Aspartate Aminotransferase-to-Platelet Ratio Index as Predictors of Recompensation in Decompensated Cirrhosis

Dedong Yin, Juanli Wu, Yuying Wang and Xu Liu

Department of Infectious Diseases and Hepatology, The Second Hospital of Shandong University, Jinan, China

ABSTRACT

Objective: To explore the relationship between aspartate aminotransferase-to-platelet ratio index (APRI) level and recompensation in patients with hepatitis B-related decompensated cirrhosis.

Study Design: Analytical study.

Place and Duration of the Study: The Second Hospital of Shandong University, Jian, China, and Weifang People's Hospital, China, from January 2016 to 2024.

Methodology: A total of 166 patients with hepatitis B-related decompensated cirrhosis without antiviral treatment were included. All patients were observed for a minimum of 18 months. The main result is recompensation, defined as the latest Baveno VII restitution standard. The predictive value of the APRI was assessed by using the receiver operating characteristic (ROC) curves and logistics regression model.

Results: In the group with baseline aspartate aminotransferase (AST) ≤40 U/L, APRI was identified as an independent predictor of recompensation in patients with hepatitis B-related decompensated cirrhosis (OR 0.04, 95% CI: 0.002 - 0.686, p = 0.026). For patients treated with nucleos(t)ide analogues (NAs), lower APRI was related to the higher rate of recompensation (OR 0.466, 95% CI: 0.291 - 0.747, p = 0.002). In the baseline AST ≤40 group and in the data one year after antiviral treatment, the AUROCs for APRI diagnosis of liver cirrhosis were 0.813 and 0.723, respectively.

Conclusion: APRI may be used as an independent predictor of recompensation in patients with hepatitis B-related decompensated cirrhosis, particularly in patients undergoing NAs therapy and with low AST levels.

Key Words: *Aspartate aminotransferase-to-platelet ratio index, Decompensated liver cirrhosis, Recompensation, Chronic hepatitis B.*

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INTRODUCTION

There are currently more than 1.32 million estimated deaths worldwide related to cirrhosis, accounting for approximately 2.4% of global deaths.[1] About 331,000 deaths were caused by hepatitis B-related cirrhosis in 2019.[2] Decompensation represents a pivotal point in the clinical course of cirrhosis, with a markedly reduced survival rate. Existing studies have shown that the five-year survival rate is only 14-35% for untreated decompensated patients, while the five-year survival rate for patients with compensatory cirrhosis is 84%.[3,4]

Correspondence to: Dr. Xu Liu, Department of Infectious Diseases and Hepatology, The Second Hospital of Shandong University, Jinan, Shandong Province, China
E-mail: xuliu1106@163.com

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In 2021 Baveno VII consensus, a novel definition of cirrhosis recompensation was proposed, which encompassed the elimination, suppression, and cure of the primary causes of cirrhosis, as well as the regression of decompensation symptoms, including ascites, hepatic encephalopathy, variceal bleeding, and a sustained improvement in liver function tests over a minimum of 12 months.[5]

A substantial body of evidence from numerous studies indicates that the probability of clinical death and liver cancer is obviously reduced in patients with decompensated cirrhosis who have undergone recompensation.[6-9] Accordingly, the identification of a biomarker that can predict the onset of cirrhosis recompensation would be beneficial to the clinical follow-up observation of decompensated cirrhosis patients.

APRI was originally identified as a predictive marker of cirrhosis in patients who are infected with the hepatitis C virus (HCV).[10] Subsequently, some studies have applied this marker to evaluate other liver diseases, involving alcoholic hepatitis and hepatitis B. Despite the ongoing debate regarding the clinical utility of aspartate aminotransferase-to-platelet ratio (APRI), it

remains a widely employed marker for evaluating patient outcomes.[11-14] APRI is a non-invasive, readily comprehensible, and expeditiously calculable instrument that can assist clinicians in expedient diagnoses, particularly in outpatient settings. Some studies have shown that APRI is a potential predictor of clinical outcomes in patients with cirrhosis.[15,16]

Nevertheless, there are currently no clinical studies investigating the application of APRI in cirrhosis recompensation. The objective of this study was to ascertain whether APRI may be applied to predict the onset of recompensation in patients with decompensated cirrhosis caused by hepatitis B. This study is also expected to contribute to clinical management for decompensated cirrhosis patients.

