelets in chronic liver disease has remained largely elusive. There are currently no available data to support that the platelet count is able to evaluate the severity of liver injury in patients with chronic HBV infection. Using the results of liver biopsy as the gold standard, the present cross-sectional study aimed to evaluate the role of the platelet count in estimating liver injury in patients with chronic HBV infection.

Materials and methods

Patients. In the present study, 1,597 patients with chronic HBV infection at the First Hospital of Lanzhou University (Lanzhou, China), who met the inclusion criterion of positive serum HBV surface antigen (HBsAg) for >6 months, were enrolled between June 2016 and August 2017. The exclusion criteria were as follows: HBsAg-negative status; age <18 years; co-infection with hepatitis A, C and/or D virus; autoimmune hepatitis; alcoholic liver disease; non-alcoholic fatty liver disease; Wilson's disease; primary biliary cholangitis; drug-induced liver injury; co-existent hematologic diseases; history of splenectomy; history of therapy with anti-platelet drugs, immune inhibitors, molecular targeted drugs and hepatotoxic drugs; incomplete data; liver transplantation; extrahepatic tumor; multiple organ failure and obstructive jaundice. In total, 941 patients were finally included, of whom 347 and 226 patients were diagnosed with cirrhosis and CHB, respectively, based on the diagnostic criteria (1,13). Diagnostic data were obtained from clinical, imaging examination or liver biopsy results. Cirrhosis was classified as the compensated (n=170) or decompensated stage (n=177). This classification depends on the presence or absence of clinically evident decompensating events (specifically ascites, variceal hemorrhage and encephalopathy) (13). A flow chart of the patients included in the study is provided in Fig. 1.

This study was approved by the Ethics Committee of the First Hospital of Lanzhou University (Lanzhou, China; no. LDYYLL2019-209).

Laboratory tests and imaging examination. All patients included had complete biochemical, routine blood and coagulation test results, which were respectively detected by an automatic biochemical analyzer (AU400; Olympos Corp.), an automatic blood cell analyzer (BC-5390CRP; Mindray) and an automatic coagulation Analyzer (Precil C3510; Beijing Precil Instrument Co., Ltd.). The serum levels of alanine

aminotransferase (ALT) and aspartate aminotransferase (AST) >40 IU/l were considered abnormal. Splenic thickness, portal vein diameter and portal vein velocity were measured on an Ultrasound Machine (GE Logiq E9; GE Healthcare) by an experienced ultrasonographer.

Pathological assessment and indices calculated. Liver pathological assessment was based on the METAVIR scoring system (14). In the present study, F4 was defined as cirrhosis. The formulas for calculating the platelet count to splenic thickness ratio (PC/ST ratio), fibrosis index based on four factors (FIB-4) and AST-to-platelet ratio index (APRI) were as follows (15,16): Platelets/splenic thickness (PC/ST) ratio=platelet count (10⁹/l)/splenic thickness (mm); APRI=AST (IU/l)/its upper limit of normal (ULN)/platelet count (10⁹/l) x100. The ULN for AST was 40 IU/l. FIB-4=age (years) x AST/platelet count x [ALT (IU/l)]^{1/2}.

Statistical analysis. Epidata Software (version 3.1; Epidata) was used to manage data. SPSS software (version 17.0; SPSS, Inc.) was used to perform statistical analysis. Continuous variables are expressed as the mean ± standard deviation and categorical variables as n (%). One-sample Kolmogorov-Smirnov test was applied to determine if a set of data was normally distributed. For intergroup comparisons of continuous variables, variables with a normal and non-normal distribution were assessed by the independent-samples t-test and the non-parametric U Mann-Whitney test, respectively. The χ^2 test was used for categorical variables. To assess the association between variables and the Child-Turcotte-Pugh (CTP) score (17) or pathological stage, Spearman's rank correlation coefficient was determined. Multivariate logistic regression analysis was performed to identify the independent factors predicting liver function impairment. Finally, receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of the platelet count. P<0.05 was considered to indicate statistical significance.

