A Simple Noninvasive Index Can Predict Both Significant Fibrosis and Cirrhosis in Patients With Chronic Hepatitis C

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Information on the stage of liver fibrosis is essential in managing chronic hepatitis C (CHC) patients. However, most models for predicting liver fibrosis are complicated and separate formulas are needed to predict significant fibrosis and cirrhosis. The aim of our study was to construct one simple model consisting of routine laboratory data to predict both significant fibrosis and cirrhosis among patients with CHC. Consecutive treatment-naive CHC patients who underwent liver biopsy over a 25-month period were divided into 2 sequential cohorts: training set (n = 192) and validation set (n = 78). The best model for predicting both significant fibrosis (Ishak score ≥ 3) and cirrhosis in the training set included platelets, aspartate aminotransferase (AST), and alkaline phosphatase with an area under ROC curves (AUC) of 0.82 and 0.92, respectively. A novel index, AST to platelet ratio index (APRI), was developed to amplify the opposing effects of liver fibrosis on AST and platelet count. The AUC of APRI for predicting significant fibrosis and cirrhosis were 0.80 and 0.89, respectively, in the training set. Using optimized cut-off values, significant fibrosis could be predicted accurately in 51% and cirrhosis in 81% of patients. The AUC of APRI for predicting significant fibrosis and cirrhosis in the validation set were 0.88 and 0.94, respectively. In conclusion, our study showed that a simple index using readily available laboratory results can identify CHC patients with significant fibrosis and cirrhosis with a high degree of accuracy. Application of this index may decrease the need for staging liver biopsy specimens among CHC patients. (HEPATOLOGY 2003;38:518-526.)

Histologic examination of the liver is an integral part of the evaluation of patients with chronic hepatitis C (CHC).[1,2] Knowledge of the stage of liver fibrosis is essential for prognostication and decisions on antiviral treatment.[3,4] CHC patients with no or minimal fibrosis at presentation appear to progress slowly and treatment possibly could be delayed or withheld. On the other hand, patients with significant fibrosis (*i.e.*, septal or bridging fibrosis) progress almost invariably to cirrhosis over a 10- to 20- year period so antiviral treatment should be strongly considered.[5] For patients with cirrhosis, surveillance for hepatocellular carcinoma and gastroesophageal varices should be considered also.[6,7]

Liver biopsy is currently the gold standard in assessing liver histology. Although percutaneous liver biopsy is in general a safe procedure, it is costly and does carry a small risk for complication.[8] In addition, there could be sampling error because only 1/50,000 of the organ is sampled. Furthermore, inter- and intraobserver discrepancies of 10% to 20% in assessing hepatic fibrosis have been reported, which may lead to understaging of cirrhosis.[9-11] Hence, there is a need to develop accurate and reliable noninvasive means to assess the severity of hepatic fibrosis.

Noninvasive approaches to assess histology in CHC patients include clinical symptoms and signs, routine laboratory tests, serum markers of fibrosis and inflammation, quantitative assays of liver function, and radiologic imag-

Abbreviations: CHC, chronic hepatitis C; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; IDU, injection drug use; ALP, alkaline phosphatase; ULN, upper limit of normal; ROC, receiver operating characteristics; AUC, area under receiver operating curves; CI, confidence interval; APRI, aspartate aminotransferase to platelet count ratio index.

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ing studies.[12-15] However, at present, none of these tests or markers alone is accurate or reliable in predicting histology, in particular, liver fibrosis. An ideal noninvasive diagnostic test for hepatic fibrosis should be simple, readily available, inexpensive, and accurate.[16] An index comprising routinely available laboratory tests would meet these criteria.

Many studies have been performed to evaluate the use of readily available laboratory test results to predict significant fibrosis or cirrhosis in patients with CHC.[17-21] However, sensitivity was generally poor, and most studies did not validate their results in a separate group of patients. A recent study by Forns et al.[21] performed internal validation using a randomly chosen cohort from the study patients and found that absence of significant fibrosis could be predicted in 39% of patients. However, only 24% of their patients had significant fibrosis so it is uncertain if the results could be extrapolated to patients with more advanced disease.