METHODOLOGY

This analytical study included patients with hepatitis B- related decompensated cirrhosis without antiviral treatment who first presented at the Weifang People's Hospital and the Second Hospital of Shandong University, between January 2016 and 2024. All patients commenced powerful nucleos(t)ide analogues (NAs) therapy immediately after enrolment, comprising tenofovir disoproxil fumarate, entecavir, and tenofovir alafenamide fumarate. This study was approved by the Ethical Review Board of the Second Hospital of Shandong University, China.

The inclusion criteria were over 18 years, diagnosis of cirrhosis on the basis of clinical, radiological or histological findings; presence of hepatic encephalopathy, ascites or variceal bleeding at the time of enrolment, and HBsAg-positive >6 months. The exclusion criteria were other viral hepatitis, HIV infection, or other chronic liver diseases, history of hepatocellular carcinoma (HCC), death or HCC occurrence within six months after enrolment, less than 18 months of follow-up, liver transplantation before or after enrolment, and splenectomy.

Diagnostic criteria of both chronic hepatitis B and cirrhosis were based on the clinical practice guidelines of the American Association for the Study of the Liver Diseases (AASLD 2018).[17] Hepatitis B-related cirrhosis recompensation criteria were sustained-hepatitis B suppression such as the clearance of serum HBV DNA (less than 20 IU/ml) or hepatitis B surface antigen (HBsAg); disappearance of ascites (diuretics not required) and hepatic encephalopathy (rifaximin or lactulose not required), at least 12 months without recurrent variceal bleeding, and sustained improvement of liver function (Child-Pugh Class A or MELD score <10).[5] The decompensated group was defined as comprising those who experienced at least one decompensated event (ascites, HE, gastrointestinal bleeding, and spontaneous bacterial peritonitis, *etc*.) during clinical follow-up and those who did not accomplish recompensation.

The main study outcome was the occurrence of recompensation. The participants were reassessed at least every six months, including liver function tests, abdominal imaging, blood routine test, serum HBV DNA levels, alpha-fetoprotein levels, and other pertinent biomarkers. The data were collected at the final follow-up point, or at the date of death, whichever occurred first.

All data were sourced from the electronic medical records of outpatient clinics or wards. Baseline data were defined as those collected when starting antiviral treatment. Gender and age were demographic characteristics. Laboratory data included platelet, haemoglobin, serum sodium, aspartate aminotransferase (AST), glutamate transpeptase (GGT), total bilirubin, serum creatinine, alpha-fetoprotein, international normalised ratio (INR), alanine aminotransferase (ALT), and serum HBV DNA (the lowest limit of detection was 20 IU/mL). The APRI value was calculated as [(AST / upper limit of normal) / platelet count (10^9/L)] × 100. The upper limit of normal AST was taken as 40 U/L.[16] Imaging data included ultrasound, CT, or MRI. Other clinical data, such as hepatic encephalopathy, ascites and esophagogastric variceal bleeding, and concomitant diseases (diabetes), were also included.

Depending on the distribution of the data, descriptive data were presented as mean (SD) or median (IQR). Normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Parametric analyses were carried out using the Student's t-test, while non-parametric analyses were carried out using the Mann-Whitney U test. Chi-squared test or Fisher's exact test was used to compare categorical variables. To assess the impact of APRI on recompensation, univariate and multivariate logistic regression models were utilised. Receiver operating characteristic (ROC) curves were also plotted to assess the diagnostic accuracy of APRI, and sensitivity, specificity, and area under the ROC curve (AUROC) were calculated. The Youden's index was used to determine the optimal cut-off values. The aforementioned statistical analyses were performed using the SPSS 27.0 software (IBM, Armonk, NY, USA). Statistically significant values were $p < 0.05$.

RESULTS

The final cohort for the present study comprised 166 patients. A total of 99 patients exhibited recompensation, while 67 patients displayed continued decompensated cirrhosis (Figure 1).

