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ORIGINAL ARTICLE

A simple, noninvasively determined index predicting hepatic failure following liver resection for hepatocellular carcinoma

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Abstract
Background A novel index, the serum aspartate aminotransferase activity/platelet count ratio index (APRI), has been identified as a biochemical surrogate for histological fibrogenesis and fibrosis in cirrhosis. We evaluated the ability of preoperative APRI to predict hepatic failure following liver resection for hepatocellular carcinoma.
Methods Potential preoperative risk factors for postoperative hepatic failure (hepatic coma with hyperbilirubinemia, four patients; intractable pleural effusion or ascites, 30 patients; and variceal bleeding, one patient) as well as APRI were evaluated in 366 patients undergoing liver resection for hepatocellular carcinoma. Prognostic significance was determined by univariate and multivariate analyses.
Results Hepatic failure developed postoperatively in 30 patients, causing death in four. APRI correlated with histological intensity of hepatitis activity and degree of hepatic fibrosis, and was significantly higher in patients who developed postoperative hepatic failure than in others without failure. Risk of postoperative hepatic failure increased as the serum albumin concentration and platelet count decreased and as indocyanine green retention rate at 15 min, aspartate and alanine aminotransferase activities, and APRI increased. Only APRI was an independent preoperative factor on multivariate analysis. Of the four patients who died of postoperative hepatic failure, three had an APRI of at least 10.
Conclusions Preoperative APRI independently predicted hepatic failure following liver resection for hepatocellular carcinoma. Patients with an APRI of 10 or more have a high risk of postoperative hepatic failure.

Keywords Liver resection · Hepatocellular carcinoma · Liver failure · APRI · Platelet count

Abbreviations

HCC	Hepatocellular carcinoma
APRI	Aspartate aminotransferase/platelet count ratio index
Anti-HCV	Anti-hepatitis C virus antibody
HBsAg	Hepatitis B surface antigen
$ICGR_{15}$	Indocyanine green retention rate at 15 min
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
AFP	α-Fetoprotein
HAI	Histological activity index

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Introduction

Liver resection in patients with hepatocellular carcinoma (HCC) may result in postoperative hepatic failure, since most patients with HCC also have chronic liver disease including cirrhosis [1–9]. To avoid resection likely to lead to postoperative hepatic failure, various methods have been developed for preoperative assessment of liver function [4,

5, 9–19]. However, some of these are complex and require calculations involving multiple formulas.

Previous studies have identified hepatic fibrosis and active hepatitis as negative predictive factors for effective liver regeneration and as risk factors for postoperative hepatic failure [3, 9, 20, 21]. Histopathologic examination of liver biopsy specimens presently remains the "gold standard" for assessing degree of active hepatitis and hepatic fibrosis. However, liver biopsy cannot be performed in all candidates for liver surgery because of its cost and risk of complications. Recently, a novel index, the aspartate aminotransferase (AST)/platelet count ratio index (APRI), has been identified as a biochemical marker for histological fibrogenesis and fibrosis in cirrhosis [22, 23]. APRI has been reported to correlate with hepatic fibrosis and magnitude of abnormalities in liver function tests [22, 23]. This simple ratio is calculated from results of routinely available, noninvasive, and inexpensive laboratory tests.

In the present study, we evaluated the relationship between preoperative APRI and postoperative hepatic failure following liver resection, and the ability of the ratio to serve as a marker to identify candidates who cannot safely undergo liver resection for HCC.

Patients and methods

Patients and determination of APRI

From the beginning of 1994 to the end of 2004, liver resection for HCC was performed for 372 patients in our department. Patients excluded from this study included five who underwent concomitant resection of a synchronous second tumor, and one who underwent liver resection combined with right atrial tumor thrombectomy requiring extracorporeal circulation. The 366 patients remaining as subjects in this study included 297 men and 69 women; their ages ranged from 30 to 85 years (mean ± SD, 63.6 ± 8.2). In total, 249 patients were positive for anti-hepatitis C antibody (anti-HCV) alone, 54 patients for hepatitis B surface antigen (HBsAg) alone, four patients for both anti-HCV and HBsAg, and 59 patients were negative for both viral markers. APRI was calculated as AST activity (IU/L)/platelet count (10^4/μl) [22].

