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AST to Platelet Ratio Index Predicts Mortality in Hospitalized Patients With Hepatitis B-Related Decompensated Cirrhosis

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Abstract: Aspartate aminotransferase to platelet ratio index (APRI) has originally been considered as a noninvasive marker for detecting hepatic fibrosis in patients with chronic hepatitis B and C. APRI has been used for predicting liver-related mortality in patients with chronic hepatitis C virus infection or alcoholic liver disease. However, whether APRI could be useful for predicting mortality in chronic hepatitis B virus (HBV) infection remains unevaluated. This study aims to address this knowledge gap.

A total of 193 hospitalized chronic HBV-infected patients (cirrhosis, n = 100; noncirrhosis, n = 93) and 88 healthy subjects were retrospectively enrolled. All patients were followed up for 4 months. Mortality that occurred within 90 days of hospital stay was compared among patients with different APRI. APRI predictive value was evaluated by univariate and multivariate regression embedded in a Cox proportional hazards model.

APRI varied significantly in our cohort (range, 0.16–10.00). Elevated APRI was associated with increased severity of liver disease and 3-month mortality in hospitalized patients with HBV-related cirrhosis. Multivariate analysis demonstrated that APRI (odds ratio: 1.456, $P < 0.001$) and the model for end-stage liver disease score (odds ratio: 1.194, $P < 0.001$) were 2 independent markers for predicting mortality.

APRI is a simple marker that may serve as an additional predictor of 3-month mortality in hospitalized patients with HBV-related decompensated cirrhosis.

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Abbreviations: ACLF = acute-on-chronic liver failure, ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, CHBc = hronic hepatitis B, CRP = C-reactive protein, HBV = hepatitis B virus, HCh = ealthy control, INR = international normalized ratio, LCl = iver cirrhosis, MELD = model for end-stage liver disease.

INTRODUCTION

Liver cirrhosis (LC) is an outcome of chronic liver injury and tissue repair that occur in chronic liver diseases. Chronic hepatitis B virus (HBV) infection remains a major cause of LC in China.[1] A cirrhotic liver may progressively deteriorate from a well-compensated state to decompensated conditions.[2–5] Each year, approximately 2% to 5% of patients with compensated cirrhosis advance into a decompensated status. Cirrhosis-related complications represent the main cause for mortality in patients with decompensated cirrhosis, and the prognosis of decompensated cirrhosis is markedly worse, with 14% to 35% 5-year survival rate, compared with 84% in compensated cirrhosis.[5,6] Although a preferable treatment option for decompensated LC is liver transplantation, constant shortage of donor livers and high cost make this approach impracticable in most cases at present.[6,7] Therefore, the discovery of a marker that is associated with disease severity would be helpful for improving clinical management.

Aspartate aminotransferase to platelet ratio index (APRI) was initially proposed as a predictive marker for liver fibrosis and cirrhosis in hepatitis C virus (HCV)-infected patients.[8] Subsequently, various studies have attempted to extend this marker for assessing other liver diseases.[9] Although its clinical value has been questioned by controversial findings, APRI remains an attractive and frequently used marker for assessing a patient's prognosis. APRI is a simple, noninvasive, and easy to calculate index that helps clinicians identify individuals in need of greater care, especially in outpatient clinics.[10–14] For instance, APRI was found to be predictive of liver mortality in a cohort of patients with alcoholic liver disease.[15] Moreover, it was suggested in a recent study that APRI also predicted liver-related mortality in HCV-infected individuals.[16]

In China and other HBV-infected endemic regions, a portion of patients with chronic HBV infection-related cirrhosis can experience unpredictable flare-ups of liver injury, resulting in acute-on-chronic liver failure (ACLF) and high mortality. There is an urgent need to evaluate and validate simple and accurate markers for predicting outcomes of these patients and improve clinical management. Liver-related mortality is largely determined by liver failure, which can trigger multi-organ failures and jeopardize a patient's life. APRI combines 2 markers to reflect extent of liver injury and compensatory state of hepatic function. In this study, we determined APRI and investigated the association of APRI with the progression of HBV-related liver disease and mortality among patients with or without HBV-related cirrhosis.