For the prediction of cirrhosis, most studies examined the usefulness of predetermined formulas such as aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio or the cirrhosis discriminant score, without analyzing other confounding factors or validating their results.[22-26] Kaul et al.[27] performed univariate and multivariate analysis on 351 patients and derived a model consisting of gender, AST, platelet count, and spider nevi. This model was validated internally and externally with good accuracy but it included one subjective variable.

We aimed to develop one single model consisting of readily available, objective laboratory data to predict both significant fibrosis and cirrhosis in treatment-naive CHC patients. To accomplish this, a training set of clinical and laboratory data from 192 consecutive CHC patients were used to formulate predictive models, which were validated in 78 subsequent patients.

Patients and Methods

Patients. This retrospective cohort study included 579 consecutive adult patients with CHC who had undergone percutaneous liver biopsy at the University of Michigan Medical Center from January 2001 to January 2003. The diagnosis of CHC was established by the presence of hepatitis C virus (HCV) RNA using polymerase chain reaction assays. Patients with the following conditions were excluded from the study: presence of other causes of liver disease, hepatocellular carcinoma, prior liver transplantation, prior interferon therapy, immunosuppressive therapy, insufficient liver tissue for staging of fibrosis, and incomplete data on complete blood counts and/or liver panel.

Patients were divided into 2 sets: consecutive patients who were biopsied between January 2001 and July 2002 constituted the training set, whereas those patients who were biopsied between August 2002 and January 2003 constituted the validation set. All study subjects gave informed consent for the liver biopsy. This study was approved by the Institutional Review Board.

Methods. A list of consecutive CHC patients who underwent percutaneous liver biopsy at the University of Michigan Medical Center was generated from the Department of Pathology. Clinical information about these patients obtained from electronic medical record and hard-copy clinical charts were reviewed by one investigator (C.T.W.) to assess eligibility for the study. Demographics and laboratory variables were recorded. Other clinical variables were extracted from the medical records according to a set of predetermined criteria.

Patients on diabetic medications or patients who had a past history of diabetes mellitus were considered to have diabetes mellitus. Patients who had been drinking more than an average of 7 drinks per week, for more than 4 weeks in a row before the liver biopsy, were considered current drinkers. Patients who drank less than 7 drinks per week for the past 4 weeks in a row were considered nondrinkers. Patients who had stopped drinking completely for more than 1 year before the biopsy were considered ex-drinkers. Patients with no explicitly mentioned amount or duration of drinking were considered to have an unknown drinking history.

Patients with a history of blood transfusion before 1992 were considered to have acquired CHC through transfusion.[28,29] For those with multiple transfusions, the date of the first transfusion was considered to be the time of infection. Patients with a history of injection drug use (IDU) were considered to have acquired CHC through IDU and the year in which IDU began was considered to be the time of infection. Patients with no history of transfusion or IDU, but who had other modes of percutaneous exposure such as a tattoo, occupational exposure, and so forth, were considered to have acquired CHC through others means and the year of first percutaneous exposure was considered as the time of infection. Patients without parenteral risk factors were considered to be unknown regarding both the mode and duration of infection.

Except for HCV genotype, only laboratory results performed within 4 months from the date of the liver biopsy were used for this study. If more than one set of laboratory test results were available, the results closest to the time of biopsy were used. Results of serum aminotransferase and alkaline phosphatase (ALP) levels were expressed as ratios of the upper limit of normal (ULN). HCV-RNA level was

expressed as $\log_{10}$ IU/mL. Abdominal ultrasound reports within 6 months from the time of biopsy were reviewed. Patients with splenomegaly, enlarged spleen, or spleen size of more than 14 cm were considered to have splenomegaly.[30]

Histologic slides of all eligible patients were retrieved. All liver biopsies were reviewed by one pathologist (J.K.G.), who had no knowledge of the clinical characteristics of the study subjects. Hepatic fibrosis was assessed using the Ishak fibrosis score.[31] Significant fibrosis was defined as Ishak score of 3 or more (presence of bridging fibrosis) and cirrhosis as Ishak score of 5 or 6.