Results

Patient characteristics. The present study included 941 patients with a mean age of 50.29±10.93 years (range, 18-90 years). The study population comprised 657 (69.82%) male patients and 284 (30.18%) female patients. These patients were stratified into a CTP class A group and a CTP class B/C group using the CTP scoring system. The characteristics of the patients included are summarized in Table SI. Compared with those of CTP class A, those with CTP class B/C had a lower age (P=0.009), platelet count (P<0.001), albumin (P<0.001) and prothrombin activity (PTA; P<0.001), and had a greater splenic thickness (P<0.001) and portal vein diameter (P<0.001). Similarly, in patients with normal ALT levels, age, platelet count, albumin and PTA were significantly lower, whilst splenic thickness and portal vein diameter were significantly higher in patients with CTP class B/C vs. A (Table I).

Platelet count is associated with the severity of liver function in patients with chronic HBV infection. In terms of liver function, correlation analysis revealed that the CTP score was inversely correlated with the platelet count, albumin,

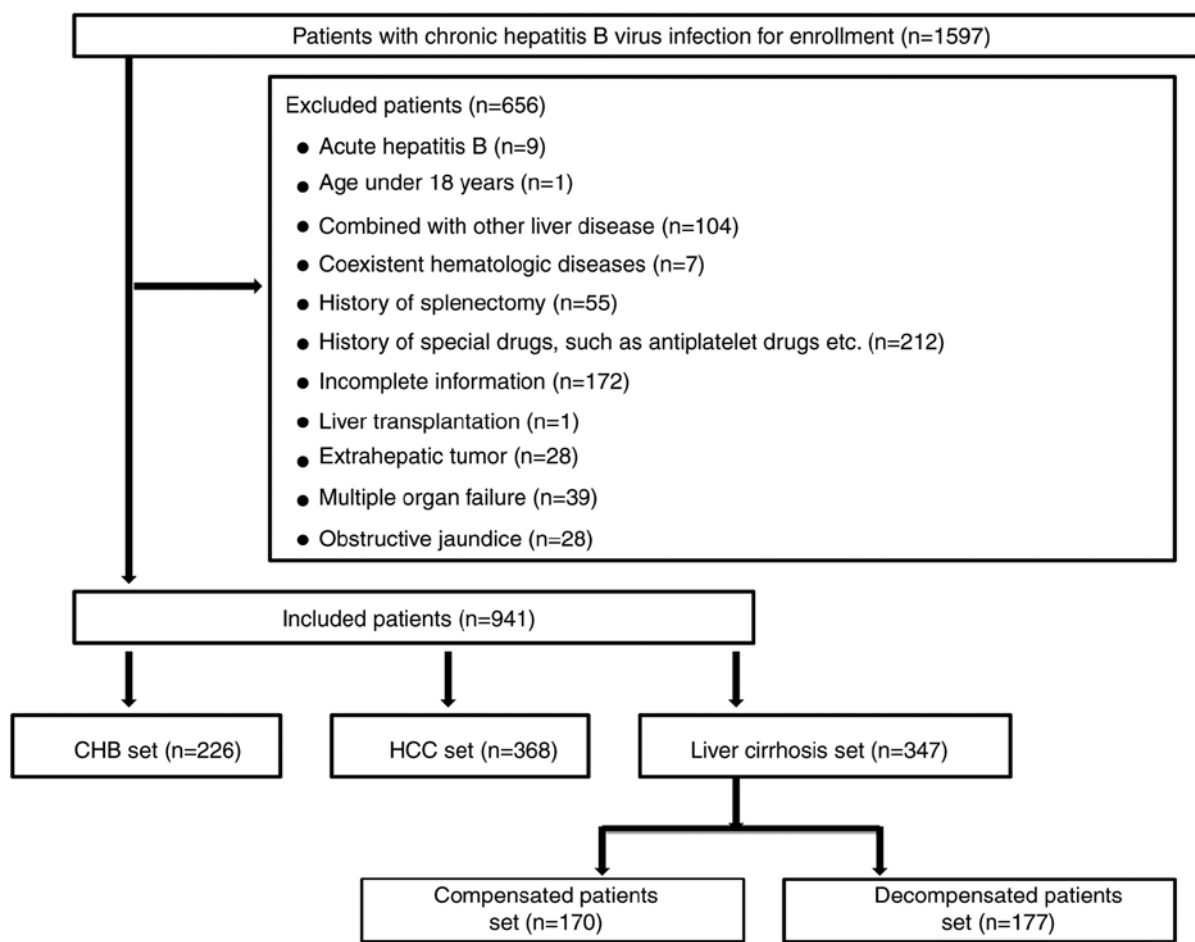


Figure 1. Flow chart of patients in the study. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma.