The study was conducted in accordance with the Helsinki Declaration and the guidelines of the Ethics Committee at our institution.

Postoperative hepatic failure

Variables previously shown to predict postoperative hepatic failure included hepatic coma with hyperbilirubinemia (total serum bilirubin concentration >5 mg/dl for more than 5 days); intractable pleural effusion or ascites requiring use of diuretics or thoracocentesis, or abdominal paracentesis on two or more occasions or institution of continuous abdominal drainage; or variceal bleeding [24, 25].

Operative procedure

The operative procedures is outlined below (major hepatectomy; segmentectomy or greater, minor hepatectomy; smaller than segmentectomy, anatomic hepatectomy; subsegmentectomy or greater, nonanatomic hepatectomy; smaller than subsegmentectomy).

Pathologic examination

Surgical specimens were cut serially into tissue blocks 5 mm thick, fixed in 10% formalin, and stained with hematoxylin and eosin. Histologic grade with respect to tumor differentiation was assigned using a modification of the classification by Edmondson and Steiner [26, 27]. The histologic activity index (HAI) was used with some modifications [28, 29] to evaluate severity of active hepatitis (histologic activity grade) and degree of hepatic fibrosis (histologic fibrosis grade). HAI scores consist of four components: component 1, periportal necrosis with or without bridging necrosis; component 2, intralobular degeneration and focal necrosis; component 3, portal inflammation; and component 4, fibrosis. Summed HAI scores of 0 for (components 1–3) indicated no activity (histologic activity score, 0); scores of 1–3, minimal activity (histologic activity score, 1); scores of 4–8, mild activity (histologic activity score, 2); scores of 9–12, moderate activity (histologic activity score, 3); and score of 13 or more indicated severe activity (histologic activity score, 4). The degree of fibrosis (histologic fibrosis score) was determined from component 4 of the HAI score. A histologic fibrosis grade of 1 indicated portal fibrous expansion; a grade of 2 indicated the presence of portal–portal septa without architectural distortion; a grade of 3 indicated portocentral septa with architectural distortion; and a grade of 4 indicated cirrhosis.

Statistics

Student's *t* test was used to examine differences in age and tumor size. The Mann–Whitney *U* test was used to examine differences in laboratory test results. Fisher's exact test or the χ^2 test was used to compare categorical data between groups. Correlations between APRI and results of other laboratory tests were determined using Pearson's correlation coefficient. The correlation between the APRI and histologic activity score or fibrosis score in noncancerous liver was determined by Spearman's rank correlation. Odds ratios were used to estimate relative risk for postoperative hepatic failure.

Logistic regression was used for univariate analysis, while multiple logistic regression analysis was used for multivariate analysis. For multivariate analysis, variables possibly significant ($P < 0.1$) on univariate analysis were evaluated. P values less than 0.05 were considered significant.

Table 1 Correlations between APRI and results of other laboratory tests

Laboratory test	Correlation coefficient	*P* value
Total bilirubin	0.306	<0.0001
Albumin	−0.248	<0.0001
$ICGR_{15}$	0.280	<0.0001
AST	0.756	<0.0001
ALT	0.625	<0.0001
Platelet count	−0.555	<0.0001
Prothrombin test (%)	−0.132	0.0119

$ICGR_{15}$ Indocyanine green retention rate at 15 min, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Results

Preoperative APRI, which ranged from 0.6 to 51.3 (mean ± SD, 5.0 ± 4.4), correlated with serum concentrations of total bilirubin and albumin, indocyanine green retention test results at 15 min ($ICGR_{15}$), serum activities of AST and alanine aminotransferase (ALT), platelet count, and prothrombin test (Table 1).

APRI also correlated with both histologic activity score ($P = 0.0003$) and histologic fibrosis score ($P = 0.0247$).