Statistical Analysis. Data were expressed as mean ± SEM unless otherwise stated. Statistical analysis was performed by SPSS software version 9.0 (SPSS Inc., Chicago, IL). There were 2 endpoints in this study: presence of significant fibrosis and cirrhosis. The following variables were included in the univariate analysis: demographics (age, sex, ethnicity), alcohol intake, viral factors (mode of HCV infection, age at infection, duration of infection, HCV-RNA level, genotype), and other test results (white cell count, platelet count, international normalized ratio, bilirubin, albumin, ALT, AST, and ALP). All continuous variables were analyzed after logarithmic transformation for normality of distribution. Categoric variables were compared by χ^2 or Fisher exact tests, whereas continuous variables were compared with the Student's *t* test. Correlation was evaluated by the Spearman correlation coefficient. A 2-sided *P* value of less than .05 was considered statistically significant.

For the formulation of predictive models, univariate analysis was performed on variables between patients with and without the study endpoints in the training set. Significant variables from the univariate analysis ($P < .05$), together with age at biopsy, were then subjected to multivariate analysis by forward logistic regression to identify independent factors associated with either endpoint. Variables with missing values in more than 20% of the patients (*i.e.*, splenomegaly on ultrasonography, body mass index, age at infection, and duration of infection) were not included in the regression analysis.

Formulas with risk scores that could best predict the study endpoints (significant fibrosis and cirrhosis) were constructed by entering different sets of independent variables into the regression model. The diagnostic value of each formula was assessed by the area under the receiver operating characteristic (ROC) curves.

The best model derived from the training set then was applied to the validation set to test for accuracy by measuring the areas under the ROC curves.

Table 1. Comparison of Patients in the Training and Validation Sets

Variable	Training Set n = 192	Validation Set n = 78	*P* Value
Age, y	46.8 ± 0.6	47.7 ± 0.9	.45
Male gender, n (%)	123 (64)	51 (66)	.89
Ethnicity, n (%)			
Caucasians	151 (77)	48 (62)	.014
African Americans	16 (8)	17 (22)	
Others	7 (4)	5 (6)	
Unknown	18 (9)	8 (10)	
Drinking history, n (%)			
Current drinker	26 (14)	8 (10)	.50
Ex-drinker	54 (28)	18 (23)	
Nondrinker	90 (47)	40 (51)	
Unknown	20 (11)	12 (15)	
Mode of transmission, n (%)			
IDU	79 (41)	24 (30)	.025
Transfusion	45 (23)	10 (13)	
IDU and transfusion	9 (5)	4 (5)	
Others	31 (16)	20 (26)	
Unknown	28 (15)	20 (26)	
Age at infection, y	21.1 ± 0.7	22.5 ± 1.5	.29
Duration of infection, y	26.6 ± 0.7	26.3 ± 1.1	.97
Genotype 1, n (%)	130/173 (75)	52/74 (70)	.43
Viral load, $\log_{10}$ (IU/mL)	5.81 ± 0.05	6.11 ± 0.09	.006
White cell count (10^9/L)	6.6 ± 0.1	6.7 ± 0.2	.65
Platelet count (10^9/L)	219 ± 5	205 ± 9	.16
International normalized ratio	1.01 ± 0.01	1.01 ± 0.02	.22
Bilirubin (mg/dL)	0.58 ± 0.02	0.61 ± 0.04	.48
Albumin (g/dL)	4.00 ± 0.04	4.09 ± 0.05	.23
ALT (/ULN)	2.63 ± 0.17	2.55 ± 0.27	.51
AST (/ULN)	2.20 ± 0.14	2.35 ± 0.23	.34
ALP (/ULN)	0.64 ± 0.02	0.71 ± 0.03	.016
Ishak fibrosis score	2.83 ± 0.10	2.88 ± 0.17	.77
Significant fibrosis, n (%)	91 (47)	39 (50)	.79
Cirrhosis, n (%)	28 (15)	13 (17)	.71

NOTE. Values are expressed as mean ± SEM.

