Usefulness of aspartate aminotransferase to platelet ratio index as a prognostic factor following hepatic resection for hepatocellular carcinoma

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Abstract. Liver function is a major prognostic factor following hepatic resection for hepatocellular carcinoma (HCC), which is well correlated with the degree of fibrosis. On the other hand, the presence of liver cirrhosis itself leads to a higher incidence of HCC than chronic hepatitis. Therefore, preoperative noninvasive markers of fibrosis are important for the assessment of prognosis for treatment of HCC. The present study aimed to analyze whether aspartate aminotransferase to platelet ratio index (APRI) could predict prognosis following hepatic resection for HCC. The subjects were 162 patients who underwent hepatic resection for HCC between January 2000 and December 2011. The relationship between APRI and disease-free and overall survival were retrospectively investigated. In multivariate analysis, indocyanine green at 15 min (ICG-R15) ≥15% (P=0.0306), APRI ≥0.45 (P=0.0184), perioperative blood transfusion of red cell concentrates (RCC; P=0.0034) and TNM stage II, III or IV (P=0.0184) were significant predictors in disease-free survival. For overall survival, ICG-R15 ≥15% (P=0.0454), APRI ≥0.45 (P=0.0417), perioperative blood transfusion of RCC (P=0.0036) and TNM stage II, III or IV (P=0.0033) were significant predictors. In addition, higher APRI values were positively correlated with hepatitis C virus infection and preoperative liver function. In conclusion, APRI is an independent risk factor for disease-free and overall survival following hepatic resection for HCC.

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Key words: aspartate aminotransferase to platelet ratio index, liver fibrosis, liver cirrhosis, hepatocellular carcinoma, hepatic resection

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most frequent cause of cancer mortality (1). Treatment strategy is determined based on liver function, number of tumors, tumor size, vascular invasion and extrahepatic metastases (2,3). The first approach in the management of HCC is to determine if either hepatic resection or liver transplantation is feasible. As the majority of HCC cases develop in patients with cirrhosis, surgical interventions may become challenging. Patients with a small solitary tumor and very well preserved liver function are the best candidates for hepatic resection. Liver transplantation is most beneficial for patients who are not good candidates for resection, particularly those with Milan criteria (solitary tumor ≤5 cm and up to three nodules ≤3 cm) (4); however, donor shortage greatly limits its applicability. Percutaneous ablation is the most frequently used treatment; however, its effectiveness is limited by tumor size and localization (5). In patients with multiple tumors without vascular invasion or extrahepatic metastases not amenable to curative treatments, chemoembolization may provide survival benefit. Findings of randomized trials of sorafenib have demonstrated survival benefits for patients with advanced HCC (6,7), suggesting that molecular-targeted therapies could be effective in this chemoresistant cancer.

Notable advances in surgical procedures and imaging modalities have improved the outcome of patients with HCC (8). However, the long-term prognosis remains unsatisfactory due to a high incidence of recurrence even after curative resection of HCC, with a 5-year actuarial recurrence rate of >80% (9-12). The main prognostic factors following hepatic resection for HCC include the stage of the cancer, vascular invasion, the number of tumors and liver function (5). As liver function correlates well with the degree of liver fibrosis (13,14), there is a need to develop accurate and reliable noninvasive means to assess the severity of liver fibrosis. The aspartate aminotransferase to platelet ratio index (APRI) is a simple noninvasive index, and may be used to predict significant fibrosis and cirrhosis in patients with chronic hepatitis C (15-17). APRI was reported to predict postoperative prognosis for solitary small hepatitis B-related HCC (18). The

present study aimed to analyze whether APRI could predict the prognosis following hepatic resection for HCC in general.

Patients and methods

Patient selection. The present retrospective study was approved by the Ethics Committee of The Jikei University School of Medicine (Tokyo, Japan). Between January 2000 and December 2011, 186 patients with HCC underwent hepatic resection at the Department of Surgery, Jikei University Hospital (Tokyo, Japan). Of these, 24 patients were excluded for the following reasons: A total of 11 patients had difficult pathological diagnosis due to complete necrosis by preoperative transcatheter arterial chemoembolization; 9 patients had additional procedures for other malignancies; 3 patients lost their lives due to other disease; and 1 patient did not have an indocyanine green test due to iodine allergy, leaving the remaining 162 patients for the present study. All patients underwent macroscopic curative resection for HCC. The patient characteristics are listed in Table I.