MATERIALS AND METHODS

Subjects

Adult patients with chronic hepatitis B (CHB) who were admitted to the First Affiliated Hospital of Zhejiang University College of Medicine between August 1, 2013 and August 1, 2014 were consecutively recruited. The diagnosis of chronic HBV infection was based on the criteria recommended by Viral Hepatitis Management Guidelines, which was adopted by the Chinese Society of Infectious Diseases and Parasitology, and the Chinese Society of Hepatology of the Chinese Medical Association.[17] In

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brief, CHB is diagnosed when a HBV positive patients experienced HBV infection for more than 6 months, and accompanied by symptoms or/and signs of hepatitis, abnormal liver biochemistry, or histological changes. Exclusion criteria included patients with acute hepatitis, hematologic disorders, hepatocellular carcinoma, pregnancy, co-infected human immunodeficiency virus (HIV), hepatitis A virus, HCV, or hepatitis D virus, or other chronic liver diseases related to alcohol, drugs, or autoimmune diseases. Among the 193 CHB patients, 100 patients were diagnosed with HBV-related cirrhosis; and the remaining 93 patients were noncirrhotic. All patients were followed-up for 3 months or longer to assess the 3-month in-hospital mortality. After discharge, all patients were followed-up monthly by phone, and every 3 months by patient's visit to the hospital.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University College of Medicine. Written informed consent was obtained from each participant prior to enrollment into this study.

Laboratory Analysis

Blood samples were collected from all CHB patients within 24 h after admission, and blood samples were collected from 88 healthy controls (HCs) at the time of recruitment. Serum creatinine, albumin, total protein, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were measured using an automatic analyzer (Hitachi 7600, Tokyo, Japan). International normalized ratio (INR) was determined using a Sysmex CA-1500 fully automated blood coagulation analyzer (Sysmex Corp, Hyogo, Japan). Platelet and hemoglobin levels were determined using a Sysmex XE-2100 automated hematology analyzer (Sysmex Corp, Kobe, Japan), as the part of the complete blood count. Serum C-reactive protein (CRP) levels were measured by immunonephelometry (IMMAGE Nephelometer; Beckman Coulter, Fullerton, CA). The diagnosis of cirrhosis was supported by liver biopsy in 30 patients (30%), while the remaining 70 patients (70%) were diagnosed through a combination of physical stigmata of cirrhosis with biochemical markers (e.g., decreased serum albumin and increased serum globulin levels), ultrasonography or computed tomography (e.g., nodular liver surface, coarsened echogenicity of liver parenchyma, enlarged spleen, or ascites) findings, if liver biopsy was not conducted.[18,19] At the same time, among the 93 noncirrhosis patients, 37 patients were diagnosed histologically; and the remaining patients were diagnosed by clinical, endoscopic, or ultrasound evaluation. Liver-related mortality in patients with cirrhosis is caused by variceal hemorrhage, liver failure, ascites complications, or development of hepatocellular carcinoma.[20] At baseline, all demographic and clinical characteristics were collected including the model for end-stage liver disease (MELD) score.

MELD Score

Liver disease severity was evaluated via MELD score, which uses the patient's serum bilirubin and creatinine levels and the INR for prothrombin time to predict survival. The MELD score was calculated using the web site calculator (http://www.mayoclinic.org/gi-rst/mayomodel7.html).

APRI Calculation

APRI was calculated using the formula: APRI = AST (U/L)/(upper limit of the normal range) × 100/platelet count (10^9/L). The 40 U/L of AST was used as the upper limit of the normal rate.[8]

Assessment for Decompensated LC

All cirrhotic patients underwent clinical and laboratory assessment to establish the liver severity using Child–Pugh classification.[21,22] Liver decompensation criterion was set at score 8 of Child–Pugh classification.[23]

Statistical Analysis

All continuous variables were expressed as mean ± standstandard deviation (SD) or medians (range), and categorical data were calculated as percentages. Differences between variables were evaluated using ANOVA, Student t tests, and the Kruskal–Wallis and Mann–Whitney U tests. Categorical data were evaluated by χ^2 test or Fisher exact test, as appropriate. Correlations between variables were examined using Spearman correlation analysis. Cox proportional hazards regression was used to conduct multivariate analysis, and all possible clinical factors were included into the analysis. Statistical analysis was performed using SPSS V.16.0 (SPSS Inc, IL, USA), and $P < 0.05$ was statistically significant.