Postoperative hepatic failure developed in 30 patients (hepatic coma with hyperbilirubinemia in four patients; intractable pleural effusion or ascites in 30 patients; and variceal bleeding in one patient). Four of these patients died of hepatic failure while still in the hospital. Clinicopathologic findings were compared between the 30 patients with postoperative hepatic failure and the 336 patients without failure (Table 2). These groups were similar in age, gender, percentage of patients with a history of alcohol abuse (defined as an estimated daily intake of 86 g of

Table 2 Demographic and clinicopathologic features of patients with and without hepatic failure after liver resection

Parameter	Hepatic failure		*P* value
	No, $n = 336$	Yes, $n = 30$	
Age, years, mean ± SD	63.6 ± 8.4	64.0 ± 6.9	0.8912
Gender, M:F	274:62	23:7	0.5125
Alcohol abuse	115	10	0.9593
History of blood transfusion	75	8	0.5922
Anti-HCV	229	24	0.1784
HBs-Ag	54	4	0.6940
Diabetes mellitus	55	7	0.4562
Total bilirubin (mg/dl)	0.8 (0.5, 1.3)	0.9 (0.5, 1.4)	0.3008
Albumin (g/dl)	3.7 (3.3, 4.2)	3.6 (2.9, 4.1)	0.0309
$ICGR_{15}$ (%)	15.0 (7.5, 25.2)	17.8 (7.0, 34.5)	0.2434
AST (IU/l)	52 (30, 96)	64 (46, 107)	0.0208
ALT (IU/l)	56 (26, 113)	70 (38, 129)	0.0232
Platelet count ($\times 10^4$/μl)	14.3 (8.4, 22.9)	11.6 (5.6, 20.5)	0.0068
Prothrombin test (%)	94 (73, 135)	94 (76, 131)	0.9798
APRI	3.8 (1.6, 9.0)	5.3 (2.6, 13.3)	0.0039
AFP, >20 ng/ml	180	18	0.5200
Tumor size, cm, mean ± SD	3.8 ± 2.8	4.2 ± 2.8	0.4504
Operative procedure, major:minor	125:211	14:16	0.3061
Operative procedure, anatomic:nonanatomic	170:166	17:13	0.2571
Intraoperative blood loss (g)	725 (196, 2595)	1450 (478, 3662)	0.0002
Time of operation (min)	282 (180, 440)	317 (213, 500)	0.1016
Histologic activity grade			
0–2	300	20	0.0003
3	34	10	
Histologic fibrosis grade			
0–3	194	11	0.0247
4, representing cirrhosis	141	19	

Most laboratory results, intraoperative blood loss, and time of operation are given as medians (with 10th and 90th percentiles)

Anti-HCV Anti-hepatitis C virus antibody, *HBsAg* hepatitis B surface antigen, *$ICGR_{15}$* indocyanine green retention rate at 15 min, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* α-fetoprotein