cholinesterase (CHE) and PTA (Table SII). In addition, the platelet count correlated positively with albumin ($r=0.350$, $P<0.001$), CHE ($r=0.500$, $P<0.001$) and PTA ($r=0.503$, $P<0.001$), and correlated inversely with prothrombin time (PT; $r=-0.522$, $P<0.001$; Table SIII). Multivariate logistic regression analysis verified that the platelet count [odds ratio (OR), 0.994; $P=0.009$], albumin (OR, 0.703; $P<0.001$), total bilirubin (OR, 1.146; $P<0.001$) and age (OR, 0.971; $P=0.010$) were independently associated with CTP class B/C (Table SIV). Furthermore, in patients with normal ALT levels, the platelet count, albumin and PTA were also independently associated with CTP class B/C (Table II). ROC curve analysis indicated that the area under the curve (AUC) of the platelet count to distinguish CTP class B/C from A were 0.712 (Fig. 2A) and 0.791 (Fig. 2B) in patients with chronic HBV infection and normal ALT levels, respectively.

The platelet count is able to identify patients with cirrhosis among those with chronic HBV infection. Among the patients with chronic HBV infection, those with cirrhosis had a significantly lower age, platelet count, albumin and PTA, and significantly higher PT, splenic thickness, portal vein diameter, CTP score, APRI and FIB-4 than those with no cirrhosis (Table SV). Correlation analysis demonstrated that the platelet count was inversely correlated with FIB-4 ($r=-0.855$, $P<0.001$) and APRI ($r=-0.741$, $P<0.001$), whereas

splenic thickness and CTP scores correlated positively with FIB-4 (Table SVI). These three indicators and age were then included in a multivariate analysis. The results suggested that the platelet count, CTP score and splenic thickness were independently associated with cirrhosis (Table SVII). The ROC curve analysis indicated that the AUC of the platelet count for cirrhosis was 0.927 ($P<0.001$), the AUC of splenic thickness for cirrhosis was 0.903 ($P<0.001$), the AUC of CTP score for cirrhosis was 0.838 ($P<0.001$; Fig. 3A and Table SVIII).

The platelet count has potential diagnostic value for early-stage cirrhosis. The stage of CHB and compensated cirrhosis are indistinguishable if no invasive examination is performed. In the present study, patients with compensated cirrhosis, compared to those with CHB, also had a lower age, platelet count and albumin, and higher splenic thickness, APRI, FIB-4 and CTP score ($P<0.001$). The differences in these groups are provided in the supplementary material (Table SIX). Logistic regression analysis indicated that the platelet count was also independently correlated with compensated cirrhosis (OR, 0.966; $P<0.001$; Table SX). The AUC of the platelet count for compensated cirrhosis was 0.912 and the optimal cut-off value was $117 \times 10^9/l$, with a sensitivity of 80.09% and a specificity of 90.00% (Fig. 3B).

Table I. Baseline characteristics of the study population of patients of chronic hepatitis B virus infection with normal ALT.

