The preoperative alkaline phosphatase-to-platelet ratio index is an independent prognostic factor for hepatocellular carcinoma after hepatic resection

Ya-Qun Yu, MD, Jun Li, MD, Yan Liao, MD, Qian Chen, MD, Wei-Jia Liao, MD, Jian Huang, PhD

Abstract
A simple, inexpensive, and readily available prognostic index is highly needed to accurately predict the prognosis of hepatocellular carcinoma (HCC). This study aimed to develop a simple prognostic index using routine laboratory tests, alkaline phosphatase-to-platelet count ratio index (APPRI), to predict the likelihood of postoperative survival in HCC patients.

A total of 246 patients with HCC undergoing curative resection were retrospectively analyzed. Cutoff point for APPRI was calculated using receiver operating characteristic curve analysis, and then the patients were divided into the low-APPRI group (APPRI < 4.0) and the high-APPRI group (APPRI > 4.0). The influences of APPRI on disease-free survival (DFS) and overall survival (OS) were tested by the Kaplan-Meier method, and multivariate analysis using Cox regression. Elevated APPRI was associated with age, cirrhosis, and aspartate aminotransferase (AST) in HCC. Univariate analysis showed that APPRI > 4.0, tumor size > 6 cm, multiple tumors, Barcelona-clinic liver cancer stages B to C, and AST > 40 U/L were significant predictors of worse DFS and OS. A multivariate analysis suggested that APPRI > 4.0 was an independent factor for DFS (hazard ratio [HR] = 1.689; 95% confidence interval [CI] = 1.139–2.505; P = 0.009) and OS (HR = 1.664; 95% CI, 1.123–2.466; P = 0.011). Preoperative APPRI > 4.0 was a powerful prognostic predictor of adverse DFS and OS in HCC after surgery. The APPRI may be a promising prognostic marker for HCC after surgical resection.

Abbreviations: AFP = alpha-fetoprotein, ALP = alkaline phosphatase, ALT = alanine aminotransferase, APPRI = ALP-to-platelet ratio index, AST = aspartate aminotransferase, BCLC = Barcelona-clinic liver cancer, CI = confidence interval, DFS = disease-free survival, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hazard ratio, OS = overall survival, ROC = receiver operating characteristic, WBC = white blood cell.

Keywords: alkaline phosphatase-to-platelet ratio index, hepatocellular carcinoma, prognosis, survival

1. Introduction
Hepatocellular carcinoma (HCC) is one of the most common cancers, posing severe threats on the health and life of people worldwide. Hepatic resection surgery is an important curative treatment and gold standard for HCC to date. However, the clinical efficacy (prognosis) is far from satisfactory because of the frequent recurrence and poor long-term survival after surgery. Tumor recurrence rates occur in more than 70% of cases at 5 years.[1,2] Therefore, developing new predictive biomarkers to evaluate the postoperative recurrence risk and poor prognosis can provide a new way for early prevention and will be significantly beneficial to patients with cancer considering timely postoperative therapeutic interventions.

The prediction of prognosis plays a key role in effective clinical therapeutic options for HCC patients. Existing prognostic factors such as serum alpha-fetoprotein (AFP), multinodular tumors,[3] tumor Barcelona-clinic liver cancer (BCLC) stage,[4] and tumor size have been identified in previous studies, their prognostic value warrants more investigation and broader applications. However, they have limitations to some extent in sensitivity and specificity. Recently, accumulating evidence has indicated that certain tangible components (e.g., white blood cells [WBCs] and platelets) of the peripheral blood are predictors of prognosis in cancer patients. For instance, a high monocyte count is an independent factor of poor prognosis for patients with HCC[4] and colorectal liver metastasis.[5] Although once primarily recognized for their roles in thrombosis and hemostasis, platelets have been increasingly recognized as a multipurpose cell type.
Platelets sequester solubilized tumor-associated proteins and have emerged as central players in the systemic and local responses to tumor growth. More importantly, a recent study showed that the serum liver enzyme (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], and γ-glutamyl transpeptidase [γ-GT]) to peripheral blood tangible component ratio is associated with prognosis in HCC patients. For example, the preoperative AST-to-platelet ratio (APR), platelet-to-lymphocyte ratio (ALP), AST-to-lymphocyte ratio, and γ-GT-to-platelet ratio. However, in patients with HCC, the ALP-to-platelet ratio and indices of based on it as prognostic factors have not yet been established, and the relationship between the clinicopathologic features of HCC, at present, is unknown. Therefore, finding a noninvasive new marker is of great importance to patients with HCC.