APRI was calculated as the ratio of [(aspartate aminotransferase/upper limit of normal value: 45 IU/l)/platelet counts ($x10^3/\mu l$)] x100. In general, the extent of hepatic resection was determined based on the retention rate of indocyanine green at 15 min (ICG-R15) before surgery (19). The type of resection was classified into two types: Anatomical resection (trisegmentectomy, extended lobectomy, lobectomy, segmentectomy or subsegmentectomy) and non-anatomical resection. The use of blood products and the dose were determined, as previously described (20). Tumor staging was based on the TNM stage classified by the Union for International Cancer Control (UICC) (21).

Univariate and multivariate analyses of disease-free and overall survival following hepatic resection, and clinicopathological factors. Initially, the relationship between clinicopathological variables and disease-free survival and overall survival following hepatic resection was investigated by univariate and multivariate analysis. The clinicopathological variables consisted of the following 15 factors: Age, sex, type of hepatitis virus, serum total bilirubin, serum albumin, prothrombin time (PT), ICG-R15, Child-Pugh classification (22), APRI, type of resection, surgery time, estimated blood loss, perioperative blood transfusion o f red cell concentrates (RCC), differentiation of tumor and TNM stage.

Determination of cut-off value of variables. Some clinicopathological continuous variables were classified into two groups for the log-rank test and the Cox proportional hazard regression models, as follows: Age, <60 or ≥60 years; albumin, ≤3.5 or <3.5 g/dl; PT, ≤80 or >80%; ICG-R15, <15 or ≥15%, according to previous studies (22,23); and serum total bilirubin, <1.4 or ≥1.4 mg/dl, based on the normal limit in our facility. The median of variables in operative factors was classified as follows: Surgery time, <360 or ≥360 min; and estimated blood loss, <745 or ≥745 ml. A cut-off value of APRI was determined by a receiver operating curve (ROC) of APRI, which was 0.45.

Assessment of clinicopathological variables and APRI. The subjects were classified into two groups: APRI, <0.45 or ≥0.45. Subsequently, patients' characteristics were analyzed in relation to APRI, using the following 18 factors: Age, sex, type of hepatitis virus, serum total bilirubin, serum albumin, PT%, ICG-R15, Child-Pugh classification, type of resection, estimated blood loss, surgery time, perioperative blood transfusion of RCC, differentiation, liver cirrhosis and UICC TNM stage.

The recurrence of HCC was defined as newly detected hypervascular hepatic or extrahepatic tumors by ultrasonography, computed tomography, magnetic resonance image or angiography with or without increase in serum a-fetoprotein, or protein induced by vitamin K absence or antagonist-II. For recurrent HCC in the liver, repeated hepatic resection, local ablation therapy, transarterial chemoembolization or molecular target therapy (sorafenib) was given based on hepatic functional reserve judged mainly by ICG-R15. Extrahepatic recurrence was mainly treated conservatively, except for solitary lung metastasis or adrenal gland metastasis, provided that the primary HCC was controlled. In such a circumstance, limited partial resections were performed.

Statistical analysis. Data were expressed as the mean ± standard deviation or median (minimum to maximum). Univariate analysis was performed using the non-paired Student's t-test and Chi-square test. Analysis of disease-free and overall survival was performed using the log-rank test. Factors that significantly influenced disease-free or overall survival were then used in the Cox proportional regression model for multivariate analysis. $P<0.05$ was considered to indicate a statistically significant difference. The accuracy of APRI for pathological liver cirrhosis was determined by calculating the area under the curve from corresponding receiver curves (AUROC) using SPSS 17.0 for Windows, (SPSS. Inc., Chicago, IL, USA). The AUROC was expressed as plots of the test sensitivity vs. 1-speificity.

Results

Clinical patient characteristics. The background characteristics of the 162 patients are summarized in Table I. There were 138 men and 24 women. The median age was 63 years (range, 29-82 years). The majority of patients had hepatitis C virus (HCV) infection (n=64), followed by those without HCV or hepatitis B virus (HBV) infection (n=53) and those with HBV infection (n=43). The majority of patients were in Child-Pugh grade A and liver damage grade A. The median APRI was 0.576 (range 0.101-5.918) and 70 patients (43.2%) had the pathological diagnosis of liver cirrhosis.