Variable	CTP class A (n=395)	CTP class B/C (n=137)	P-value
Age (years)	51.61±11.19	49.22±11.59	0.028
Male sex	250 (63.29)	84 (61.31)	0.757
Platelet count (x10 ⁹ /l)	124.76±67.60	64.18±44.70	<0.001
PC/ST ratio	172,2.80±2.15	92,1.12±0.94	<0.001
AST (U/l)	33.21±16.77	49.68±49.11	<0.001
TP (g/l)	69.91±7.56	62.08±10.20	<0.001
Albumin (g/l)	43.24±4.28	34.30±6.20	<0.001
TBIL (μmol/l)	20.10±8.64	46.54±34.41	<0.001
DBIL (μmol/l)	4.66±2.15	15.09±15.48	<0.001
CHE (KU/l)	6.19±1.88	3.28±1.56	<0.001
TC (mmol/l)	3.78±0.92	2.55±0.95	<0.001
PT (sec)	12.41±1.17	16.42±4.38	<0.001
PTA (%)	86.32±14.57	59.29±14.67	<0.001
APTT (sec)	33.86±5.58	38.67±15.65	<0.001
Splenic thickness (n, mm)	172,45.09±11.82	92,57.49±10.78	<0.001
Portal vein diameter (n, mm)	211,11.71±1.95	90,13.48±2.30	<0.001
FIB-4	4.14±4.75	9.63±7.43	<0.001
APRI	1.02±1.31	2.56±2.00	<0.001

Values are expressed as the mean ± standard deviation or n (%). CTP, Child-Turcotte-Pugh; PC/ST ratio, platelet count to splenic thickness ratio; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; TP, total protein; CHE, cholinesterase; TC, total cholesterol; PT, prothrombin time; PTA, prothrombin activity; APTT, activated partial thromboplastin time; FIB-4, fibrosis index based on four factors; APRI, AST-to-platelet ratio index.

Table II. Independently associated indicators of moderate to severe liver function impairment in patients with normal alanine aminotransferase obtained by multivariate analysis of the indicators with statistical differences in Table I.

Variable	OR	95% CI	P-value
Platelet count	0.991	0.985-0.998	0.007
Albumin	0.773	0.719-0.831	<0.001
PTA	0.902	0.875-0.931	<0.001
Age	0.973	0.946-1.002	0.067

OR, odds ratio; CI, confidence interval; PTA, prothrombin activity.

Platelet count is closely associated with histological severity in patients with chronic HBV infection. A total of 53 patients included underwent liver biopsy and were stratified into the ≤F3 set (n=6) and F4 set (n=47) according to the METAVIR scoring system. The study population with a mean age of 50.15±8.55 years comprised 40 (75.47%) male patients and 13 (24.53%) female patients. The baseline characteristics of these patients are provided in Table III. The patients with F4 had a significantly lower platelet count, albumin, CHE and PTA (P<0.05), and correlation analysis suggested that these parameters were significantly negatively correlated with all pathological stages (Table IV). The multivariate logistic regression analysis revealed that only the platelet count (OR, 0.978;

P=0.026) was independently associated with F4 (Table V). The AUC of the platelet count to distinguish F4 from ≤F3 was 0.761 with a sensitivity of 66.7% and specificity of 80.9% (Fig. 4).

Discussion

Several clinical studies indicated that the platelet count is able to distinguish significant fibrosis in patients with hepatitis C infection and may be used to assess the degree of liver steatosis and fibrosis in patients with non-alcoholic fatty liver disease (11,18). Furthermore, it has been indicated that the platelet count is able to modulate the quantitative association between HBV DNA and surface antigen concentrations (19), and HBsAg levels were able to predict the degree of fibrosis in patients with CHB (20). Therefore, the platelet count is closely linked to the HBV infection status. Furthermore, a study reported that the platelet count was associated with inflammation and fibrosis of the liver in patients with chronic HBV infection (21). However, at present, only a small amount of evidence is available to support the association of the platelet count with the severity of liver injury in patients with chronic HBV infection. In the present study, a cohort of patients with chronic HBV infection that met the study requirements based on rigorous criteria were ultimately included. Based on the above standards and the liver biopsy data, the ability of the platelet count to evaluate chronic liver injury in patients with HBV infection was confirmed. The results suggested that the platelet count was closely linked to the severity of liver injury in patients with chronic HBV infection.