The present study aimed to investigate the optimal value of the ALP-to-platelet ratio index (APPRI) and evaluate the correlation of the preoperative APPRI with clinicopathologic features and prognosis in patients with HCC who underwent curative resection. We conducted a retrospective study of 246 patients with HCC to explore their prognostic value for overall survival (OS). The optimal cutoff points for the APPRI were determined. The association between the levels of the APPRI and clinicopathologic characteristics was analyzed. Their prognostic value was explored by univariate and multivariate analysis, and as a basis, initial construction of a preoperative prognostic scoring model.

2. Materials and methods

2.1. Study population

Source of Specimens and Clinical Data from 256 cases of patients with HCC underwent hepatic resection at the Affiliated Hospital of Guilin Medical University (Guilin, People’s Republic of China) from August 1999 to February 2008, and these patients were recruited for this study. These subjects were confirmed by clinical, serological, and ultrasonography (US), computed tomography, magnetic resonance imaging, and pathologic examination. In addition, HCC diagnoses in this study followed the Primary Liver Cancer Clinical Diagnosis and Staging Criteria (Ministry of Health, Beijing, China). The baseline and clinical data include age, gender, liver enzymes (such as AST, ALT, ALP, and γ-GT), serum AFP, hepatitis B virus (HBV) infection, the size and number of tumors, combined liver cirrhosis, and BCLC stage. All of the subjects gave written informed consent, and the local ethics committee approved that this study conformed to the standards of the Declaration of Helsinki. This study was conducted as a retrospective analysis of a prospectively collected computerized database at a single hospital. Among them, 246 patients who met the inclusion criteria were enrolled in this study. These patients met all the following criteria: had been diagnosed with only HCC without portal vein tumor thrombus, lymph node metastasis, or extrahepatic distant metastases; had their clinical background data confirmed; had no lymphatic system disease or other infectious disease, for example, human immunodeficiency virus or hepatitis C virus infection; and were alive during the perioperative period. Our research group continuously monitored these 246 patients by long-term follow-up after surgery, including using the serum AFP test and US examination every 2 months and chest radiography every 6 months during the first 2 postoperative years and at 3- to 6-month intervals thereafter. Computed tomography or magnetic resonance imaging was performed if recurrence was suspected due to an abnormal AFP test or US examination. The mean postoperative follow-up time was 36.7 months (range, 2.0–84.0 months). Disease-free survival (DFS) was measured from the date of surgery to the date of recurrence, metastasis, death, or last follow-up. OS was measured from the date of surgery to the date of death or last follow-up.

2.2. Selection of cutoff score

To determine the optimal cutoff value of the APPRI, ALP, and platelets to predict HCC prognosis after liver resection, we analyzed the outcome of 246 HCC patients who underwent liver resection. Receiver operating characteristic (ROC) curve analysis was applied to define the cutoff value of the APPRI (≤4.0 vs >4.0). Other clinicopathologic parameters used were dichotomized: age (≤50 vs >50 years), gender (female vs male), family history (no vs yes), hepatitis B surface antigen (HBsAg) (negative vs positive), AFP level (≤20 vs >20 ng/mL), tumor size (≤6 vs >6 cm), cirrhosis (no vs yes), tumor number (single vs multiple), drinking (no vs yes), BCLC stage (0–A vs B–C), AST (<40 vs >40 U/L), and recurrence (no vs yes). Subsequently, the clinicopathologic and prognostic significance of the APPRI level in HCC was investigated.

2.3. Statistical analysis

SPSS version 13.0 software (SPSS Inc; Chicago, IL) and MedCalc statistical version 11.3.0.0 software (MedCalc Software; Brockstraat 52, Mariakerke, Belgium) were used to analyze the data. Pearson χ² test was used to compare qualitative variables. Univariate analysis was performed to determine the significance of variables using the logistic regression model for the response rate and the Cox regression model for DFS and OS. Survival curves were estimated by Kaplan–Meier analysis, and the log-rank test was used to examine the difference in the survival distributions between groups. Subsequently, the variables with P < 0.05 were subjected to multivariate analysis. The Cox proportional hazards regression model was used to determine the independent prognostic factors. A P value less than 0.05 was considered to be statistically significant.

