Can Non-Invasive Assessment of Liver Fibrosis Be Used As A Predictor of Prognosis for HCC Patients with HBV-Related Cirrhosis?

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Research Article

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Abstract

Backgroud: Most liver cancer patients have backgroud of HBV-related liver cirrhosis. We are still not sure whether non-invasive assessments of liver fibrosis can be used as predictors of prognosis. In this study, we investigate the relationship between aspartate aminoytransferase (AST)-to-platelet(PLT) ratio index (APRI) and the prognosis of hepatocellular carcinoma (HCC) patients with liver cirrhosis.

Methods: The clinical data of HCC patients with cirrhosis who received hapatectomy in our hospital were analyzed retrospectively. Receiver Operating Characteristic (ROC) curve was used to determine APRI cut-off value to predict the prognosis. Kaplan-Meier survival (Log-rank test) and Cox regression analyses were used for univariate and multivariate analysis of the prognosis in all patients, and the differences were compared between the APRI high-value and low-value groups. Independent sample *t* test was used to compare the differences of clinical data between the APRI high-value and low-value groups.

Results: The cut-off value was determined as 0.61 according to the ROC curve, and the high-value group was defined as APRI ≥ 0.61, while the low-value group was defined as APRI<0.61. By the end of follow-up data, the proportion of patients died from liver failure in high-value group was higher than that in low-value group (χ^2 =5.232, P=0.022). The results of survival analysis showed that the maximum of tumor diameter >0.5cm, multiple tumors, invasion of liver capsule, vascular tumor thrombus, AFP>20ng/ml and APRI ≥ 0.61were independent risk factors influencing the disease free survival (DFS) time after resection for HCC patients with cirrhosis (P<0.05). The 1-year, 2-year, and 5-year disease free survival rates of APRI low-value and high-value groups were 79.4%, 61.4%, 43.7% and 71.4%, 51.6%, 27.0%. The recurrence rate of APRI low-value and high-value groups were 20.5%, 38.1%, 54.1% and 28.0%, 47.1%, 69.8%, respectively (P=0.000). APRI value of patients with portal hypertension (PH) and Child-pugh B class were higher than those without PH and Child-pugh A class (P<0.05).

Conclusion: HCC patients with liver cirrhosis whose APRI ≥ 0.61 had worse prognosis after resection.

Background

Liver cancer is one the most common malignant tumors, with the second highest cancer-related mortality worldwide. Primary HCC is the most common pathological type, surgical resection is one of the therapeutic methods [1]. Repeated inflammation of the liver caused by hepatitis B virus infection can lead to liver fibrosis, cirrhosis and eventually HCC. Studies have showen that more than 50% HCC patients have liver cirrhosis and have a worse prognosis[2-3]. APRI proposed by Wai *et al*[4], combined with AST and PLT, has certain application value in predicting the degree of liver fibrosis[5-6]. At present, liver function status and reserve function have taken into account in preoperative evaluation of HCC, but there is no evaluation of liver fibrosis degree. It is not clear that whether different degrees of liver fibrosis can affect the prognosis of HCC patients. In this study, APRI was used as a non-invasive method to evaluate the degree of liver fibrosis, and the relationship between APRI and the prognosis of HCC patients with liver cirrhosis was analyzed.

Methods

Patient data

Clinical data of patients undergoing HCC resection in Affiliated hospital of Qingdao university from 2000 to 2104 were collected retrospectively. This study was approved by hospital ethics committee. Inclusion criteria: (a) tumor were pathologically confirmed as HCC with liver cirrhosis; (b) HCC were associated with hepatitis B virus infection. Exclusion criteria: (a) patients with previous splenectomy history; (b) patients missed follow-up; (c) patients died of perioperative complications such as liver failure, pulmonary infection and abdominal hemorrhage. According to HCC guidelines, the diagnosis of all HCC patients complicated with cirrhosis was based on postoperative pathological and clinical evaluation. A total of 655 cases were included, including 561 males and 94 females with a median age of 55 years (17-82 years). All methods were performed in accordance with the relevant guidelines and regulations.

Observation indexes and follow-up

Periopertive clinical data were extracted in the form of data tables. Preoperative data: gender, age, oral anti-hepatitis B virus drugs status,Child-pugh classification, portal hypertension status, alpha fetalin(AFP) level, PLT number. Intraoperative situation: portal vein block time, blood loss, blood transfusion. Postoperative tumor pathological data: tumor number, maximum diameter, invasion of liver capsule, microvascular tumor thrombus, minimum surgical margin. APRI value is calculated according to the following formula[4]: AST/upper limit of normal AST/platelet count (10^9/L)×100.