Results

Characteristics of the Patients in the Training Set. From January 2001 to July 2002, 428 percutaneous liver biopsies were performed on patients with CHC at our institution. A total of 236 patients were excluded from the study: 102 had prior interferon therapy, 82 had prior liver transplants, 23 had concomitant liver diseases, 9 were on immunosuppressive therapy, 4 had insufficient liver tissues for staging of fibrosis, and 16 had incomplete data on complete blood count and/or liver panel.

The mean age of the 192 patients included in the training set was 46.8 ± 0.6 years, 123 (64%) were men, 151 (79%) were Caucasians, and 16 (8%) were African Americans. Thirteen (7%) patients had diabetes mellitus (Table 1). The age at infection and duration of infection, available in 65% of the patients, were 21.1 ± 0.7 years and 26.7 ± 0.7 years, respectively. Of the 98 patients who had ultrasound results, 18 (18%) had splenomegaly. The mean Ishak fibrosis score was 2.83 ± 0.10. Ninety-one

Table 2. Univariate Analysis of Variables Associated With the Presence of Significant Fibrosis and Cirrhosis in the Training Set

Variable	No Significant Fibrosis Ishak Score 0-2 (n = 101)	Significant Fibrosis Ishak Score 3-6 (n = 91)	*P* Value	No Cirrhosis Ishak score 0-4 (n = 164)	Cirrhosis Ishak Score 5-6 (n = 28)	*P* Value
Age, y	45.5 ± 0.8	47.9 ± 0.9	.069	46.5 ± 0.6	47.7 ± 1.7	.54
Male gender, n (%)	60 (59)	60 (69)	.18	101 (62)	22 (79)	.092
Ethnicity, n (%)						
Caucasians	77 (76)	74 (81)	.13	128 (78)	23 (83)	.40
African Americans	12 (12)	4 (4)		15 (9)	1 (4)	
Others	5 (5)	2 (2)		7 (4)	0	
Unknown	7 (7)	11 (12)		14 (9)	4 (13)	
Drinking history, n (%)						
Current drinker	2 (12)	14 (15)	.106	23 (14)	3 (11)	.20
Ex-drinker	22 (22)	32 (35)		42 (26)	12 (43)	
Nondrinker	55 (56)	35 (39)		81 (50)	9 (32)	
Unknown	10 (10)	10 (11)		16 (10)	4 (14)	
Mode of transmission, n (%)						
IDU	45 (44)	34 (37)	.009	68 (42)	11 (39)	.004
Transfusion	20 (20)	25 (28)		39 (24)	6 (18)	
IDU and transfusion	0	9 (10)		4 (2)	5 (21)	
Others	19 (19)	12 (13)		30 (18)	1 (4)	
Unknown	17 (17)	11 (12)		23 (14)	5 (18)	
Age at infection, y	20.4 ± 0.8	21.9 ± 1.2	.29	21.1 ± 0.8	21.1 ± 1.8	.61
Duration of infection, y	25.9 ± 0.9	27.7 ± 1.1	.32	26.5 ± 0.8	27.7 ± 2.0	.47
Genotype 1, n (%)	67/90 (75)	63/83 (76)	.86	112/149 (75)	18/24 (76)	1.00
HCV-RNA titer, $\log_{10}$ (IU/mL)	5.73 ± 0.07	5.91 ± 0.08	.091	5.82 ± 0.05	5.76 ± 0.16	.73
White cell count (10^9/L)	6.8 ± 0.2	6.3 ± 0.2	.033	6.7 ± 0.2	5.7 ± 0.4	.015
Platelet count (10^9/L)	246 ± 6	140 ± 8	<.001	234 ± 5	136 ± 11	<.001
INR	0.99 ± 0.01	1.04 ± 0.01	<.001	1.00 ± 0.01	1.09 ± 0.02	<.001
Bilirubin (mg/dL)	0.52 ± 0.03	0.64 ± 0.04	.009	0.55 ± 0.02	0.75 ± 0.09	.008
Albumin (g/dL)	4.8 ± 0.5	4.3 ± 0.4	.86	4.7 ± 0.4	3.7 ± 0.1	.034
ALT (/ULN)	1.95 ± 0.13	3.37 ± 0.30	<.001	2.54 ± 0.18	3.16 ± 0.36	.041
AST (/ULN)	1.49 ± 0.08	3.00 ± 0.06	<.001	1.99 ± 0.15	3.44 ± 0.38	<.001
ALP (/ULN)	0.58 ± 0.02	0.72 ± 0.34	<.001	0.60 ± 0.01	0.88 ± 0.09	.001
AST/ALT ratio	0.65 ± 0.02	0.74 ± 0.03	.004	0.65 ± 0.01	0.93 ± 0.07	<.001