The cohort included 100 males (60.2%) with a mean age of 54.4 ± 10.9 years. The median length of follow-up was 41 months. Subjects were divided into two groups based on their AST levels, with those exceeded the upper limit of the normal range comprising one group. Table I presents a detailed overview of the baseline data and data collected after one year of antiviral treatment. The baseline AST was predominantly distributed within the range above 80 U/L, with a considerable part exceeding 240 U/L. However, after one year, the distribution of AST levels was predominantly below 40 U/L (Figure 2 A,B).

Univariate logistic regression analysis was conducted to ascertain potential predictors for cirrhosis recompensation based on baseline data and one-year post-antiviral treatment data (Table II). Subsequently, to further evaluate the relationship between APRI and cirrhosis recompensation, multivariate logistic regression analyses were performed.

Table I: Baseline and one year later clinical characteristics of 166 patients.

Variables	Baseline				one year later (n = 166)
	All, N = 166	AST ≤40 (n = 40)	AST >40 (n = 126)	p-value	
Male gender, n (%)	100 (60.2%)	27 (67.5%)	73 (57.9%)	0.282[c]	100 (60.2%)
Age, y (median ± SD)	54.4 ± 10.9	56.3 ± 11.6	53.8 ± 10.7	0.212[a]	55.4 ± 10.9
Haemoglobin (median, range, g/L)	116 (89, 129)	111 (87, 126)	116 (90, 130)	0.440[b]	130 (105, 142)
Platelet (median, range, 10^9/L)	85 (57, 111)	64 (47, 102)	89 (62, 113)	0.016[b]	83 (55, 116)
ALT (median, range, U/L)	48 (30, 108)	24 (18, 33)	65 (40, 139)	<0.001[b]	24 (18, 33)
AST (median, range, U/L)	63 (41, 113)	30 (25, 36)	85 (54, 133)	<0.001[b]	33 (25, 43)
GGT (median, range, U/L)	45 (28, 86)	31 (18, 46)	55 (32, 104)	<0.001[b]	27 (19, 44)
Totalbilirubin (median, range, umol/L)	31.9 (20.5, 52.8)	24.2 (14.9, 33.3)	36.6 (24.3, 68.3)	<0.001[b]	21.1 (14.1, 29.0)
Creatinine (median, range, mmol/L)	61 (50, 69)	64 (51, 75)	60 (50, 68)	0.157[b]	61 (53, 72)
NA^+ (median, range, mmol/L)	139 (137, 141)	139 (138, 141)	139 (137, 141)	0.139[b]	140 (138, 142)
AFP (median, range, ng/ml)	12.8 (4.1, 77.2)	3.3 (1.7, 5.5)	22.6 (7.9, 120.9)	<0.001[b]	3.3 (2.2, 5.8)
INR (median, range)	1.40 (1.27, 1.68)	1.32 (1.20, 1.40)	1.45 (1.29, 1.74)	<0.001[b]	1.22 (1.10, 1.34)
HBV DNA (median, range, log_{10}IU/mL)	5.54 (3.91, 6.81)	3.83 (1.86, 4.83)	5.92 (4.96, 7.12)	<0.001[b]	-
Diabetes, n (%)	33 (19.9%)	10 (25%)	23 (18.3%)	0.352[c]	33 (19.9%)
MELD score (median, range)	13 (10, 16)	11 (9, 14)	13 (11,1 8)	<0.001[b]	10 (8, 12)
APRI (median, range)	2.21 (1.23, 3.63)	1.06 (0.77, 1.45)	2.64 (1.69, 4.61)	<0.001[b]	1.05 (0.66, 1.67)

(a): Student's t-test; (b): Mann-Whitney U test; (c): Chi-squared test or Fisher's exact test. Abbreviations: AFP, Alpha-fetoprotein; AST, Aspartate aminotransferase; MELD, Model for End-Stage Liver Disease; INR, International normalised ratio; GGT, γ-glutamyl transferase; ALT, Alanine aminotransferase; SD, Standard deviation; IQR, Interquartile range.