All patients were regularly followed up after surgery. Serum AFP assessment, liver function tests, liver ultrasonography or CT, and lung CT were performed monthly for the first 3 months, and then, every 3 months after treatment for recurrence assessment. The follow-up ended on September 30, 2017 or at HCC recurrence.We declare that informed consents for the use of their clinical data in this study were obtained from all participants or their next of kin before follow up and before the study began.

Statistical analysis

All statistical analysis was completed by IBM SPSS 23.0 software. Normal distribution data were expressed as mean ± standard deviation (± SD), and analyzed by *t* test. Classified variable data were analyzed by χ^2 test. The APRI predictive value was evaluated by ROC and the area under the curve (AUC). APRI cut-off value was determined when the Youden index is at its maximum. The preoprative and postoperative clinical pathology data were included in the Kaplan-Meier survival (Log-rank test), and data with significant differences (P<0.05) were included in the Cox regression model for multivariate analysis. P<0.05 was considered statistically significant.

Results

Among 655 HCC patients with liver cirrhosis, 452 patients had HCC recurrence, 324 patients died of liver failure, 27 patients died of liver cancer. The median DFS time of 655 patients was 31.4 months, median overall survival time was 75.4 months. The 1-year, 2-year, and 5-year survival rates were 93.6%, 80.0% and 55.7%, respectively. The 1-year, 2-year, and 5-year disease free rates were 74.7%、56.6%、34.6%.

The area under the ROC of APRI was 0.602 (95% CI:0.554-0.650, P=0.000). The maximum value of Youden index was 0.192 (sensitivity 56.8%, specificity 62.4%), and the cut-off value was 0.61(Figure 1). Patients with APRI <0.61 were included in the low-value group, and those with APRI ≥0.61 were included in high-value group. The mortality rate due to liver failure in high-value group was higher than that of low-value group (20/204 and 4/128, P=0.022) (Table 1). The results of univariate and multivariate analysis showed that the maximum tumor diameter >0.5cm, multiple tumors, invasion of liver capsule, vascular tumor thrombus, AFP>20ng/ml and APRI ≥ 0.61were independent risk factors influencing the disease free survival (DFS) time after resection for HCC patients with cirrhosis (P<0.05). The median disease-free time of low-value and high-value groups was 49.5 moths and 25.0 months (P=0.000) (Table 2). The 1-year, 2-year, and 5-year DFS rates of low-value and high-value groups were 79.4%, 61.4%, 43.7% and 71.4%, 51.6%, 27.0%, respectively (P=0.000) (Figure 2a). The 1-year, 2-year, and 5-year recurrence rates of low-value and high-value groups were 20.5%, 38.1%, 54.1% and 28.0%, 47.1% and 69.8% (P=0.000) (Figure 2b). Comparison of the differences in clinical and pathological features between low-value and high-value groups showed that patients with PH and Child-pugh B class had higher APRI value (P<0.05) (Table 3, Figure 3).

Discussion

HCC is a highly malignant tumor and hepatitis B virus (HBV) infection is the most important risk factor[7]. Liver fibrosis occurs under repeated infection of HBV, resulting in liver cirrhosis or liver cancer. Most HCC patients have backgroud of HBV-related liver cirrhosis. Studies in recent years have shown that cirrhosis can increase the recurrence rate and reduce the survival rate. Besides, the higher the degree of cirrhosis, the worse the prognosis[2-3,8]. The assessment of liver fibrosis is of vital importance, which may be related to the selection of treatment methods and prognosis of HCC patients with liver cirrhosis. Liver biopsy is gold standard for assessing the degree of liver fibrosis, but it is limited by compliations. Other non-invasive evaluation methods mainly use biochemical indicators, such as liver transaminase, liver synthetic function related indicators (albumin, bilirubin, prothrombin time) and related indicators of liver cirrhosis degree (PLT), and establish score model to predict the degree of fibrosis[9-11]. APRI has certain predictive value in the diagnosis of fibrosis (F≥2) and cirrhosis (F5-F6)[4-5,12]. However, it is not clear whether it is approriate to assess the prognosis of HCC patients with liver cirrhosis. Therefore, this study investigated the relationship between APRI and prognosis.