RESULTS

Baseline Characteristics of the Study Population

A total of 193 chronic HBV-infected patients (100 cirrhotic and 93 noncirrhotic) and 88 HCs were recruited into this study. Mean age of patients on admission was 47.1 years (range, 21–72 years; SD, 13.1 years). In comparing the age and gender composition among the 3 groups, we found that older men were associated with cirrhotic patients. We also found that liver disease in the cirrhotic group was more severe, as demonstrated by low levels of total proteins and serum albumin, and high INR, total bilirubin, APRI, and MELD score. Baseline characteristics are shown in Table 1.

Baseline Characteristics and Factors Associated With APRI in Cirrhotic Patients

Positive correlations between APRI and both CRP ($r = 0.459$, $P < 0.001$) and MELD scores ($r = 0.433$, $P < 0.001$), and an inverse correlation with serum albumin concentrations ($r = -0.242$, $P = 0.016$) were detected in cirrhotic patients (Figure 1).

We divided cirrhotic patients into 3 groups for further analysis based on APRI levels: group A (APRI ≤ 1.0), group B (>1.0, but <2.0), and group C (≥2.0). Clinical and laboratory characteristics among patients with various APRI levels are listed in Table 2. There were significant differences in INR, MELD score, ALT, and total bilirubin among the 3 groups ($P < 0.001$, $P < 0.001$, $P = 0.026$, and $P = 0.002$, respectively). Moreover, highly elevated APRI was associated with higher frequencies of clinical complications such as ascites and encephalopathy (all $P < 0.01$). Furthermore, increased APRI was associated with worsened Child–Pugh grade and increased the proportion of decompensated patients (both $P = 0.001$). There were no significant differences detected in serum total proteins, albumin, hemoglobin and creatinine levels, gender, and age among the 3 groups. MELD scores in groups A, B, and C were 7.1 ± 6.0, 13.3 ± 7.4, and 17.2 ± 7.4, respectively. The increase in APRI was in parallel with the increase in MELD scores ($P = 0.001$ between groups A and B, and $P = 0.040$ between groups B and C; Figure 2, left). In addition, group C patients had significantly higher AST levels compared with patients in groups A and B, and platelet count was lower in patients in group C than in groups A and B. These data suggest that higher

TABLE 1. Clinical Characteristics of Subjects at Baseline

	Cirrhosis (n = 100)	Noncirrhosis (n = 93)	HCs (n = 88)	*P*
Gender, male/female	76/24	71/22	40/48	<0.001
Age, y	52.1 ± 11.7	44.7 ± 10.2	41.7 ± 12.3	<0.01
Total protein, g/L	60.4 ± 7.7	64.4 ± 7.2	70.5 ± 4.0	<0.001
Albumin, g/L	31.1 ± 5.3	37.5 ± 5.8	45.4 ± 3.2	<0.001
ALT, U/L	33.0 (18.3–54.5)	91.0 (40.5–220.5)	16.5 (12.0–24.0)	<0.01
Total bilirubin, μmol/L	39.5 (19.0–78.0)	51.0 (18.5–69.0)	12.0 (9.0–15.0)	<0.001
INR	1.47 ± 0.52	1.12 ± 0.15	0.88 ± 0.30	<0.01
Creatinine, mmol/L	71.0 (60.0–109.3)	64.0 (49.0–79.5)	62.0 (55.0–78.0)	<0.001
MELD score	12.0 (7.0–18.0)	6.7 (3.8–10.8)	–	<0.001
APRI	1.61 (0.90–2.68)	0.91 (0.50–1.72)	0.22 (0.19–0.32)	<0.001
AST, U/L	42.5 (29.0–62.3)	51.0 (26.5–87.0)	19.0 (17.0–24.0)	<0.001
Platelet count	69.5 (46.7–118.5)	151.0 (104.5–188.0)	214.0 (180.3–245.0)	<0.001
HBsAg-positive, n	100	93	0	–
HBeAg-positive, n	45	93	0	–
HBV-DNA positive, n	100	93	0	–