Cut-off value of APRI using a ROC. A cut-off value of APRI was determined by a ROC of APRI, which predicted liver cirrhosis based on pathological diagnosis (Fig. 1). APRI yielded high AUROC with a level of 0.736 at a cut-off value of 0.45 (sensitivity, 0.829; 1-specificity, 0.424).

Variables associated with overall and disease-free survival in univariate and multivariate analyses. Table II demonstrates the relationship between the clinicopathological variables and disease-free survival following hepatic resection for HCC. In univariate analysis, disease-free survival was significantly

Table I. Patient characteristics.

Factor	Ratio or median	Range
Sex (male:female)	138:24	-
Age, years	63	29-82
Virus type (NBNC:HBV:HCV:HBV+HCV)	53:43:64:2	-
Total bilirubin, mg/dl	0.8	0.1-3.0
Albumin, g/dl	3.9	2.5-5.0
Aspartate aminotransferase, IU/l	38	8-261
Alanine aminotransferase, IU/l	36	9-269
Platelet, $x10^3/\mu l$	15.1	5.1-50.7
Prothrombin time, %	90	54-100
Retention rate of indocyanine green at 15 min, %	12	2-51
Child-Pugh (A:B)	150:12	-
Liver damage (A:B)	124:38	-
Aspartate aminotransferase to platelet ratio index	0.58	0.101-5.918
Surgery (anatomical:partial)	93:69	-
Estimated blood loss, ml	745	(0-25, 770)
Surgery time, min	365	100-1,030
Perioperative blood transfusion of red cell concentrates (present:absent)	47:115	-
Perioperative blood transfusion of fresh frozen plasma (present:absent)	55:107	-
Maximum diameter of tumor, cm	3.5	0.9-18.0
Number of tumors (solitary:multiple)	132:30	-
Vascular invasion (present:absent)	40:122	-
Differentiation (well or moderately:poorly)	147:15	-
Liver cirrhosis (present:absent)	70:92	-
Union for International Cancer Control TNM classification (stage I:II:IIIA:IIIB:IIIC:IVB)	99:48:7:6:1:1	-

NBNC, negative for both markers of HBV and HCV infection (non-B, non-C); HCV, hepatitis C virus; HBV, hepatitis B virus.

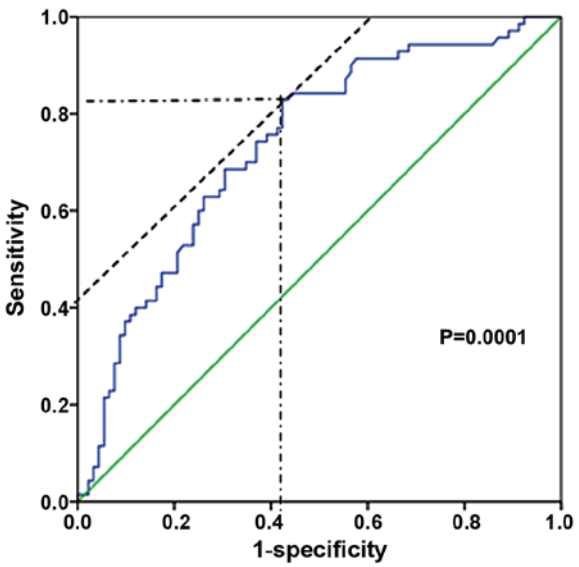

Figure 1. Receiver operating curve of aspartate aminotransferase to platelet ratio index for the prediction of liver cirrhosis. The blue line shows the receiver operating curve of aspartate aminotransferase to platelet ratio index. The green line shows the reference line. Cut-off, 0.45; sensitivity, 0.829; 1-specificity, 0.424; area under receiver operating curve, 0.736; 95% confidence interval, 0.659-0.813; standard error, 0.039; P=0.0001.

poor in patients with age ≥65 years (P=0.0244), ICG-R15 ≥15% (P=0.0043), APRI ≥0.45 (P=0.0216; Fig. 2A), perioperative blood transfusion of RCC (P=0.0008), and TNM stage II, III or IV (P=0.0076). In multivariate analysis, ICG-R15 ≥15% (P=0.0306), APRI ≥0.45 (P=0.0184), perioperative blood transfusion of RCC (P=0.0034), and TNM stage II, III or IV (P=0.0184) were independent and significant predictors of poor disease-free survival.