Cox multivariate regression analysis showed that most of independent risk factors affecting DFS and recurrence rates were tumor-related factors, including tumor size, number, blood vessels invasion and liver capsule invasion, which are not exactly the same with other similar studies[13-15]. It is worth noting that

APRI value can affect the DFS rate and recurrence rate independently. The selected treatment pattern after recurrence may affect long-term survival. Therefore, correlation analysis between APRI and overall survival was not performed in this study. As liver fibrosis worsens, platelets are retained and destroyed in the enlarged spleen[16]. The decrease of PLT count in patients with cirrhosis is also associated with the decrease of thrombopoietin (TPO) in hepatocytes[17]. The ability to clear AST is reduced in cirrhotic liver, and elevated AST in serum is also a characteristic of liver fibrosis progression. In addition, in patients with advanced liver disease, the mitochandria are damaged seriously, resulting in more AST being released into blood[18]. Among various factors that may be associated with APRI, significant elevation of APRI was only found in patients with the higher Child-pugh grade and PH. This result confirmed the correlation between APRI and cirrhosis, instead of characteristics of oncology[19]. APRI high-value group had worse prognosis and higher proportion of death rate due to liver failure, which suggested it was necessary to strengthen efforts to protect liver function and avoid the aggravation of fibrosis, so as to improve the prognosis. Could APRI be used as a non-invasive indicator to evaluate the progress of liver fibrosis in terms of monitoring the therapeutic effect of anti-HBV, instead of just focusing on the level of transaminase and HBV DNA? This may be worth further study.

In summary, APRI value was found in this study to be able to predict the prognosis of HCC patients with liver cirrhosis. Strengthening the protection of liver with HBV infection and slow down the progress of fibrosis can improve the prognosis.

Declarations

Ethics approval

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Affiliated Hospital of Qingdao University.

Consent to participate

Written informed consent was obtained from individual or guardian participants.

Consent to publish

The authors declare that written informed consent for publication was obtained.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due data on all patients in our regional hospitals are protected, but are available from the corresponding author on reasonable request.

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Not applicable

Competing interests

The authors declare that they have no conflict of interest.

Authors' contributions

Lin Xu and Siyu Mu analyzed the data. Siyu Mu wrote the manuscript.

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Tables

Due to technical limitations, table 1,2,3 is only available as a download in the Supplemental Files section.