Data are expressed as n, mean ± standard deviation, or median (interquartile range).
ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, HBV = hepatitis B virus, HC = healthy control, INR = international normalized ratio, MELD = model for end-stage liver disease.

APRI in cirrhotic patients could be primarily attributed to increased AST levels and decreased platelet count.

Association of APRI With 3-Month Mortality in Cirrhotic Patients

These patients were followed for a median 60 days (interquartile range: 20–95). During the follow up, 54 patients died within 3 months from liver failure (n = 42) or variceal bleeding (n = 12). Three-month mortality significantly increased with the increase in APRI values; from 19.2% in group A to 54.3% in group B and 76.9% in group C ($P = 0.012$ between groups A and B, and $P = 0.040$ between groups B and C; Figure 2, right).

Univariate logistic regression analysis demonstrated that patients with higher APRI and MELD score and lower albumin concentrations had a significantly higher death hazard. Multivariate logistic regression analysis revealed that APRI and MELD score were 2 independent factors for predicting the mortality rate (Table 3). Receiver operating characteristic curves were obtained to evaluate the clinical value of APRI and MELD score in predicting mortality (Figure 3). Area under the curve (AUC) was calculated as 0.844 ± 0.039 for the MELD score and 0.738 ± 0.049 for APRI (both $P < 0.001$). When APRI and the MELD score were combined, AUC reached 0.935 ± 0.023 ($P < 0.001$); which increased the efficiency of prediction by nearly 10%.

DISCUSSION

A daunting challenge in managing chronic HBV-infected patients with cirrhosis is to accurately predict prognosis with simple and reliable markers. This study aimed to evaluate the clinical value of APRI as a marker in predicting the 3-month mortality in our cohort, which consisted of 100 cirrhotic patients. We found that patients with cirrhosis exhibited a significantly higher APRI compared with noncirrhotic patients and HCs. Increased APRI was accompanied by increased MELD scores, which is an established marker for reflecting the severity of end-stage liver disease. Both APRI and MELD score could predict the 3-month mortality of patients with HBV-related cirrhosis effectively. A combination of APRI and MELD score could increase prediction efficiency to 94%.

Chronic HBV infection is often accompanied by an ongoing liver injury. Repeated repairs of damaged liver parenchyma could lead to fibrosis and cirrhosis. A cirrhosis patient, who has advanced to the decompensatory stage, can be very

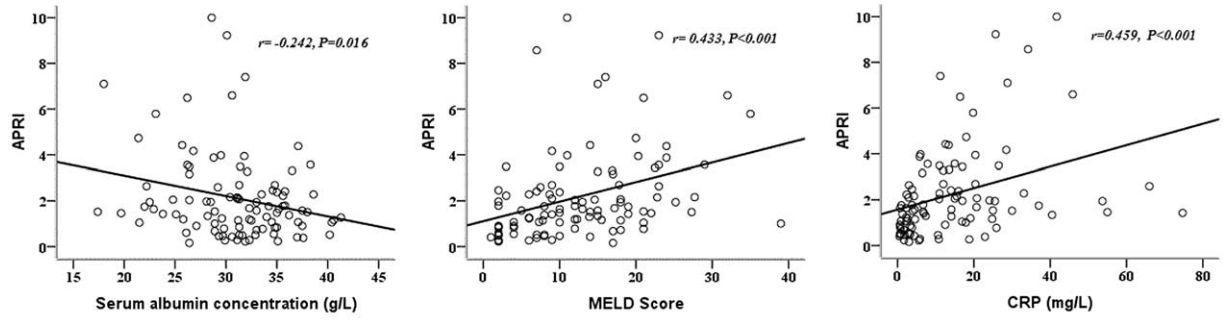

FIGURE 1. Correlation between serum albumin concentrations (left), MELD scores (middle), and CRP levels (right) with APRIs in patients with hepatitis B virus-related liver cirrhosis. APRI = aspartate aminotransferase to platelet ratio index, CRP = C-reactive protein, MELD = model for end-stage liver disease.