Table III demonstrates the relationship between the clinicopathological variables and overall survival following hepatic resection for HCC. In univariate analysis, overall survival was poor in patients with ICG-R15 ≥15% (P=0.0084), APRI ≥0.45 (P=0.0274; Fig. 2B), perioperative blood transfusion of RCC (P=0.0002), and TNM stage II, III or IV (P=0.0003). In multivariate analysis, ICG-R15 ≥15% (P=0.0454), APRI ≥0.45 (P=0.0417), perioperative blood transfusion of RCC (P=0.0036), and TNM stage II, III or IV (P=0.0033) were independent and significant negative predictors.

Univariate analysis of patient characteristics in relation to APRI. Table IV demonstrates the relationship between clinicopathological variables and APRI. In univariate analysis, type of hepatitis virus (HCV infection, P=0.002), liver function tests (serum total bilirubin, P=0.0044; albumin, P=0.0002; PT%,

Table II. Univariate and multivariate analysis of disease-free survival following hepatic resection.

		Univariate analysis		Multivariate analysis	
Factor	Patient no.	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years					
≥65	73	1.606 (1.063-2.427)	0.0244	1.37 (0.915-2.050)	0.1263
<65	89				
Sex					
Male	138	1.096 (0.5981-2.007)	0.7671	-	-
Female	24				
Hepatitis virus					
HCV infection	66	1.256 (0.8377-1.883)	0.27	-	-
Non-HCV infection	96				
Total bilirubin, mg/dl					
≥1.4	9	2.008 (0.7999-5.039)	0.1377	-	-
<1.4	153				
Albumin, g/dl					
≤3.5	33	1.437 (0.8660-2.386)	0.1605	-	-
>3.5	129				
Prothrombin time, %					
>80	129	1.522 (0.8694-2.665)	0.1415	-	-
≤80	33				
Retention rate of indocyanine green at 15 min, %					
≥15	67	1.876 (1.219-2.889)	0.0043	1.586 (1.044-2.410)	0.0306
<15	95				
Child-Pugh					
B	12	2.124 (0.9176-4.917)	0.0785	-	-
A	150				
Aspartate aminotransferase to platelet ratio index					
≥0.45	97	1.598 (1.071-2.382)	0.0216	1.692 (1.093-2.620)	0.0184
<0.45	65				
Surgical procedure					
Anatomical	93	1.003 (0.6753-1.491)	0.9868	-	-
Non-anatomical	69				
Surgery time, min					
≥360	82	1.274 (0.8522-1.903)	0.238	-	-
<360	80				
Estimated blood loss, g					
≥745	81	1.417 (0.9524-2.109)	0.0856	-	-
<745	81				
Perioperative blood transfusion of red cell concentrates					
Present	47	2.257 (1.404-3.628)	0.0008	1.875 (1.231-2.857)	0.0034
Absent	115				
Differentiation					
Well or moderate	147	1.062 (0.5238-2.154)	0.8669	-	-
Poor	15				
Union for International Cancer Control Stage					
I	99	1.783 (1.166-2.727)	0.0076	1.637 (1.087-2.465)	0.0184
II, III or IV	63				

CI, confidence interval; HCV, hepatitis C virus.

Table III. Univariate and multivariate analysis of overall survival following hepatic resection.

		Univariate analysis		Multivariate analysis	
Factor	Patient no.	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years					
≥65	73	1.520 (0.8026-2.880)	0.1987	-	-
<65	89				
Sex					
Male	138	2.007 (0.7824-5.148)	0.1472	-	-
Female	24				
Hepatitis virus					
HCV infection	66	1.317 (0.6969-2.492)	0.7155	-	-
Non-HCV infection	96				
Total bilirubin, mg/dl					
≥1.4	9	1.381 (0.3641-5.2236)	0.6353	-	-
<1.4	153				
Albumin, g/dl					
≤3.5	33	1.561 (0.6987-3.488)	0.2776	-	-
>3.5	129				
Prothrombin time, %					
>80	129	2.078 (0.8750-4.936)	0.0974	-	-
≤80	33				
Retention rate of indocyanine green at 15 min, %					
≥15	67	2.460 (1.260-4.804)	0.0084	1.966 (1.014-3.813)	0.0454
<15	95				
Child-Pugh					
B	12	3.252 (0.8717-12.13)	0.0792	-	-
A	150				
Aspartate aminotransferase to platelet ratio index					
≥0.45	97	2.054 (1.083-3.896)	0.0274	2.239 (1.031-4.862)	0.0417
<0.45	65				
Surgical procedure					
Anatomical	93	1.859 (0.9857-3.505)	0.0554	-	-
Non-anatomical	69				
Surgery time, min					
≥360	82	1.000 (0.5297-1.889)	0.9994	-	-
<360	80				
Estimated blood loss, g					
≥745	81	1.764 (0.9402-3.309)	0.0771	-	-
<745	81				
Perioperative blood transfusion of red cell concentrates					
Present	47	3.679 (1.801-7.519)	0.0002	2.607 (1.366-4.974)	0.0036
Absent	115				
Differentiation					
Well or moderate	147	2.237 (0.7414-6.752)	0.153	-	-
Poor	15				
Union for International Cancer Control stage					
I	99	3.366 (1.732-6.542)	0.0003	2.738 (1.399-5.358)	0.0033
II, III or IV	63				