| Table 1 |
| --- |
| **Clinical and biochemical data of examined patients.** |
| Parameter | Mean ± SD |
| Age, y | 40.95 ± 0.73 |
| Median size (range), cm | 7.62 ± 0.30 |
| AFP, ng/mL | 2576.15 ± 1034.03 |
| WBC, ×10⁹/L | 5.92 ± 0.14 |
| Lymphocyte, ×10⁹/L | 1.68 ± 0.04 |
| Platelets, ×10⁹/L | 170.10 ± 5.06 |
| Albumin, g/L | 30.91 ± 0.29 |
| Globulin, g/L | 29.46 ± 0.35 |
| Total bilirubin, µmol/L | 16.96 ± 1.67 |
| Direct bilirubin, µmol/L | 5.86 ± 0.90 |
| ALT, U/L | 45.77 ± 2.70 |
| AST, U/L | 53.19 ± 4.33 |
| ALP, U/L | 88.71 ± 2.53 |
| γ-GT, U/L | 99.89 ± 7.16 |
| APPRI | 6.68 ± 0.34 |

γ-GT = γ-glutamyl transpeptidase, γ-GT = γ-glutamyl transpeptidase, γ-GT = γ-glutamyl transpeptidase, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, ALP = alkaline phosphatase, γ-GT = γ-glutamyl transpeptidase, APPRI = ALP-to-platelets ratio index, AST = aspartate aminotransferase, SD = standard deviation, WBC = white blood cell.
3. Results

3.1. Basic clinical and biochemical data of the examined patients

The clinical and biochemical data of the examined patients are listed in Table 1, including age, median size, AFP, WBC count, lymphocytes, platelets, albumin, globulin, total bilirubin, direct bilirubin, ALT, AST, ALP, γ-GT, and the APPRI. All 246 HCC patients met the inclusion criteria and provided complete clinical background information for our study. Preoperative APPRI was calculated by using the following formula: (ALP value/platelets count) × 10^{10}/U.

3.2. An optimal cutoff value for the elevated APPRI

According to the ROC curve, the optimal cutoff value of the preoperative APPRI that had a relatively high specificity was 4.0. The area under the ROC curves was 0.674 with a 95% confidence interval (95% CI) for the area between 0.612 and 0.733. A cutoff value of 4.0 presented a sensitivity of 68.5% and a specificity of 61.2% (Fig. 1A).

3.3. Stratified analysis according to age, cirrhosis, and AST

Patients were stratified according to age, cirrhosis, and AST to compare the preoperative APPRI in 2 different HCC subgroups. We found that, when HCC patients were >50 years old, the preoperative APPRI was significantly higher than those aged ≤50 years (8.22 ± 0.60, 5.33 ± 0.33, respectively, *t* = 4.342, *P* < 0.0001, Fig. 1B). This tendency was also found in HCC patients with cirrhosis in contrast to those without cirrhosis (6.88 ± 0.36, 3.58 ± 0.37, respectively, *t* = 2.313, *P* = 0.0216, Fig. 1B). In addition, the preoperative APPRI in HCC patients with AST > 40 U/L was increased significantly compared with those with AST ≤ 40 U/L (8.09 ± 0.63, 5.48 ± 0.31, respectively, *t* = 3.895, *P* = 0.0001, Fig. 1B).

3.4. The preoperative APPRI in patients with HCC and its relationship with clinical pathologic characteristics

As shown in Table 2, the relationship between the preoperative peripheral blood APPRI and clinical pathologic characteristics was investigated. One hundred sixty-five patients (67.07%) identified as the high-APPRI group had an elevated APPRI (>4.0), and 81 patients (32.93%) were identified as the low-APPRI (≤4.0) group. The preoperative APPRI level was closely correlated with age (>50 years, χ² = 8.730, *P* = 0.0033), combination of liver cirrhosis (χ² = 5.112, *P* = 0.024), and the serum AST level (χ² = 12.928, *P* < 0.001). The mean age (51.14 ± 11.07) in patients with APPRI > 4.0 was higher than that (47.43 ± 11.72) in APPRI ≤ 4.0 group (χ² = 5.378, *P* = 0.0216, Fig. 2A). No obvious correlations with gender, tumor family history, HBsAg, median size, number of tumors, drinking, BCLC stage, recurrence, or serum AFP level were observed (all *P* > 0.05). The data demonstrated that the preoperative APPRI has a strong correlation with older age, cirrhosis, and high AST level, suggesting that these factors may be related to patients with HCC in liver damage.