(47%) patients had significant fibrosis and 28 (15%) had cirrhosis.

Predictors of Significant Fibrosis and Cirrhosis From the Training Set. Variables associated with the presence of significant fibrosis and cirrhosis were first assessed by univariate analysis (Table 2). Subsequent multivariate analysis showed that platelet count ($P < .001$), AST level ($P < .001$), and ALP level ($P = .029$) were the independent predictors of significant fibrosis whereas platelet count ($P < .001$), AST level ($P = .017$), white cell count ($P = .01$), ALP level ($P = .019$), and AST/ALT ratio ($P = .001$) were the independent predictors of cirrhosis.

Variables in the best models for prediction of significant fibrosis included platelet count, AST levels, and ALP levels, and for prediction of cirrhosis platelet count, white cell count, AST level, ALP level, and AST/ALT ratio (Table 3). Models with only platelet count and AST level were more simple and had accuracies comparable with those with 3 or more variables in prediction of both endpoints.

Regression formula for prediction of significant fibrosis:

$$\text{Risk score} = 2.318 + 0.274 \cdot \ln(\text{AST level [/ULN]}) - 0.375 \cdot \ln(\text{platelet count [}10^9\text{/L]}).$$

Regression formula for prediction of cirrhosis:

$$\text{Risk score} = 2.411 + 0.100 \cdot \ln(\text{AST level [/ULN]}) - 0.436 \cdot \ln(\text{platelet count [}10^9\text{/L]}).$$

Although both histologic endpoints could be predicted by the same variables, 2 separate formulas were required and cumbersome calculation was needed.

Validation Set. From August 2002 to January 2003, 151 liver biopsies were performed on adult patients with CHC. Seventy-three patients were excluded from the study: 39 had prior interferon therapy, 23 had prior liver transplant, 5 had concomitant liver diseases, 2 were on immunosuppressive therapy, and 4 had incomplete re-

Table 3. Models With Different Combination of Variables for Predicting Significant Fibrosis and Cirrhosis in the Training Set and the Validation Set

	Training Set		Validation Set	
Variables in the Model	Prediction of Significant Fibrosis AUC (95% CI)	Prediction of Cirrhosis AUC (95% CI)	Prediction of Significant Fibrosis AUC (95% CI)	Prediction of Cirrhosis AUC (95% CI)
Platelets, AST, ALP, White blood count, AST/ALT ratio	NA	0.93 (0.88-0.97)	NA	0.94 (0.89-0.99)
Platelets, AST, ALP	0.82 (0.76-0.88)	0.92 (0.87-0.91)	0.87 (0.80-0.95)	0.94 (0.88-1.00)
Platelets, AST	0.80 (0.74-0.86)	0.91 (0.86-0.96)	0.87 (0.79-0.95)	0.93 (0.85-1.00)
Platelets, AST/ALT ratio	0.73 (0.66-0.81)	0.90 (0.83-0.98)	0.74 (0.63-0.85)	0.90 (0.81-0.99)
APRI	0.80 (0.74-0.87)	0.89 (0.84-0.94)	0.88 (0.80-0.96)	0.94 (0.89-1.00)

NOTE. NA, not applicable because not all the variables were significant in the regression model.

sults on blood count or liver panel. Seventy-eight patients fulfilled the study entry criteria and comprised the validation set. Characteristics of the validation set were similar to that of the training set, in particular, there was no difference in the mean fibrosis score and the proportion with significant fibrosis and cirrhosis. The 2 groups also were comparable in platelet count and AST value. However, there were more African Americans, a higher proportion with acquisition of hepatitis C through other means besides transfusion and IDU, a higher viral load, and a higher ALP level in the validation set (Table 1).