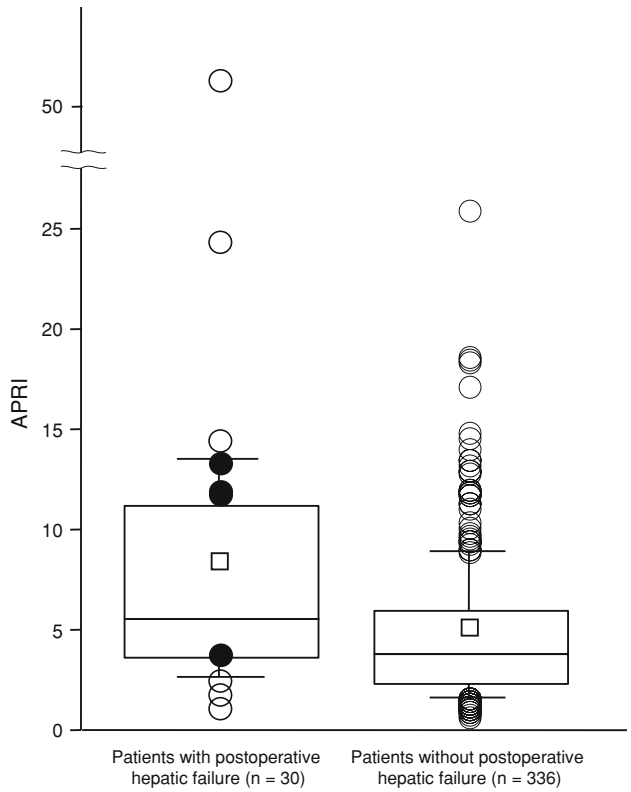

Fig. 1 APRI in two groups of patients who underwent liver resection for hepatocellular carcinoma. APRI values of patients with and without postoperative hepatic failure ranged from 0.6 to 26 and from 1.1 to 51.3, respectively (mean ± SD, means shown as *small squares*, 8.3 ± 9.3 and 4.7 ± 3.5). *Bars*, 10th and 90th percentiles; *bottoms* and *tops* of boxes, 25th and 75th percentiles; *lines* across boxes, medians; *circles*, outliers; *closed circles*, patients who died of postoperative hepatic failure

ethanol for at least 10 years, according to the criteria of the Liver Cancer Study Group of Japan [30]), diabetes mellitus, blood transfusion, and anti-HCV and HBsAg positivity. Although serum total bilirubin concentration, $ICGR_{15}$, and prothrombin test results did not differ between groups, serum albumin concentration and platelet count were significantly lower in patients with postoperative hepatic failure than in these without it. Serum activities of AST and ALT and also the APRI (Fig. 1) were significantly higher in patients with than without postoperative hepatic failure. Although no difference was noted in tumor size, operative procedure, or operative time was noted between them, intraoperative blood loss was significantly greater in patients who developed postoperative hepatic failure. The percentage of patients with moderate hepatitis activity (histologic activity grade 3) or cirrhosis (histologic fibrosis grade 4) was significantly greater in patients who developed postoperative hepatic failure.

Table 3 shows odds ratios (OR) for the candidate risk factors associated with postoperative hepatic failure as

Table 3 Risk factors for hepatic failure after liver resection for hepatocellular carcinoma, evaluated by univariate analysis

Variable	Odds ratio	95% CI	*P* value
Age (per 1 year)	1.003	0.958–1.050	0.8908
Gender			
Female	1.000		
Male	0.743	0.305–1.810	0.5138
Alcohol abuse			
(−)	1.000		
(+)	0.979	0.441–2.177	0.9593
History of blood transfusion			
(−)	1.000		
(+)	1.261	0.539–2.947	0.5929
Anti-HCV			
(−)	1.000		
(+)	1.869	0.742–4.707	0.1844
HBsAg			
(−)	1.000		
(+)	0.803	0.270–2.395	0.6945
Diabetes mellitus			
(−)	1.000		
(+)	1.406	0.572–3.456	0.4580
AFP (ng/ml)			
≤20	1.000		
>20	1.283	0.599–2.748	0.5208
Total bilirubin (per 1 mg/ml)	1.788	0.616–5.184	0.2848
Albumin (per 1 g/dl)	0.241	0.086–0.678	0.0070
$ICGR_{15}$ (per 1%)	1.046	1.005–1.088	0.0272
AST (per 1 IU/l)	1.008	1.000–1.017	0.0459
ALT (per 1 IU/l)	1.008	1.000–1.016	0.0572
Platelet count (per 1×10^4/μl)	0.925	0.860–0.996	0.0385
Prothrombin test (per 1%)	0.999	0.983–1.016	0.9279
APRI (per 1)	1.125	1.045–1.211	0.0017
Operative procedure			
Minor	1.000		
Major	1.477	0.697–3.129	0.3085
Operative procedure			
Non-anatomic	1.000		
Anatomic	1.529	0.736–3.175	0.2545
Intraoperative blood loss (per 1 g)	1.000	1.000–1.001	0.0147
Time of operation (per 1 min)	1.003	1.000–1.006	0.0804
Histologic activity grade			
0–2	1.000		
3	4.286	1.858–9.888	0.0006
Histologic fibrosis grade			
1–3	1.000		
4, representing cirrhosis	2.377	1.096–5.152	0.0283