3.5. Association of the APPRI or clinical pathologic index between postoperative DFS and OS

Kaplan–Meier survival analysis showed that an APPRI > 4.0 was associated with a shorter DFS (Fig. 2A) and OS (Fig. 2B). Univariate analysis revealed that an obvious association existed between clinical parameters and both DFS (Table 3) and OS (Table 4). The mean DFS in patients with APPRI ≤ 4.0 was 54.50 months (95% CI, 46.90–62.11) compared with 36.87 months (95% CI, 31.77–41.97) in patients with APPRI > 4.0 (*P* < 0.001). The mean OS rates in the APPRI ≤ 4.0 group and APPRI > 4.0 group were 58.60 months (51.88–65.31) and 44.05 months (39.30–48.80), respectively (*P* = 0.001). In addition to the high-APPRI group (APPRI > 4.0), a size of the tumor > 6 cm, multiple tumors, a BCLC stages B to C, and a serum AST level > 40 U/L were also associated with a shorter DFS and OS (*P* < 0.001; Table 4).

3.6. Independent predictors of DFS and OS in the stepwise multivariate Cox proportional hazards model

The Cox proportional hazards model was used to examine the association between clinicopathologic factors and DFS/OS after the surgical resection of HCC. After adjusting for other...
confounding factors, except for recurrence associated with OS, 5 associated factors (high APPRI, size of tumor $>6\text{cm}$, multiple tumors, BCLC stages B to C, and AST $>40\text{U/L}$) were analyzed for DFS and OS using the stepwise multivariate Cox proportional hazards model. Three factors were significant in the Cox proportional hazards model. The hazard ratio (HR), 95% CI, and $P$ values of the 3 independent predictors are listed in Tables 3 and 4. The stepwise multivariate Cox proportional hazards model revealed that a high APPRI (HR, 1.689; 95% CI, 1.139–2.466; $P=0.011$), a size of tumor $>6\text{cm}$ (HR, 1.897; 95% CI, 1.301–2.767; $P=0.001$), and an AST $>40\text{U/L}$ (HR, 1.829; 95% CI, 1.302–2.589; $P<0.001$) were independent predictors of OS (Table 4).

### 3.7. Kaplan–Meier analysis of DFS and OS in 246 HCC patients based on statistically significant clinical parameters

We established a preoperative prognostic score model by calculating the number of independent predictors (APPRI, size of tumor, and AST) for each patient. Each positive factor as a score of 1, and then the patients were divided into 4 categories.
Table 3
Association between APPRI level or clinical parameters and DFS.

| Clinical character | Category | No. of patients | Univariate analysis, mo | Multivariate analysis |
|--------------------|----------|-----------------|-------------------------|----------------------|
|                    |          | Mean            | 95% CI                  | P        | HR          | 95% CI     | P    |
| APPRI              | ≤4.0     | 81              | 54.50                   | 46.90–62.11 | <0.001     | 1.689      | 1.139–2.505 | 0.009 |
|                    | >4.0     | 165             | 36.87                   | 31.77–41.97 |            |            |            |      |
| Gender             | Female   | 34              | 46.15                   | 33.62–58.67 | 0.617      |            |            |      |
|                    | Male     | 212             | 42.36                   | 37.69–47.02 |            |            |            |      |
| Age, y             | ≤50      | 131             | 46.35                   | 40.29–52.40 | 0.089      |            |            |      |
|                    | >50      | 115             | 38.80                   | 32.57–45.03 |            |            |            |      |
| Family history     | No       | 214             | 41.17                   | 36.52–45.81 | 0.091      |            |            |      |
|                    | Yes      | 32              | 53.63                   | 41.30–65.86 |            |            |            |      |
| HBsAg              | Negative | 30              | 44.55                   | 32.26–56.85 | 0.627      |            |            |      |
|                    | Positive | 216             | 42.52                   | 37.84–47.20 |            |            |            |      |
| Median size (range), cm | ≤6 | 130             | 53.38                   | 47.40–59.28 | <0.001     | 1.881      | 1.289–2.747 | 0.001 |
|                    | >6       | 116             | 31.25                   | 25.45–37.05 |            |            |            |      |
| Liver cirrhosis    | No       | 15              | 48.79                   | 30.77–66.80 | 0.678      |            |            |      |
|                    | Yes      | 231             | 42.46                   | 37.95–46.97 |            |            |            |      |
| Tumor number       | Single   | 168             | 48.76                   | 43.49–54.06 | <0.001     | 1.326      | 0.616–2.556 | 0.470 |
|                    | Multiple | 78              | 29.98                   | 23.08–36.88 |            |            |            |      |
| Drinking           | No       | 116             | 40.29                   | 33.99–46.58 | 0.282      |            |            |      |
|                    | Yes      | 130             | 44.98                   | 38.92–51.04 |            |            |            |      |
| BCLC stage         | 0–A      | 171             | 48.14                   | 42.88–53.40 | <0.001     | 1.002      | 0.471–2.129 | 0.996 |
|                    | B–C      | 75              | 30.65                   | 23.52–37.78 |            |            |            |      |
| APP, ng/mL         | ≤20      | 74              | 40.75                   | 33.00–48.50 | 0.570      |            |            |      |
|                    | >20      | 172             | 43.71                   | 38.41–49.01 |            |            |            |      |
| AST, U/L           | ≤40      | 133             | 51.81                   | 45.88–57.74 | <0.001     | 1.742      | 1.237–2.453 | 0.001 |
|                    | >40      | 113             | 32.42                   | 26.49–38.45 |            |            |            |      |