TABLE 2. Clinical and Laboratory Characteristics of Cirrhotic Patients With Different Aspartate Aminotransferase/Platelet Ratio Index Values at Admission

	Group A (APRI ≤ 1.0, n = 26)	Group B (1.0 < APRI < 2.0, n = 35)	Group C (APRI ≥ 2.0, n = 39)	*P*
APRI	0.54 ± 0.23	1.46 ± 0.29	4.00 ± 2.12	<0.001
Age, y	54.4 ± 13.2	51.7 ± 11.2	51.0 ± 12.1	0.482
Gender, male/female	21/5	30/5	25/14	0.076
Hemoglobin, g/dL	95.0 ± 20.9	101.8 ± 23.4	101.5 ± 25.0	0.468
Total protein, g/L	61.4 ± 6.0	59.4 ± 9.1	60.6 ± 7.9	0.614
Albumin, g/L	32.3 ± 3.6	30.9 ± 6.3	30.6 ± 5.3	0.442
ALT, U/L	21.7 ± 10.2	46.9 ± 43.4	82.6 ± 136.9	0.026
INR	1.20 ± 0.17	1.43 ± 0.32	1.69 ± 0.71	<0.001
Creatinine, mmol/L	89.9 ± 43.4	95.3 ± 66.5	110.6 ± 164.3	0.735
Total bilirubin, μmol/L	22.9 ± 18.8	72.0 ± 71.1	114.8 ± 140.3	0.002
MELD score	7.1 ± 6.0	13.3 ± 7.7	17.2 ± 8.2	<0.001
AST, U/L	29.2 ± 12.6	46.6 ± 26.1	82.6 ± 64.9	<0.001
Platelet count	156.3 ± 76.6	83.4 ± 54.5	53.3 ± 28.2	<0.001
Ascites, yes/no	10/16	25/10	26/13	0.022
Encephalopathy, yes/no	2/24	6/29	15/24	0.009
Decompensatory state, yes/no	12/14	27/8	34/5	0.001
Child-Pugh classification, A/B/C	14/11/1	8/13/14	5/13/21	<0.001
Mortality, yes/no	5/21	19/16	30/9	0.001
Cause of liver-related deaths				
Liver failure, n	3	14	25	–
Variceal bleeding, n	2	5	5	–

Data are expressed as n, or mean ± standard deviation.

ALT = alanine aminotransferase, APRI = aspartate aminotransferase/platelet ratio index, AST = aspartate aminotransferase, INR = international normalized ratio, MELD = model for end-stage liver disease.

vulnerable to new insults including reactivation of HBV replication in the infected liver; which frequently develops into liver failure (or ACLF). A liver failure can trigger multi-organ failures, which is the main cause of death in HBV cirrhotic patients. In our cohort, 73 of 100 cirrhosis patients deteriorated into a decompensatory state with cirrhosis-related complications of ascites, encephalopathy, or/and variceal bleeding. Furthermore, 54 of 100 patients died during the 3-month follow-up period; and majority of them (n = 42, 77.8%) died from liver failure. Thus, underlying pathologic changes leading to mortality in HBV cirrhotic patients include decompensated liver function and new insults to an already fragile liver.