Table II: For liver cirrhosis recompensation, univariate logistic regression of baseline, and one year later demographic data.

Variables	Baseline				One year later (n = 166)	
	AST ≤40 (n = 40) OR (95%, CI)	p-value	AST >40 (n = 126) OR (95%, CI)	p-value	OR (95%, CI)	p-value
Male gender	0.263 (0.066, 1.056)	0.06*	0.466 (0.213, 1.017)	0.055*	0.390 (0.200, 10.762)	0.006*
Age (years)	0.998 (0.945, 1.055)	0.946*	0.967 (0.933, 1.002)	0.065*	0.973 (0.945, 1.002)	0.066*
Haemoglobin (g/L)	1.004 (0.980, 1.028)	0.765*	1.001 (0.988, 1.013)	0.910*	1.002 (0.991, 1.013)	0.753*
Platelet (10^9/L)	1.018 (1.0, 1.037)	0.046*	1.001 (0.992, 1.010)	0.880*	1.020 (1.010, 1.029)	<0.001*
ALT (U/L)	0.964 (0.9, 1.031)	0.286*	1.007 (1.001, 1.014)	0.027*	0.995 (0.976, 1.014)	0.602*
AST (U/L)	0.919 (0.836, 1.010)	0.08*	1.003 (1.0, 1.007)	0.074*	0.982 (0.968, 0.996)	0.012*
GGT (U/L)	1.003 (0.984, 1.023)	0.738*	0.998 (0.994, 1.002)	0.282*	0.992 (0.984, 1.000)	0.048*
Totalbilirubin (umol/L)	0.976 (0.933, 1.022)	0.299*	1.001 (0.996, 1.007)	0.714*	0.967 (0.947, 0.998)	0.002*
Creatinine (mmol/L)	0.999 (0.980, 1.019)	0.949*	0.990 (0.967, 1.012)	0.372*	0.994 (0.985, 1.003)	0.202*
NA^+ (mmol/L)	1.105 (0.903, 1.352)	0.333*	1.015 (0.941, 1.095)	0.697*	1.113 (1.018, 1.217)	0.019*
AFP (ng/ml)	1.034 (0.976, 1.096)	0.259*	1.001 (0.999, 1.002)	0.437*	1.0 (1.000, 1.001)	0.638*
INR	0.416 (0.022, 8.002)	0.561*	2.999 (0.870, 10.346)	0.082*	0.749 (0.377, 1.487)	0.409*
HBVDNA (log_{10}IU/mL)	0.868 (0.601, 1.253)	0.449*	1.353 (1.092, 1.675)	0.006*	-	-
Diabetes N (%)	1.727 (0.407, 7.327)	0.458*	0.613 (0.244, 1.542)	0.298*	0.770 (0.357, 1.662)	0.506*
MELD score	0.931 (0.756, 1.147)	0.503*	1.054 (0.972, 1.143)	0.20*	0.898 (0.824, 0.980)	0.015*
APRI	0.06 (0.007, 0.495)	0.009*	1.127 (1.002, 1.268)	0.047*	0.538 (0.370, 0.785)	0.001*

**Univariate logistic regression.*

Table III: Relationship between APRI and recompensatory cirrhosis in different species models in the baseline and after one year of antiviral treatment.

	APRI (AST ≤40 group)		APRI (AST >40 group)		One year later	APRI	
Baseline	OR (95% CI)	p-value	OR (95% CI)	p-value		OR (95% CI)	p-value
Model I	0.068 (0.007, 0.641)	0.019°	1.102 (0.985, 1.234)	0.091°	Model I'	0.562 (0.386, 0.819)	0.003°
Model II	0.04 (0.002, 0.686)	0.026°	0.904 (0.757, 1.078)	0.263°	Model II'	0.466 (0.291, 0.747)	0.002°

° Multivariate logistic regression models; CI, Confidence interval; OR, Odds ratio.
Model I: Adjusted for gender and age. Model II: Adjusted for gender, age, HBV DNA, alanine aminotransferase, serum sodium, international normalised ratio, and total-bilirubin. Model I': Adjusted for gender and age. Model II': Adjusted for gender, age, γ-glutamyl transferase, alanine aminotransferase, serum sodium, international normalised ratio, and total-bilirubin.