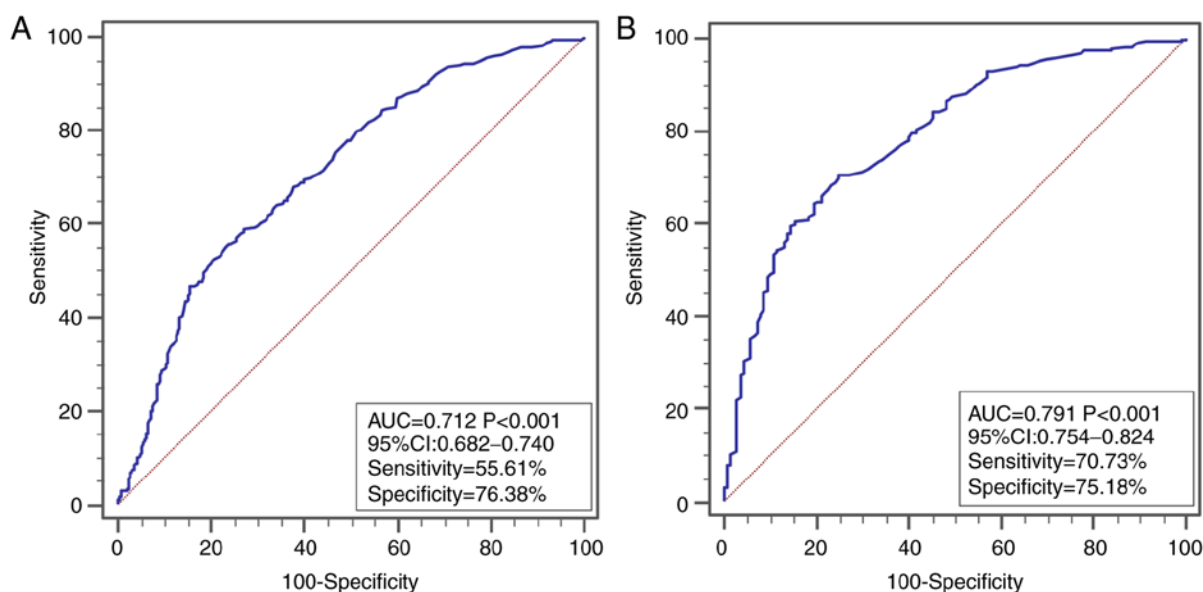


Figure 2. The ROC of platelet count for moderate to severe liver function impairment in (A) patients with chronic HBV infection and (B) patients with chronic HBV infection and normal alanine aminotransferase levels. AUC, area under the ROC curve; ROC, receiver operating characteristic; HBV, hepatitis B virus.