APP = alpha-fetoprotein, APPRI = ALP-to-platelets ratio index, AST = aspartate aminotransferase, BCLC = Barcelona-clinic liver cancer, CI = confidence interval, HBsAg = hepatitis B surface antigen, HR = hazard ratio.

Table 4
Association between APPRI level or clinical parameters and OS.

| Clinical character | Category | No. of patients | Univariate analysis, mo | Multivariate analysis |
|--------------------|----------|-----------------|-------------------------|----------------------|
|                    |          | Mean            | 95% CI                  | P        | HR          | 95% CI     | P    |
| APPRI              | ≤4.0     | 81              | 58.60                   | 51.88–65.31 | 0.001      | 1.664      | 1.123–2.466 | 0.011 |
|                    | >4.0     | 165             | 44.05                   | 39.30–48.80 |            |            |            |      |
| Gender             | Female   | 34              | 52.48                   | 41.42–63.53 | 0.436      |            |            |      |
|                    | Male     | 212             | 48.37                   | 44.11–52.63 |            |            |            |      |
| Age, y             | ≤50      | 131             | 50.98                   | 45.44–56.52 | 0.216      |            |            |      |
|                    | >50      | 115             | 46.62                   | 40.95–52.29 |            |            |            |      |
| Family history     | No       | 214             | 47.56                   | 43.32–51.80 | 0.090      |            |            |      |
|                    | Yes      | 32              | 57.96                   | 46.99–68.92 |            |            |            |      |
| HBsAg              | Negative | 30              | 50.25                   | 39.92–61.58 | 0.817      |            |            |      |
|                    | Positive | 216             | 48.73                   | 44.49–52.98 |            |            |            |      |
| Median size (range), cm | ≤6 | 130             | 59.41                   | 54.34–64.48 | <0.001     | 1.897      | 1.301–2.767 | 0.001 |
|                    | >6       | 116             | 36.67                   | 31.34–42.04 |            |            |            |      |
| Liver cirrhosis    | No       | 15              | 53.12                   | 37.00–69.24 | 0.682      |            |            |      |
|                    | Yes      | 231             | 48.67                   | 44.57–52.77 |            |            |            |      |
| Tumor number       | Single   | 168             | 54.80                   | 50.15–59.45 | <0.001     | 1.377      | 0.596–3.180 | 0.454 |
|                    | Multiple | 78              | 35.82                   | 29.26–42.38 |            |            |            |      |
| Drinking           | No       | 116             | 47.20                   | 41.43–52.97 | 0.392      |            |            |      |
|                    | Yes      | 130             | 50.43                   | 44.96–55.90 |            |            |            |      |
| BCLC stage         | 0–A      | 171             | 54.29                   | 49.67–58.92 | <0.001     | 1.008      | 0.443–2.292 | 0.985 |
|                    | B–C      | 75              | 36.25                   | 29.48–43.01 |            |            |            |      |
| APP, ng/mL         | ≤20      | 74              | 47.62                   | 40.65–54.59 | 0.580      |            |            |      |
|                    | >20      | 172             | 49.47                   | 44.64–54.30 |            |            |            |      |
| AST, U/L           | ≤40      | 133             | 57.64                   | 52.49–62.79 | <0.001     | 1.829      | 1.302–2.589 | <0.001 |
|                    | >40      | 113             | 38.69                   | 33.07–44.32 |            |            |            |      |
| Recurrence         | No       | 150             | 44.29                   | 38.78–49.79 | 0.028      | 1.268      | 0.621–2.665 | 0.387 |
|                    | Yes      | 96              | 56.13                   | 51.01–61.25 |            |            |            |      |