Anti-HCV Anti-hepatitis C virus antibody, *HBsAg* hepatitis B surface antigen, *$ICGR_{15}$* indocyanine green retention rate at 15 min, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* α-fetoprotein

calculated by univariate analysis. Serum albumin concentration (OR = 0.241), $ICGR_{15}$ (OR = 1.046), AST (OR = 1.008), ALT (OR = 1.008), platelet count (OR = 0.925), APRI (OR = 1.125), histologic activity grade 3 (OR = 4.286), and cirrhosis (OR = 2.377) were risk factors for postoperative hepatic failure. APRI in three of the four patients who died of postoperative hepatic failure was 10 or more. Risk of postoperative hepatic failure increased as serum albumin concentration and platelet count decreased, and as $ICGR_{15}$, AST, and ALT activities and APRI increased. Risk of postoperative hepatic failure also increased with greater intraoperative blood loss, and was also high in patients with moderately active hepatitis or cirrhosis according to histopathologic examination. Risk of postoperative hepatic failure correlated closely with both severity of active hepatitis and degree of hepatic fibrosis.

Multivariate analysis was used to estimate the adjusted odds ratio for postoperative hepatic failure based on preoperative data (Table 4). Because the aim of this study was to evaluate the role of the APRI as preoperative prediction of postoperative hepatic failure; significant risk factors on univariate analysis which were acquired postoperatively were eliminated. APRI was the only independent preoperative risk factor for postoperative hepatic failure (adjusted OR = 1.098, 95% CI; 1.018–1.184).

We next compared the 330 patients with a low APRI (<10) with the 33 patients whose APRI was high (≥10) (Table 5). A cut-off line for APRI of 10 yielded the most significant differences in cut off lines (counting number) which we decided. The sensitivity, specificity, and positive predictive value of APRI ≥ 10 for postoperative hepatic failure were 27.3%, 7.8%, and 27.3%, respectively. The prevalence of hepatic coma and intractable pleural effusion or ascites was significantly higher among patients with a high APRI than in those with a low APRI. Variceal bleeding developed in only one patient, who had an elevated APRI (≥10). Although only 1 of the 333 patients with a low APRI died of postoperative hepatic failure, 3 of 33 patients with a high APRI died of this complication ($P = 0.0025$). APRI was ≥10 in three of four patients who died of postoperative hepatic failure. The serum concentrations of total bilirubin and albumin, $ICGR_{15}$, and prothrombin test results were distributed over wide ranges in these four patients (Table 6).

The clinical significance of the APRI in the determination of operative methods was investigated. The APRI was 10 or greater in only 4 of 139 patients who underwent major hepatectomy; it is thus not possible to evaluate the role of APRI in only patients who underwent major hepatectomy. For the 227 patients who underwent minor hepatectomy, APRI was a significant risk factor for postoperative hepatic failure.

Table 4 Risk factors for hepatic failure after liver resection for hepatocellular carcinoma, evaluated by multivariate analysis

Variable	Odds ratio	95% CI	*P* value
Albumin (per 1 g/dl)	0.360	0.114–1.140	0.0823
$ICGR_{15}$ (per 1%)	1.026	0.975–1.081	0.3222
Prothrombin test (per 1%)	1.007	0.990–1.025	0.4052
APRI	1.098	1.018–1.184	0.0149

$ICGR_{15}$ Indocyanine green retention rate at 15 min, *APRI* AST to platelet ratio index

Table 5 Features of hepatic failure in patients with high or low APRI

Feature	APRI		*P* value
	≤10 ($n = 333$)	>10 ($n = 33$)	
Hepatic coma	2	2	0.0422
Intractable pleural effusion or ascites	23	10	<0.0001
Variceal bleeding	0	1	0.0902
Death from hepatic failure	1	3	0.0025

Discussion

In this study, we attempted to develop a preoperative risk marker for predicting postoperative hepatic failure in patients with hepatocellular carcinoma who are candidates for hepatic resection using only routine laboratory tests. High APRI was a risk factor for postoperative hepatic failure on univariate analysis and the only independent preoperative risk factor on multivariate analysis.