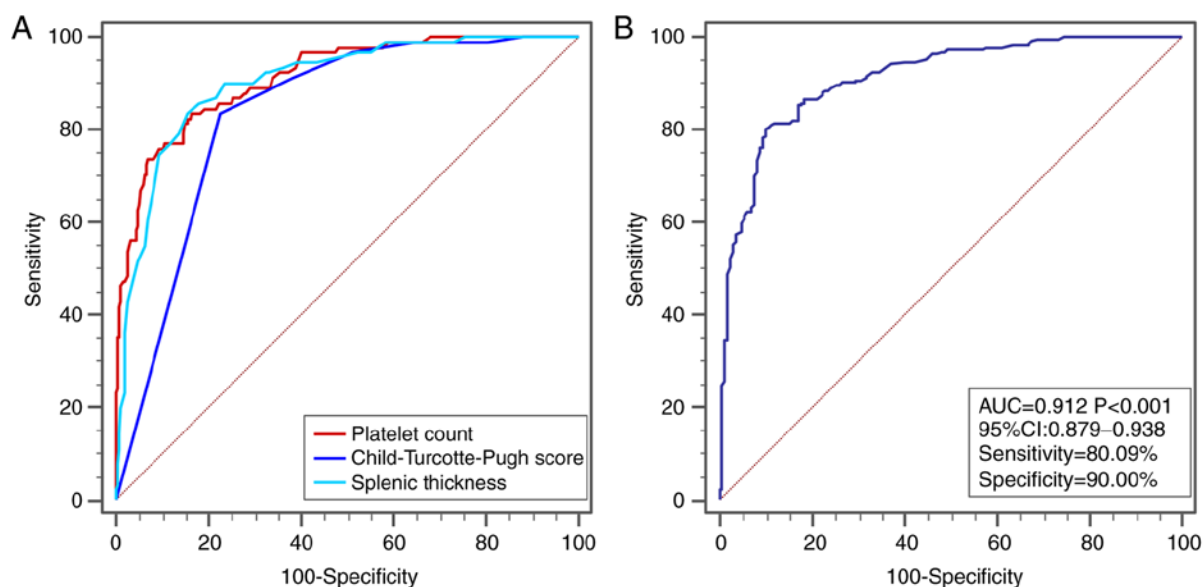


Figure 3. The discriminative ability of platelet count for early-stage cirrhosis. (A) Comparison of ROC curves for the use of platelet count, Child-Turcotte-Pugh score and splenic thickness to identify cirrhosis; (B) ROC curve of platelet count for diagnosing compensated cirrhosis. AUC, area under the ROC curve; ROC, receiver operating characteristic.

Over the past decades, certain studies have attempted to demonstrate that certain non-invasive indicators are able to distinguish liver fibrosis, liver inflammation or liver function (22,23). Furthermore, the platelet count was able to indicate the degree of fibrosis in non-alcoholic fatty liver disease (10,11), and the platelet count was associated with the degree of hepatic fibrosis in chronic hepatitis C via the mRNA expression of platelet-derived growth factor A (24). An animal study also suggested that platelets produce platelet-derived growth factor-b to activate hepatic stellate cells and promote fibrosis (25). Thus, these studies demonstrated that the platelet count was closely linked to liver function and liver fibrosis.

In the present study, the platelet count was significantly lower in patients with chronic HBV infection and CTP-B/C, and inversely correlated with the CTP score. In particular, the platelet count was found to be independently associated with CTP-B/C and used to distinguish CTP-B/C with an AUC of 0.791, optimal cut-off value of $73 \times 10^9/l$, sensitivity of 70.73% and specificity of 75.18% in patients with normal ALT levels. Therefore, platelets were confirmed to be linked to the severity of liver function in patients with chronic HBV infection. Another study suggested that the increase of platelets was associated with the improvement of liver fibrosis in patients with CHB with significant fibrosis

Table III. Baseline characteristics of patients who underwent liver biopsy.

Variable	≤F3 (n=6)	F4 (n=47)	P-value
Age (years)	47.83±5.15	50.45±8.88	0.486
Male sex	5 (83.33)	35 (74.47)	0.635
Platelet count (x10 ⁹ /l)	152.83±58.78	103.15±42.97	0.013
AST (U/l)	40.67±22.93	44.11±26.71	0.764
ALT (U/l)	59.50±39.07	41.15±23.94	0.107
TP (g/l)	74.66±5.08	70.10±7.62	0.162
Albumin (g/l)	47.10±4.52	42.88±4.26	0.027
TBIL (μmol/l)	20.08±8.69	21.32±12.17	0.902
DBIL (μmol/l)	3.77±1.56	5.87±7.41	0.207
IBIL (μmol/l)	16.32±7.16	15.45±6.41	0.758
CHE (KU/l)	8.05±1.22	5.85±1.55	0.002
TC (mmol/l)	4.40±0.73	3.58±0.76	0.016
PT (sec)	11.53±1.18	12.91±1.62	0.049
PTA (%)	99.18±19.54	81.87±13.43	0.007
APTT (sec)	34.22±6.70	33.69±5.91	0.840
Splenic thickness (n, mm)	2,38.50±7.78	19,47.47±8.00	0.147
Portal vein diameter (n, mm)	5,10.80±1.48	24,11.79±1.32	0.145

Values are expressed as the mean ± standard deviation or n (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; TP, total protein; CHE, cholinesterase; TC, total cholesterol; PT, prothrombin time; PTA, prothrombin activity; APTT, activated partial thromboplastin time.