APP = alpha-fetoprotein, APPRI = ALP-to-platelets ratio index, AST = aspartate aminotransferase, BCLC = Barcelona-clinic liver cancer, CI = confidence interval, HBsAg = hepatitis B surface antigen, HR = hazard ratio.
according to their risk scores (RSs) (0–3). For example, a “risk score = 0” indicates patients without any of the above factors, and this group accounted for 13.41% (33/246) of the patients, and a “risk score = 3” indicates patients with all 3 factors, and this group accounted for 19.51% (48 of 246) of the patients carrying all 3 factors (Fig. 3). Because no significant difference was observed in DFS and OS between patients whose RS was 0 or 1 (Fig. 3A and B, \( P = 0.103 \) and 0.131, respectively), these patients were merged as the score \( \leq 1 \) group. By combining 3 independent predictors, patients with different RSs showed distinguishable DFS (RS \( \leq 1 \) vs RS = 2, \( P < 0.001 \); RS = 2 vs RS = 3, \( P = 0.002 \), Fig. 3C) and OS (RS \( \leq 1 \) vs RS = 2, \( P < 0.001 \); RS = 2 vs RS = 3, \( P = 0.009 \), Fig. 3D). Surprisingly, the proportion of HCC patients with RS = 3 was very high, occupying 19.51% (48 of 246) of all patients. The DFS and OS in 48 patients with a score of 3 decreased sharply, and all of these patients showed a much shorter DFS and OS.

4. Discussion

ALP is an enzyme widely distributed in the human tissues of the liver, bone, intestine, and kidney, and low-density ALP is measured in normal human serum. However, serum ALP, mainly from the liver, has a high specificity. Except for ALP, serum liver enzymes such as ALT and AST are routinely tested in HCC patients. These enzymes are commonly elevated in patients with liver cirrhosis, portal hypertension, hypersplenism, and low platelet and WBC levels. Development of HCC patients with liver cirrhosis, portal hypertension, hypersplenism, and low platelet and WBC levels develop HCC; on the other hand, due to liver damage, serum liver biochemistry enzyme indexes are increased—for example, ALP, AST, ALT, and γ-GT levels—primarily leading to an increased APPRI. Furthermore, platelets have been well established to play a key role in liver fibrosis, cirrhosis, and development to HCC; on the other hand, due to liver damage, serum liver biochemistry enzyme indexes are increased—for example, ALP, AST, ALT, and γ-GT levels—primarily leading to an increased APPRI. Furthermore, platelets have been well established to play a key role in liver fibrosis, cirrhosis, and development to HCC; on the other hand, due to liver damage, serum liver biochemistry enzyme indexes are increased—for example, ALP, AST, ALT, and γ-GT levels—primarily leading to an increased APPRI. 

In the present study, the prognostic role of preoperative APPRI in patients with HCC was investigated. The data from 246 patients with HCC who underwent liver resection were analyzed. Our results revealed that a preoperative APPRI > 4.0 was an independent predictor of DFS and OS in HCC patients after hepatectomy. To our knowledge, this study is the first article in investigating the prognostic significance of the preoperative APPRI in HCC patients.

Based on the results of univariate analysis, except for APPRI, we found that a tumor size > 6 cm, multiple tumors, BCLC stages B to C, and AST were associated with a short DFS and OS. The
prognostic relevance of the tumor size,\textsuperscript{24,25} tumor number,\textsuperscript{26} BCLC stage,\textsuperscript{5} and AST\textsuperscript{27,28} for survival in HCC patients was confirmed by previous studies. In Roayaie et al.'s\textsuperscript{29} report, tumor size was an important determinant for the survival of HCC patients. Obviously, individuals with multinodular HCC tumors had a relatively short survival and poor prognosis compared with those with a single tumor.\textsuperscript{26}