Figures

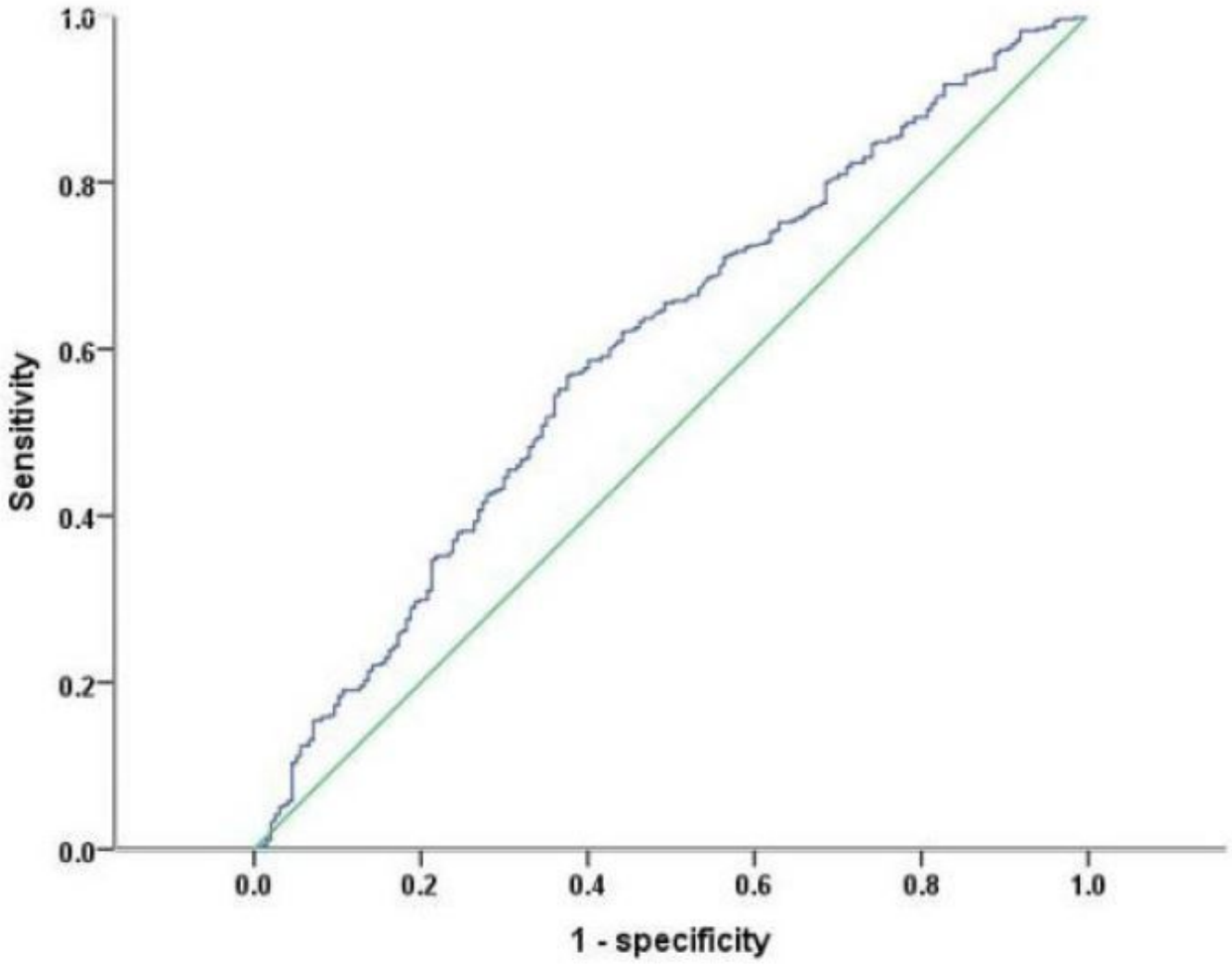

Figure 1

ROC of APRI and HCC recurrence

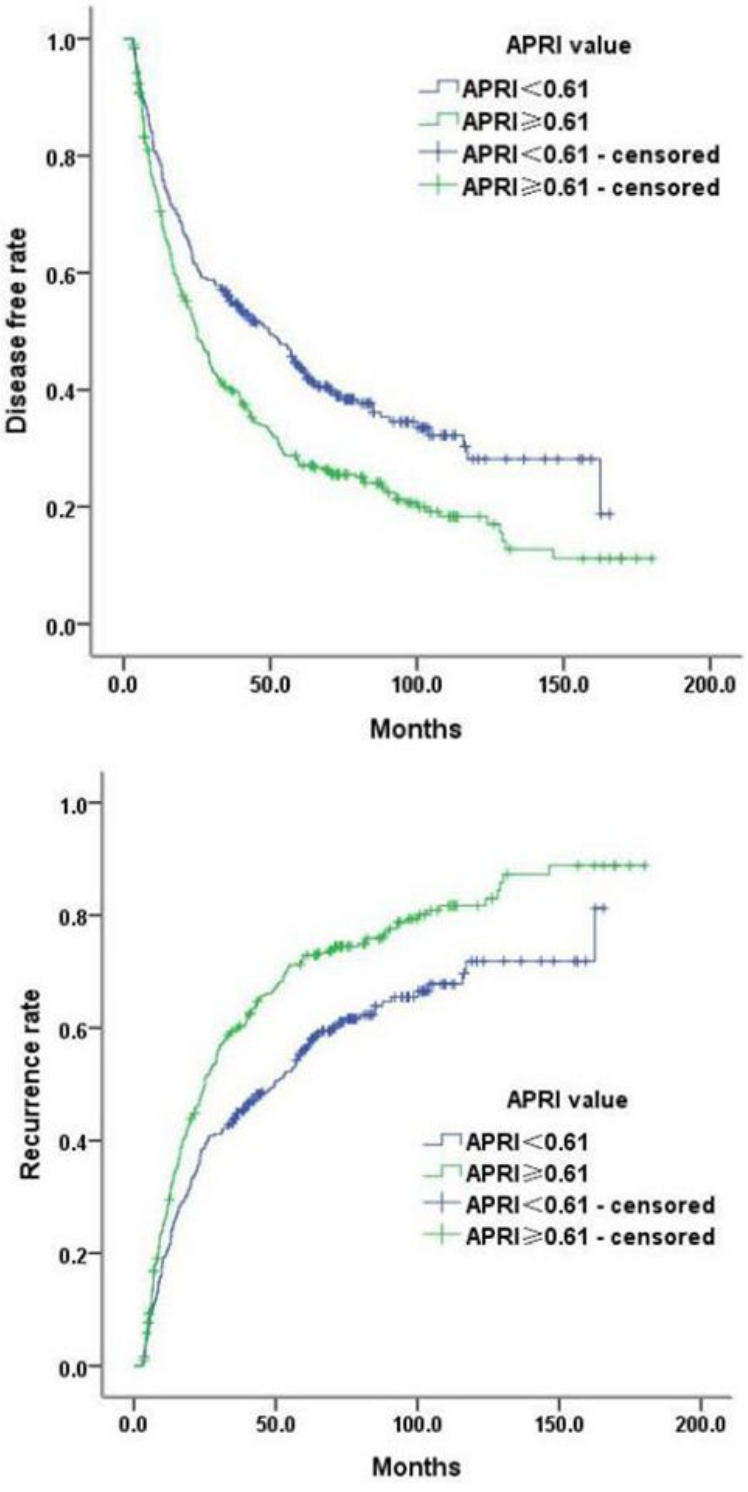

Figure 2

(a) Disease free survival curve of APRI groups (b) HCC recurrence curve of APRI groups