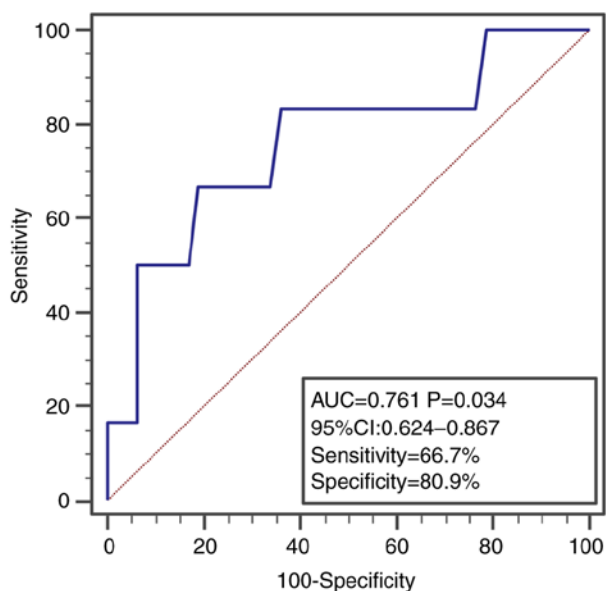


Figure 4. ROC of the platelet count for identifying pathological stage F4 in patients with chronic hepatitis B infection who underwent liver biopsy. AUC, area under the ROC curve; ROC, receiver operating characteristic.

receiving anti-viral therapy (8). This also indirectly indicated the close association between platelets and fibrosis in patients with hepatitis B.

The stage of compensated cirrhosis in CHB is difficult to distinguish without performing an invasive examination. Furthermore, compensated cirrhosis is associated with an increased risk of developing varices, overt

Table IV. Correlation between variables and the pathological stage.

Variable	r-value	P-value
Platelet count	-0.295	0.032
Albumin	-0.279	0.043
CHE	-0.392	0.004
PT	0.334	0.014
PTA	-0.328	0.016

CHE, cholinesterase; PT, prothrombin time; PTA, prothrombin activity.

Table V. Independently associated indicators for cirrhosis (pathological stage IV) obtained by multivariate analysis of the indicators with statistical differences in Table III.

Variable	OR	95% CI	P-value
Platelet count	0.978	0.960-0.997	0.026
ALT	0.980	0.950-1.010	0.170
Age	1.034	0.913-1.171	0.425

ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval.

clinical decompensation (ascites, variceal hemorrhage, hepatic encephalopathy), post-surgical decompensation and

hepatocellular carcinoma (26). Therefore, the present study focused on the association between platelets and cirrhosis, particularly compensated cirrhosis. The results indicated that the platelet count was inversely correlated with FIB-4 and APRI, which are a non-invasive diagnostic model for hepatic fibrosis. The platelet count was independently associated with cirrhosis. The AUC for the platelet count to indicate cirrhosis (0.927) was significantly higher than that for splenic thickness and CTP score. For early-stage cirrhosis, the platelet count had the best discriminative ability in distinguishing compensated cirrhosis. The AUC was 0.912 with an optimal cut-off value of $117 \times 10^9/l$, sensitivity of 80.09% and specificity of 90.00%. Therefore, it may be speculated that patients with chronic HBV infection with platelet counts of $<117 \times 10^9/l$ were likely to already have early-stage cirrhosis based on the results.

In addition, the liver biopsy results were used to confirm the above-mentioned association. The results indicated that the platelet count was inversely correlated with the histological stage of fibrosis and independently associated with F4. ROC curve analysis demonstrated that the platelet count is an effective diagnostic indicator for the F4 stage with an AUC of 0.761. Therefore, the present study further confirmed that the platelet count is closely associated with histological severity in patients with chronic HBV infection.

Of note, the present study had certain limitations. First, no basic experiments were performed to confirm the relevant mechanisms. Additionally, the predictive value of the platelet count to assess the severity of liver injury was not proven. However, based on the rigorous research design and associated results, it was possible to draw conclusions.

In conclusion, the present study confirmed for the first time that the platelet count is independently associated with moderate to severe liver function impairment and cirrhosis in patients with chronic HBV infection. The platelet count may be used to determine the severity of liver injury and liver fibrosis.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JFL and ZPD designed the study; YTY, LTY, LLW, WZ and YC collated the data; YTY, LTZ, SJZ and QFC analyzed the data; YTY, LLW and ZPD wrote the paper; JFL, YC, SJZ and ZPD revised the paper. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

The current study meets the ethical requirements of the Ethics Committee of the First Hospital of Lanzhou University (Lanzhou, China) and received approval. Patients were not required to give informed consent, as the analysis used anonymous clinical data obtained after each patient agreed to treatment by written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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