There are several biochemical markers that can reveal both liver function and the extent of liver injury. APRI uses platelet count and AST levels to reflect insufficient liver function and new stress/damage to the liver. Decreased platelet count and increased AST levels are known as clinical manifestations of progression of LC. A reduction in platelet count can be caused by the accelerating destruction of an enlarged spleen,[24–26] which is termed as ''hypersplenism'' secondary to portal hypertension in cirrhosis. It can be also induced by reduced production. Studies of liver functions in transplant patients revealed that liver fibrosis progression was associated with decreased production of thrombopoietin by hepatocytes, leading to reduced platelet production.[27,28] A cirrhotic liver can often be subjected to new stresses or insults from different etiologies. Reactivation of HBV replication represents a frequent cause for new liver injury in HBV-related cirrhosis. Liver

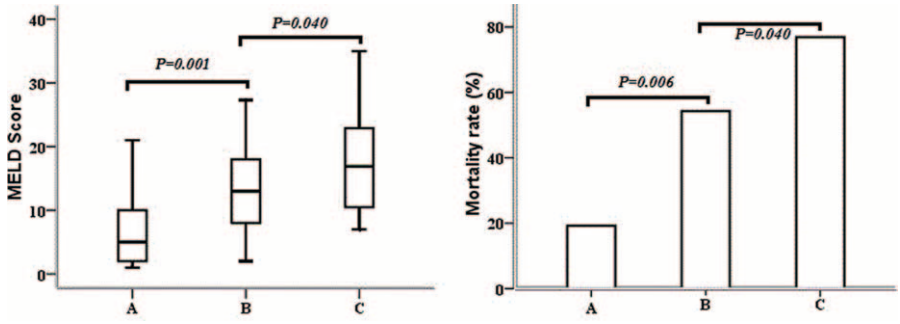

FIGURE 2. Comparisons of MELD scores (left) and mortality rates (right) among patients with different APRI levels. Patients were divided into 3 groups: groups A (APRI ≤ 1.0), B (1.0 < APRI < 2.0), and C (APRI ≥ 2.0). APRI = aspartate aminotransferase to platelet ratio index, MELD = model for end-stage liver disease.

TABLE 3. Cox Proportional Hazards Analysis for Predictors of Death

	Univariable			Multivariable		
	OR	**95% CI**	***P***	**Odds Ratio**	**95% CI**	***P***
APRI	1.861	1.296–2.674	0.001	1.456	1.021–2.077	0.038
MELD score	1.237	1.137–1.347	0.001	1.194	1.095–1.303	0.001
Age, y	1.041	1.000–1.016	0.283	–	–	–
Total protein, g/L	0.957	0.907–1.009	0.102	–	–	–
Albumin, g/L	0.865	0.791–0.945	0.001	0.897	0.804–1.001	0.052
Hemoglobin, g/dL	0.995	0.978–1.012	0.551	–	–	–
ALT, U/L	1.003	0.997–1.010	0.325	–	–	–

ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, CI = confidence interval, MELD = model for end-stage liver disease, OR = odds ratio.

injury including mitochondrial injury results in the release of more AST, which is more abundantly present in the mitochondria and cytoplasm relative to ALT.[29,30] Liver fibrosis progression may also reduce the clearance of AST, leading to the retention of AST in blood.[31] Therefore, high AST levels combined with low platelet count may be used to predict the severity and progression of liver injury in cirrhotic patients. Thus, APRI prediction is built on a sound pathologic foundation (increased hepatic necro-inflammatory activity and worsening liver function).

Moreover, we found a strong positive correlation between APRI and CRP levels in cirrhotic patients. CRP is synthesized in the acute phase of inflammation in response to interleukin-6,[32] and an elevated CRP suggests the presence of hepatic inflammation as a response to liver injury. We also detected the inverse correlation of APRI with serum albumin levels. Albumin is exclusively synthesized by hepatocytes, and a reduction in albumin levels suggests a significant reduction of the number of functioning hepatocytes. Thus, the pathologic validity of APRI for predication was further independently supported by CRP and albumin levels.