In the baseline AST ≤40 group, low APRI was identified as an independent predictor of recompensation (OR 0.04, 95% CI: 0.002-0.686, p = 0.026). However, in the baseline AST >40 group, the APRI did not achieve statistical significance (OR 0.904, 95% CI: 0.757-1.078, p = 0.263, Table III). In the data after one year of antiviral treatment, APRI remained a significant independent variable for the prediction of recompensation (OR 0.46, 95% CI: 0.291-0.747, p = 0.002, Table III).

In the baseline AST ≤40 group, the AUROC of APRI for the diagnosis of cirrhosis recompensation was 0.813 (Figure 3A). When the cut-off value of APRI was 1.0, the diagnostic sensitivity was 75% and the specificity was 87.5% (Figure 3C).

With regard to the data after one year of antiviral treatment, the AUROC of APRI for the diagnosis of cirrhosis compensation was 0.723 (Fiugre 3B). When the cut-off value of APRI was 0.8, the diagnostic sensitivity was 85.1%, and the specificity was 51.5% (Figure 3C).

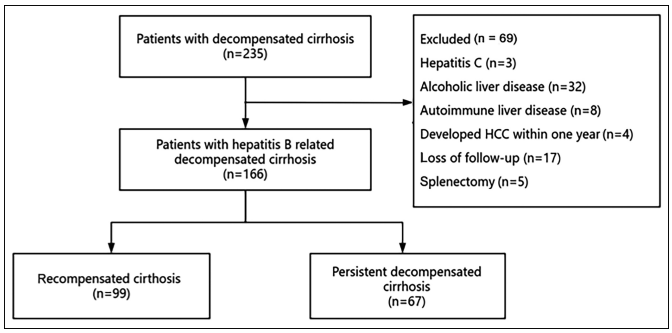


Figure 1: The flow chart of patients included. HCC: Hepatocellular carcinoma.

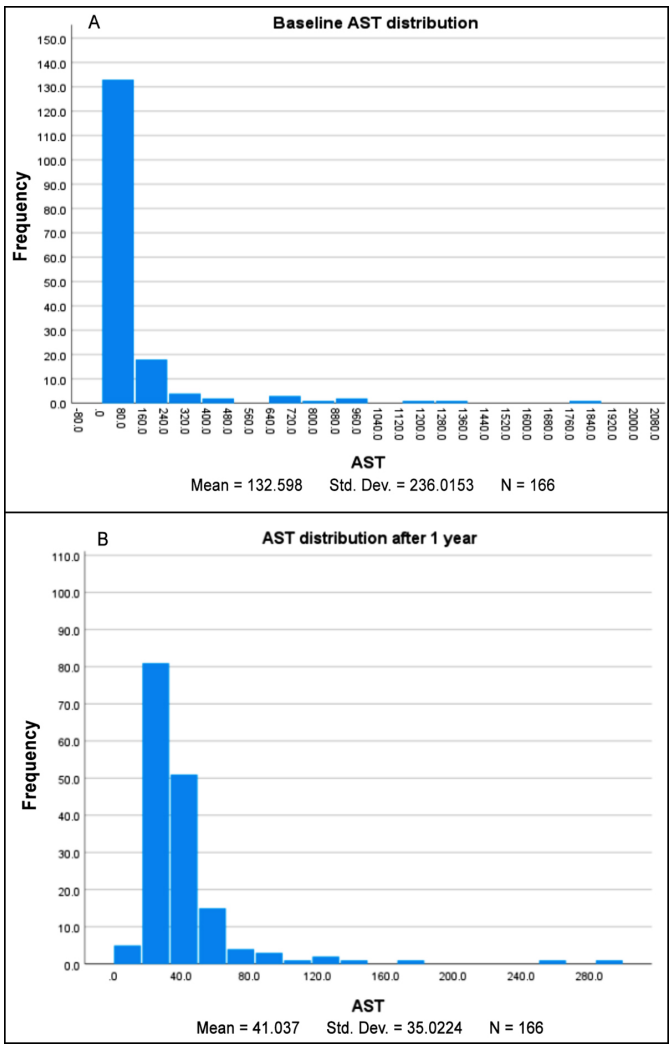
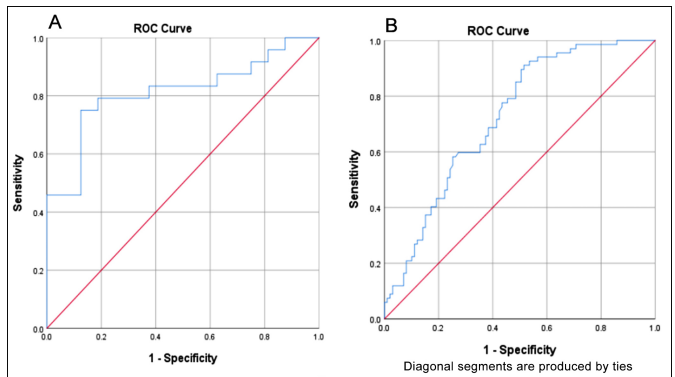