CI, confidence interval; HCV, hepatitis C virus.

Table IV. Univariate analysis of patient characteristics in relation to APRI.

Factor	APRI ≥0.45 (n=97)	APRI <0.45 (n=65)	Univariate P-value
Sex (male:female)	82:15	56:9	0.7763
Age, years	63±9	60±13	0.0524
Virus type (NBNC:HBV:HCV:HBV+HCV)	21:27:48:1	32:16:16:1	0.0015
HCV:non-HCV	49:48	17:48	0.0020
Total bilirubin, mg/dl	0.9±0.4	0.8±0.3	0.0044
Albumin, g/dl	3.8±0.4	4.0±0.4	0.0002
Prothrombin time, %	87±10	93±8	<0.0001
Retention rate of indocyanine green at 15 min, %	16±9	12±7	0.0005
Child-Pugh (A:B)	87:10	63:2	0.0849
Type of resection (anatomical:non-anatomical)	50:47	43:22	0.0653
Estimated blood loss, ml	1,478±2,853	1,409±2,280	0.8707
Surgery time, min	358±144	398±174	0.1558
Perioperative blood transfusion of red cell concentrates (present:absent)	27:70	20:45	0.6867
Differentiation (well or moderate:poor)	88:9	59:6	0.9918
Liver cirrhosis (present:absent)	58:39	12:53	<0.0001
Union for International Cancer Control stage (I:II, III or IV)	60:37	39:26	0.8123

APRI, aspartate aminotransferase to platelet ratio index; NBNC, negative for both markers of HBV and HCV infection (non-B, non-C); HCV, hepatitis C virus; HBV, hepatitis B virus.

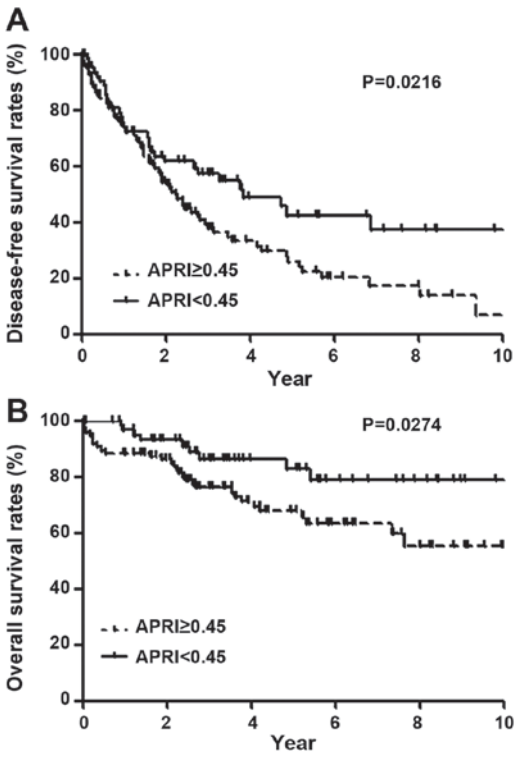

Figure 2. Disease-free and overall survival following hepatic resection for hepatocellular carcinoma in relation to APRI. Higher APRI values were associated with significantly worse (A) disease-free and (B) overall survival. The significant differences in disease-free survival and overall survival were observed after 2 years and immediately after hepatic resection, respectively. APRI, aspartate aminotransferase to platelet ratio index.

P<0.0001; ICG-R15, P=0.0005), and pathology-proven liver cirrhosis (P<0.0001) were positively associated with APRI. Age (P=0.0524), type of resection (P=0.0653), and Child Pugh classification (P=0.0849) demonstrated a trend toward a positive association with APRI; however, these were not significant.