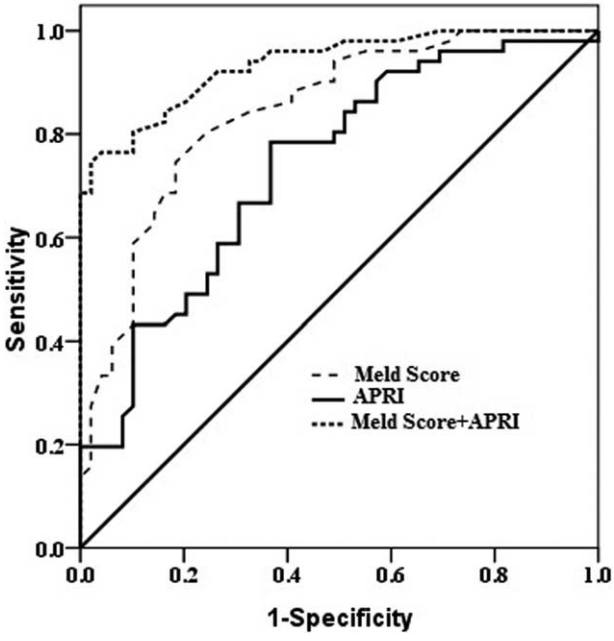

FIGURE 3. Mortality prediction efficiency by APRI (—), MELD score (•••), and their combination (••••). All markers were measured at the time of admission. Data are plotted as receiver operating characteristic curve. APRI = aspartate aminotransferase to platelet ratio index, MELD = model for end-stage liver disease.

In this study, APRI was identified as an independent predictor for mortality in patients with cirrhosis (Table 3). The MELD score has been frequently used to predict patient survival with end-stage liver disease and to determine the urgency of liver transplantation.[33] Our previous study reported that the MELD score reflected the prognosis of patients with ACLF.[34] In this present study, a positive correlation between the MELD score and APRI was identified; and multivariate logistic regression analysis has shown that APRI and MELD score were 2 independent markers for predicting the 3-month mortality in our cohort. However, APRI only involves 2 markers, which is simpler and easier to calculate than MELD score. A combination of APRI and MELD score further augmented the predicting power.

A few limitations of this study warrant mention. First, our study was retrospectively conducted, which carried bias in selecting participants. We acknowledge that the historical diagnosis of LC was made only in a portion of patients in our cohorts, because many of them were not suitable for or declined liver biopsy. Second, this was a single-center study, and sample size was relatively small. Our findings need to be verified in large multi-center and prospective studies. Finally, APRI was not kinetically monitored. We were not able to determine which APRI over time would perform better in predicting outcomes of HBV cirrhotic patients.

In summary, our study demonstrates that APRI is a simple and noninvasive scoring system that could predict risk for the development of liver-related complications and mortality in patients with HBV-related cirrhosis. APRI can be used as an additional marker for managing HBV-related cirrhosis patients.

REFERENCES

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet.* 2014;383:1749–1761.
2. Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and portal hypertension. *Korean J Hepatol.* 2010;16:347–352.
3. Jang JW. Current status of liver diseases in Korea: liver cirrhosis. *Korean J Hepatol.* 2009;15:S40–S49.
4. Wang SB, Wang JH, Chen J, et al. Natural history of liver cirrhosis in South China based on a large cohort study in one center: a

follow-up study for up to 5 years in 920 patients. *Chin Med J (Engl).* 2012;125:2157–2162.