Figure 2: Baseline and 1-year AST distribution.



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Index	$AUROC_{cut\text{-}off}$	Cut-off	$Sensitivity_{cut\text{-}off}$	$Specificity_{cut\text{-}off}$
Baseline AST ≤40 data				
APRI	0.813 (0.678-0.947)	1	75%	87.5%
Data after 1 year late				
APRI	0.723 (0.648-0.799)	0.8	85.1%	51.5%

APRI, Aspartate aminotransferase-to-platelet ratio index; AUROC, Area under receiver operating characteristic

Figure 3: The efficiency of APRI in predicting recompensation in the group with AST <40 at baseline (A) and in the one year of antiviral treatment group (B) all data were measured separately at beseline and after one year of antiviral treatment. The data are plotted as receiver operating characteristics curve. APRI asparate aminosferase to platelet ratio index (C) diagnostic accuracy of APRI in predicting liver cirhosis recompensation.

DISCUSSION

The present study revealed that the APRI is an effective marker for predicting recompensation in patients with hepatitis B-related decompensated cirrhosis. This is particularly relevant for individuals undergoing nucleos-(t)-ide analogue (NAs) therapy and those exhibiting low AST levels. The utilisation of APRI can facilitate more effective clinical management of decompensated cirrhosis patients.

For the past few years, the Baveno VII consensus has presented a new definition of recompensation for cirrhosis.[5] Several studies have corroborated the finding that patients with recompensated cirrhosis exhibit a markedly diminished risk of clinical liver-related death and hepatocellular carcinoma.[6-9] To improve the clinical management of cirrhosis decompensation, it is essential to identify a simple and readily calculable indicator for predicting cirrhosis recompensation.

APRI utilises platelet counts and AST levels as a means of reflecting the degree of fibrosis and damage to the liver. A reduction in platelet counts, coupled with an increase in AST levels, is indicative of the advancement of chronic liver disease. The decline in platelet count is attributable to increased destruction caused by hypersplenism, providing further insight into the severity of end-stage liver disease.[18-20] Other studies have suggested that the progression of fibrosis in the liver may lead to the decrease in the levels of thrombopoietin.[21] Additionally, compared with ALT, AST is present in greater quantities within mitochondria and cytoplasm. Consequently, greater quantities of AST are released when mitochondrial damage occurs.[22] Furthermore, the progression of liver fibrosis may also impair AST clearance, leading to its retention in the bloodstream.[22] Consequently, the elevated AST levels in conjunction with reduced platelet counts can be employed to forecast the severity and progression of cirrhosis. Therefore, the predictive value of APRI is contingent upon the pathological basis of augmented inflammatory

activity within the liver and the progression of liver fibrosis. The reliability of APRI as a predictor of liver fibrosis and cirrhosis prognosis has been substantiated by a substantial body of evidence from a series of studies.[11-14]

The study by Yen *et al*. demonstrated that the different levels of AST had a significant impact on the diagnostic efficacy of APRI in cirrhosis.[23] In this study, the authors enrolled 166 patients with hepatitis B-related decompensated cirrhosis who were initiating antiviral treatment, observing a substantial range in baseline AST levels. The use of APRI may mis-estimate the risk of cirrhosis decompensation due to the effect of necrotic inflammatory activity on transaminases. The authors calculated APRI by stratifying the AST levels to predict liver cirrhosis recompensation, dividing the baseline data into two groups: AST ≤40 and AST >40 for data analysis.