The findings in the multivariate analysis showed that a preoperative APPRI > 4.0, a tumor size >6 cm, and an AST > 40 U/L were independent prognostic markers of DFS and OS in HCC patients. This finding is consistent with previously reported results that tumor size may act as an independent prognostic factor for resected small HCC.\textsuperscript{29} Generally, small HCC tumors have a better prognosis.\textsuperscript{23}

From our study, the optimal cutoff value of preoperative APPRI for predicting the prognosis of HCC was 4.0. Calculating the preoperative APPRI is a simple method for the judgment of prognosis in HCC patients. However, our survey also has some limitations. Many other factors affecting APPRI, such as antiviral therapy before surgery, may impair the accuracy of the prognostic prediction. In the follow-up, we found that the success of the antiviral therapies might decrease HCC recurrence and improve postoperative survival in a minority of patients who receive antiviral therapies. Yet, we discovered that only about 5% of the HCC patients who were conventional candidates for antiviral treatment receive the antiviral therapies, while the vast majority of patients give up antiviral treatment because of economic or other reasons. In addition, the AFP level and HBV infection might also affect the prognosis of HCC, although the effect was not significant in our study, probably due to the limited number of patients. The prognostic role of the APPRI only by retrospectively analyzing the clinical data of 246 patients from our hospital, it would be necessary to validate the prognostic significance of the APPRI levels in a larger cohort of HCC patients.

We found a significant elevation in the APPRI levels before surgery, which independently predicted prognosis in HCC patients. In addition, this effect was also significantly increased when we combined the tumor size and AST; based on the 3 parameters, we successfully constructed a model of the preoperative prognostic score. This provided a new RS for HCC. However, the small sample size of the present study limits its clinical value. The validation of the prognostic value of the preoperative prognostic scoring model should be best warranted in future clinical trials from other institutions. A prospective study with a larger population should be conducted to justify our studies.

In conclusion, our data suggest that an elevated preoperative APPRI is an independent predictor of poor prognosis for patients with HCC after hepatic resection. HCC patients with an elevated APPRI should be subjected to close follow-up and timely postoperative therapeutic intervention to improve their life quality. The combined use of the existing prognostic biomarkers with the APPRI will offer incremental predictive information and will substantially enhance the sensitivity and specificity of predicting prognosis in HCC patients. As expected, a size of the tumor >6 cm and an AST >40 U/L were also independent prognostic factors in our study. It is likely that we could use the APPRI to evaluate the prognosis of HCC patients. In addition, the above 2 factors (tumor size and AST) comprehensively will improve the predicting accuracy.

Most importantly, the APPRI, as a novel predictive tool in clinical practice, has major advantages concerning its simplicity and objectivity. It is derived from 2 easily available laboratory results (ALP level and platelet count). Both the ALP level and platelet count are routine tests performed in HCC patients in clinical practice, and no extra tests are needed. Therefore, it is simple, objective, and inexpensive. In addition, the APPRI is expected to provide more biomarkers of diagnosis and monitoring to implement personalized medicine in patients with cancer.