5. Harrison PM. Management of patients with decompensated cirrhosis. *Clin Med.* 2015;15:201–203.
6. Chung GE, Lee JH, Kim YJ. Does antiviral therapy reduce complications of cirrhosis? *World J Gastroenterol.* 2014;20:7306–7311.
7. Chan AC, Fan ST, Lo CM, et al. Liver transplantation for acute-on-chronic liver failure. *Hepatol Int.* 2009;3:571–581.
8. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* 2003;38:518–526.
9. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: a systematic review. *Hepatology.* 2007;46:912–921.
10. Shin WG, Park SH, Jang MK, et al. Aspartate aminotransferase to platelet ratio index (APRI) can predict liver fibrosis in chronic hepatitis B. *Dig Liver Dis.* 2008;40:267–274.
11. Yu ML, Lin SM, Lee CM, et al. A simple noninvasive index for predicting long-term outcome of chronic hepatitis C after interferon-based therapy. *Hepatology.* 2006;44:1086–1097.
12. Lieber CS, Weiss DG, Morgan TR, et al. Aspartate aminotransferase to platelet ratio index in patients with alcoholic liver fibrosis. *Am J Gastroenterol.* 2006;101:1500–1508.
13. Wai CT, Cheng CL, Wee A, et al. Non-invasive models for predicting histology in patients with chronic hepatitis B. *Liver Int.* 2006;26:666–672.
14. Calès P, Oberti F, Michalak S, et al. A novel panel of blood markers to assess the degree of liver fibrosis. *Hepatology.* 2005;42:1373–1381.
15. Naveau S, Gaudé G, Asnacios A, et al. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. *Hepatology.* 2009;49:97–105.
16. Nunes D, Fleming C, Offner G, et al. Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. *Am J Gastroenterol.* 2010;105:1346–1353.
17. Anonymous. Management scheme of diagnostic and therapy criteria of viral hepatitis. *Zhonghua Gan Zang Bing Za Zhi.* 2000;6:324–329.
18. Huo TI, Wu JC, Lin HC, et al. Evaluation of the increase in model for end-stage liver disease (DMELD) score over time as a prognostic predictor in patients with advanced cirrhosis: Risk factor analysis and comparison with initial MELD and Child–Turcotte–Pugh score. *J Hepatol.* 2005;42:826–832.
19. Zeng DW, Zhang JM, Liu YR, et al. A new model for predicting liver cirrhosis in chronic hepatitis B virus carriers with low serum alanine transaminase activity. *Clin Res Hepatol Gastroenterol.* 2014;38:727–734.
20. Fevery J, Nevens F. Oesophageal varices: assessment of the risk of bleeding and mortality. *J Gastroenterol Hepatol.* 2000;15:842–848.
21. Tarantino G, Citro V, Esposito P, et al. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. *BMC Gastroenterol.* 2009;9:21.
22. Tarantino G, Citro V, Conca P, et al. What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? *BMC Gastroenterol.* 2009;9:89.
23. Planas R, Balleste B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *J Hepatol.* 2004;40:823–830.
24. Toghill PJ, Green S, Ferguson F. Platelet dynamics in chronic liver disease with special reference to the role of the spleen. *J Clin Pathol.* 1977;30:367–371.
25. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of ''hypersplenic'' thrombocytopenia. *J Clin Invest.* 1966;45:645–657.
26. McCormick PA, Murphy KM. Splenomegaly, hypersplenism and coagulation abnormalities in liver disease. *Baillières Best Pract Res Clin Gastroenterol.* 2000;14:1009–1031.
27. Kawasaki T, Takeshita A, Souda K, et al. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis. *Am J Gastroenterol.* 1999;94:1918–1922.
28. Adinolfi LE, Giordano MG, Andreana A, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. *Br J Haematol.* 2001;113:590–595.
29. Okuda M, Li K, Beard MR, et al. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology.* 2002;122:366–375.
30. Nalpas B, Vassault A, Le Guillou A, et al. Serum activity of mitochondrial aspartate aminotransferase: a sensitive marker of alcoholism with or without alcoholic hepatitis. *Hepatology.* 1984;4:893–896.
31. Kamimoto Y, Horiuchi S, Tanase S, et al. Plasma clearance of intravenously injected aspartate aminotransferase isozymes: evidence for preferential uptake by sinusoidal liver cells. *Hepatology.* 1985;5:367–375.
32. Bota DP, Van Nuffelen M, Zakariah AN, et al. Serum levels of C-reactive protein and procalcitonin in critically ill patients with cirrhosis of the liver. *J Lab Clin Med.* 2005;146:347–351.
33. Freeman RB Jr, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl.* 2002;8:851–858.
34. Mao W, Ye B, Lin S, et al. The prediction value of MELD scores system on prognosis in the acute on chronic liver failure patients with artificial liver support system. *ASAIO J.* 2010;56:475–478.