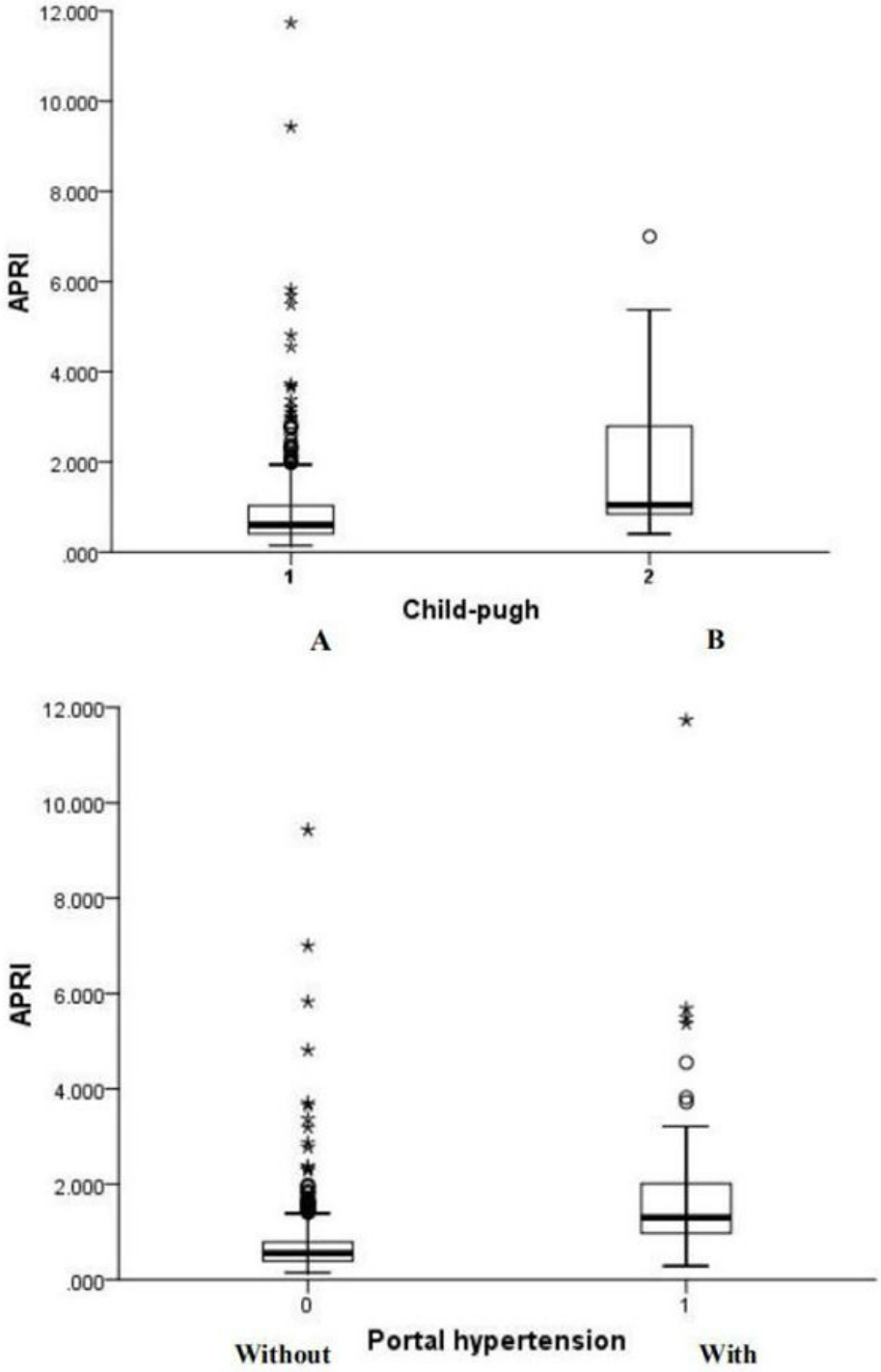

Figure 3

(a) APRI value of Child -pugh A and B class (b) APRI value of patients with and without PH

Supplementary Files

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- Tables.pdf