In this study, for the group with baseline AST ≤40, APRI was identified as an independent predictor of recompensated cirrhosis. A study by Oikonomou *et al*. showed that higher APRI levels correlate with an elevated risk of clinical death and liver transplantation in decompensated cirrhosis patients.[24] To further validate these findings, the present research analysed the data after one year of antiviral treatment. Following one year of antiviral treatment, 157 (94.6%) out of 166 patients achieved a virological response. Compared to baseline AST distribution, the AST levels concentrated below 40 U/L in most patients. APRI remained a reliable predictor of cirrhosis recompensation, which further confirmed the present findings. Additionally, the authors observed that for patients undergoing treatment with NAs, lower APRI, female gender, and younger age were identified as the protective factors for recompensation among decompensated cirrhosis patients.

In the baseline AST >40 group, participants with the higher HBV DNA loads and female gender were more likely to achieve cirrhosis recompensation. In a previous study, it was also determined that higher levels of HBV DNA at baseline were linked to recompensation in patients with decompensated cirrhosis caused by hepatitis B,[25] which in accordance with the findings of the present study. It may be supposed that serum HBV levels gradually decrease with the progression of cirrhosis, which largely reflects the stage of cirrhosis. Consequently, patients with higher HBV DNA loads before antiviral therapy may have less advanced cirrhosis, which, if they survive in the early stages, will result in more recompensation.

Concurrently, the effectiveness of APRI in predicting cirrhosis recompensation was evaluated by using the ROC curve analysis. In the baseline AST ≤40 group, the optimal cut-off value of APRI was identified as 1.0. In patients with APRI less than 1.0, the incidence of cirrhosis recompensation was 70%. However, in the data one year after antiviral treatment, the optimal cut-off value for APRI was found to be 0.8. In patients with APRI less than 0.8, 85% of patients achieved cirrhosis recompensation. The difference in the optimal cut-off values may be associated with the reduction of liver inflammatory activity following antiviral medicine treatment, which results in a decline in the overall APRI level.

Although, a study had developed a prediction model for cirrhosis recompensation, designated as the BC2AID score.[25] APRI, which relies on only two markers, is more straightforward and convenient to compute, making it particularly well--suited for outpatient management.

However, this study has some limitations. It is essential to acknowledge that the study was conducted retrospectively, which may have introduced bias in the selection of participants. Although the study was conducted at two centres, the sample size was relatively limited. The results of this study require validation in larger, multicentre, prospective studies. Additionally, liver pathology examination was not conducted on patients with cirrhosis recompensation. To gain a better understanding of the pathology of recompensated cirrhosis, future prospective studies with liver biopsy are needed.

In a nutshell, the study provides a simple and effective marker for the recompensation of patients with decompensated liver cirrhosis caused by hepatitis B. However, these findings need further validation in a larger cohort.

CONCLUSION

APRI is an independent predictor of recompensation in hepatitis B-related decompensated cirrhosis, particularly in patients undergoing NAs therapy and with low AST levels. APRI can be employed as a straightforward marker for the management of patients with hepatitis B-related decompensated cirrhosis.

ETHICAL APPROVAL:

Ethical approval for this study (ID No: KYLL-2016(LW)-0032) was obtained from the Ethics Committee of the Second Hospital of the Shandong University.

PATIENTS' CONSENT:

Written informed consent was obtained from all patients.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

DY: Interpretation of data and writing the original draft.
JW: Data follow-up and participating in discussion writing.
YW: Data collection and abstract writing.
XL: Study design, methodology, and revision of the manuscript.
All authors approved the final version of the manuscript to be published.

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