References

\begin{footnotesize}
\begin{enumerate}
\item [1] Poon RT. Prevention of recurrence after resection of hepatocellular carcinoma: a daunting challenge. Hepatology 2011;54:757–9.
\item [2] Thrall JG, Dagheti I, Lino T, et al. Treatment of tumour recurrence after resection of hepatocellular carcinoma. Analysis of 97 consecutive patients. Eur J Surg Oncol 2007;33:746–51.
\item [3] Giannini EG, Farnanti F, Ciccarese F, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology 2015;61:884–90.
\item [4] Sasaki A, Iwashita Y, Shibata K, et al. Prognostic value of preoperative peripheral blood monocyte count in patients with hepatocellular carcinoma. Surgery 2006;139:755–64.
\item [5] Sasaki A, Kai S, Endo Y, et al. Prognostic value of preoperative peripheral blood monocyte count in patients with colorectal liver metastasis after liver resection. J Gastrointest Surg 2007;11:596–602.
\item [6] Klement GL, Yip TT, Cassofa F, et al. Platelets actively sequester angiogenesis regulators. Blood 2009;113:2833–42.
\item [7] Nilsson RJ, Balaj I, Hulleman E, et al. Blood platelets contain tumor-derived RNA biomarkers. Blood 2011;118:3680–3.
\item [8] Best MG, Sol N, Kooi I, et al. RNA-seq of tumor-educated platelets enables blood-based pan-cancer, multiclass, and molecular pathway cancer diagnostics. Cancer Cell 2015;28:666–76.
\item [9] Shen SL, Fu SJ, Chen B, et al. Preoperative aspirate aminotransferase to platelet ratio is an independent prognostic factor for hepatitis B-induced hepatocellular carcinoma after hepatic resection. Ann Surg Oncol 2014;21:3802–9.
\item [10] Li X, Chen ZH, Xing YF, et al. Platelet-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. Tumour Biol 2015;36:2263–9.
\item [11] Jin J, Zhu P, Liao Y, et al. Elevated preoperative aminotransferase to lymphocyte ratio index as an independent prognostic factor for patients with hepatocellular carcinoma after hepatic resection. Oncotarget 2015;6:19217–27.
\item [12] Lemoine M, Shmakova Y, Nayagam S, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut 2016;65:1369–76.
\item [13] Pratt DS, Kaplan MM. Evaluation of abnormal liver enzyme results in asymptomatic patients. N Engl J Med 2000;342:666–71.
\item [14] Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
\item [15] Yu MW, Yeh SH, Chen PJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst 2005;97:625–72.
\item [16] Xu C, Zhou W, Wang Y, et al. Hepatitis B virus-induced hepatocellular carcinoma. Cancer Lett 2014;345:216–22.
\item [17] Kodama T, Takehara T, Hikita H, et al. Thrombocytopenia exacerbates cholestasis-induced liver fibrosis in mice. Gastroenterology 2010;138:2487–98.
\item [18] Kurokawa T, Murata S, Zheng YW, et al. The Eltrombopag antitumor effect on hepatocellular carcinoma. Nat J Oncol 2015;7:1696–702.
\item [19] Carr BI, Lin CY, Lu SN. Platelet-related phenotypic patterns in hepatocellular carcinoma patients. Semin Oncol 2014;41:415–21.
\item [20] Cho MS, Bottsford-Miller J, Vasquez HG, et al. Platelets increase the proliferation of ovarian cancer cells. Blood 2012;120:4559–67.
\item [21] Alkozai EM, Porte RJ, Adelmeijer J, et al. Levels of angiogenic proteins in asymptomatic patients. N Engl J Med 2000;342:666–71.
\item [22] Franco AT, Corken A, Ware J. Platelets at the interface of thrombosis, inflammation, and cancer. Blood 2015;126:382–9.
\item [23] Yu LX, Yan L, Yang W, et al. Platelets promote tumour metastasis via interaction between TLR4 and tumour cell-released high-mobility group box1 protein. Nat Commun 2014;5:3236.
\item [24] Kow AW, Kwok CH, Song S, et al. Risk factors of peritoneal recurrence and outcome of resected peritoneal recurrence after liver resection in HCC. Jpn J Clin Oncol 2015;45:1093–103.
\item [25] Yu LX, Yan L, Yang W, et al. Platelets promote tumour metastasis via interaction between TLR4 and tumour cell-released high-mobility group box1 protein. Nat Commun 2014;5:3236.
\item [26] Kow AW, Kwok CH, Song S, et al. Risk factors of peritoneal recurrence and outcome of resected peritoneal recurrence after liver resection in HCC. Jpn J Clin Oncol 2015;45:1093–103.
\end{enumerate}
\end{footnotesize}
hepatocellular carcinoma: review of 1222 cases of hepatectomy in a tertiary institution. Ann Surg Oncol 2012;19:2246–55.

[25] Roayaie S, Obeidat K, Sposito C, et al. Resection of hepatocellular cancer ≤2 cm: results from two Western centers. Hepatology 2013;57:1426–35.

[26] Goh BK, Chow PK, Teo JY, et al. Number of nodules, Child–Pugh status, margin positivity, and microvascular invasion, but not tumor size, are prognostic factors of survival after liver resection for multifocal hepatocellular carcinoma. J Gastrointest Surg 2014;18:1477–85.

[27] Pinter M, Sieghart W, Huckle F, et al. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. Aliment Pharmacol Ther 2011;34:949–59.

[28] Liao W, Liu W, Liu X, et al. Upregulation of FAM83D affects the proliferation and invasion of hepatocellular carcinoma. Oncotarget 2015;6:24132–47.

[29] Chen YL, Ko CJ, Chien SY, et al. Tumor size as a prognostic factor in resected small hepatocellular carcinoma: a controversy revisited. J Gastroenterol Hepatol 2011;26:851–7.