Table 6 Results of laboratory tests and operative methods in four patients who died of postoperative hepatic failure

Patient no.	Age (year)	T-bil (mg/dl)	Albumin (g/dl)	$ICGR_{15}$ (%)	Prothrombin test (%)	APRI	Operative method
1	72	0.3	3.0	37.4	74	11.0	Partial
2	62	0.9	3.0	13.0	94	12.7	Partial
3	59	1.4	3.8	23.1	100	3.96	Rt. lobectomy
4	55	1.3	2.9	26.9	104	11.5	Partial

T-bil Total bilirubin, *$ICGR_{15}$* indocyanine green retention rate at 15 min, *APRI* AST to platelet ratio index

Cirrhosis is a well-known risk factor for postoperative hepatic failure [3, 10, 13, 20, 31, 32]. Degree of hepatic fibrosis is a negative predictor of liver regeneration and restoration of liver function after liver resection [33] that also influences the risk of postoperative ascites and pleural effusion [34] and duration of postoperative hepatic failure [9]. Active hepatitis has also been reported to be a potential risk factor for hepatic failure following liver resection [9, 31, 35]. We previously reported that active hepatitis and severe hepatic fibrosis are each risk factors for postoperative hepatic failure [25]. However, since biopsy specimens of noncancerous hepatic tissue are not readily obtainable preoperatively from all patients for reasons of safety and other issues, less invasive markers are needed. Recently, the APRI, which is calculated from AST activity and the platelet count, has been reported to correlate with histologic degree of hepatic fibrosis [22, 23]. In the present study we confirmed that APRI correlated with both histologic activity grade and histologic fibrosis grade in patients with HCC. Thus, preoperative determination of the APRI informs the surgeon about severity of active hepatitis and degree of fibrosis, and provides a measure of the risk of postoperative hepatic failure.

The indocyanine green clearance test has been used to develop guidelines for extent of liver resection [3, 5, 7, 18, 21, 36–42]. In this study, the role of the APRI in decision-making concerning extent of liver resection since remained unclear. In fact, it was not possible to evaluate the role of the APRI, since the APRI was 10 or greater in only 4 of 139 patients who underwent major hepatectomy. The percentage of patients with postoperative hepatic failure was significantly higher among those with a high APRI ($\geq$10) than among those with a low APRI (<10). The percentage of patients who died of hepatic failure also was significantly higher among those with a high APRI than among those with a low APRI. We suggest that APRI $\geq$ 10 is a more useful marker for postoperative death than any other laboratory tests (total bilirubin, albumin, $ICGR_{15}$, and prothrombin test). The APRI was thus useful for determining whether liver resection itself is indicated in patients with chronic liver disease. Since patients who have a high APRI have active hepatitis and severe hepatic fibrosis, care is needed to avoid postoperative hepatic failure. Treatments for HCC include locoregional treatment including percutaneous ethanol injection, microwave coagulation therapy, and radiofrequency ablation therapy and transarterial therapy, including transcatheter arterial embolization and hepatic arterial infusion chemotherapy [43]. These alternatives can be considered for patients with a high APRI.

Other reported risk factors for postoperative hepatic failure include patient age [10, 31], diabetes mellitus [13], and excessive intraoperative blood loss [7, 13, 18, 21, 32, 33]. Although excessive intraoperative blood loss was a risk factor on univariate analysis, age and diabetes mellitus were not found to be risk factors in the present study.

In conclusion, preoperative APRI was correlated with postoperative hepatic failure; in particular, APRI of ten or more carries a high risk of postoperative hepatic failure.

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