Discussion

Histological examination by biopsy remains an important diagnostic modality to estimate the degree of liver fibrosis (24). Although percutaneous liver biopsy is, in general, a safe procedure, it is costly and does carry a small risk of complication (25). Therefore, it is difficult to perform liver biopsy for all preoperative patients with liver diseases. In addition, sampling error may occur as only 1/50,000 of the whole liver is sampled. Furthermore, inter- and intra-observer discrepancies of 10-20% in assessing hepatic fibrosis have been reported, which may lead to the misunderstanding of cirrhosis (26-28). Therefore, the development of noninvasive markers of liver fibrosis is a clinical and research priority.

Some noninvasive indices, such as the amino-terminal propeptide of collagen III, hyaluronic acid, Fibrotest, Fibrometer test, Hepascore and FibroScan (transient elastography or liver stiffness), have been introduced to assess the degree of fibrosis (29). However, these tests usually require special and costly equipment for daily practice. On the other hand, APRI is a simple, noninvasive index derived from routine blood tests, and correlates significantly with the stage of fibrosis, with a higher correlation coefficient than platelet count, or aspartate aminotransferase level alone, because it

amplifies the opposing effects of liver fibrosis on aspartate aminotransferase and platelet count (15). Although APRI is a promising index with limited expense and widespread availability, it has never been reported as a prognostic factor of patients with HCC following hepatic resection except in one report, in which APRI was advocated to predict postoperative outcome in patients with solitary small hepatitis B-related HCC (18). The cut-off value of APRI in their report was 0.47, which was very similar to the value in the present study of 0.45. On the other hand, a difference was the patient criteria: The present study was applied to operable patients with HCC regardless of type of hepatitis virus, but the previous report was limited to solitary and small hepatitis B-related HCC (18).

In patients with HCC, the incidence of concomitant liver cirrhosis is much higher than chronic hepatitis, regardless of type of hepatitis virus (30-32). Depending on the etiology of liver cirrhosis, the lifetime risk for the development of HCC is as high as 80% in patients with liver cirrhosis (3). Therefore, noninvasive fibrosis markers may be an important predictor of HCC occurrence. In the present study, the difference in disease-free survival is clearer later than 2 years after hepatic resection. Then, this difference is due to multicentric occurrence of HCC because intrahepatic recurrence via vascular invasion generally occurs in the early period compared with multicentric recurrence (9). The present study suggested that APRI is a predictor of multicentric recurrence. Other significant factors associated with overall or disease-free survival on multivariate analysis were ICG-R15, TNM stage and perioperative blood transfusion of RCC, which were consistent with other reports (10,20,33-35).

In the present study, higher APRI values had a positive association with the ratio of HCV infection. A meta-analysis of patients undergoing hepatic resection for HCC demonstrated that preoperative liver function, such as AST, platelet count and Child-Pugh classification was worse in the HCV-HCC group than in either the HBV-HCC or negative for both markers of HBV and HCV infection [non-B, non-C (NBNC)]-HCC group (36). The prevalence of liver cirrhosis was the highest in the HCV-HCC group, followed by the HBV-HCC group and the NBNC-HCC group (36). Therefore, the ratio of HCV infection may be higher in the group of APRI ≥0.45 than APRI <0.45.

There are several limitations in the present study. First, this is a retrospective study. It was not possible to compare the APRI to other noninvasive indices, including the amino-terminal propeptide of collagen III, hyaluronic acid, FibroTest, FibroMeter test, Hepascore and Fibroscan (transient elastography for liver stiffness). Second, the number of patients who underwent hepatic resection was small, and so validation for the survival rate following hepatic resection by using the value of APRI could not be performed. To confirm the influence of APRI on survival following hepatic resection, more case numbers or prospective studies are required.

In conclusion, the present study suggests that APRI derived from routine blood tests appears to be a significant predictive factor of overall and disease-free survival following hepatic resection for HCC.

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Availability of data and materials

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

Authors' contributions

The all authors conducted surgery and perioperative management for patients, MM, SW, KH and HS contributed to the clinical data analysis. MM and KY wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Appropriate ethical approval was obtained from the Institutional Review Board of The Jikei University School of Medicine (Tokyo, Japan). Patient consent was not required for the present study as it was conducted retrospectively.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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