Models comprising platelet count and AST level for prediction of significant fibrosis and cirrhosis were applied to the validation set. The area under ROCs (AUC) for prediction of significant fibrosis and cirrhosis were 0.87 (95% confidence interval [CI], 0.79-0.95) and 0.93 (95% CI, 0.85-1.0), respectively. Formulas with more variables did not improve the AUC for either significant fibrosis or cirrhosis in the validation set (Table 3).

Novel Index in Predicting Liver Fibrosis. Because platelet count and AST level were the most important predictors of both significant fibrosis and cirrhosis, we further analyzed the relationship between these 2 factors and the stage of hepatic fibrosis. Figure 1A and B showed that severity of liver fibrosis was correlated significantly with a gradual increase in AST level ($r = .50$, $P < .001$) as well as a decrease in platelet count ($r = -.46$, $P < .001$). However, there was significant overlap in AST and platelet among patients with different stages of fibrosis. To amplify the difference in AST and platelet values among patients with different fibrosis stages, we devised a novel index, called the AST to platelet ratio index (APRI):

$$\text{APRI} = \frac{\text{AST level (/ULN)}}{\text{Platelet counts } (10^9/\text{L})} \times 100 \qquad (1)$$

APRI was correlated significantly with the stage of fibrosis, with a higher correlation coefficient than platelet count, or AST level alone ($r = .60$, $P < .001$) (Fig. 1C).

ROC curves of APRI for predicting significant fibrosis and cirrhosis in the training set were plotted in Fig. 2A with AUC of 0.80 and 0.89, respectively (Table 3). Based on the ROC, 2 cut-off points were chosen to predict the absence (coordinate A: APRI $\leq$ 0.50) or presence (coordinate B: APRI $>$ 1.50) of significant fibrosis (Fig. 2A). For patients with APRI of 0.50 or less, 47 of 55 (85%) would not have significant fibrosis. Among the 91 patients who had significant fibrosis, only 8 (9%) would have APRI of 0.50 or less, 7 of whom had an Ishak score of 3 and 1 had an Ishak score of 4. For patients with APRI greater than 1.50, 37 of 42 (88%) would have significant fibrosis, and only 5 of 101 (5%) without significant fibrosis would be classified incorrectly. Together, using APRI below the lower cut-off value (0.50) and above the higher cut-off value (1.50), 51% of the patients could be identified correctly as either without or with significant fibrosis (Table 4).

Similarly, 2 cut-off points were chosen to predict the absence (coordinate C: APRI $\leq$ 1.00) or presence (coordinate D: APRI $>$ 2.00) of cirrhosis (Fig. 2A). For patients with APRI of 1.00 or less, 123 of 126 (98%) would not have cirrhosis. Only 3 of 28 (11%) with cirrhosis would be classified falsely. On the other hand, for patients with APRI greater than 2.00, 16 of 28 (57%) had cirrhosis, and only 12 of 164 (7%) without cirrhosis would be identified falsely. Among the 12 patients with APRI greater than 2.00 but who did not have cirrhosis, 1 had an Ishak score of 2, 6 had an Ishak score of 3, and 5 had an Ishak score of 4. Using the cut-off values of 1.00 and 2.00, the absence or presence of cirrhosis can be identified in 81% of patients (Table 4).

Applying APRI to the validation set, AUC for prediction of significant fibrosis and cirrhosis were 0.88 (95% CI, 0.80-0.96) and 0.94 (95% CI, 0.89-1.0), respectively (Fig. 2B). Accuracy of using APRI for prediction of significant fibrosis and cirrhosis in the validation set is comparable with models with a formula comprising more

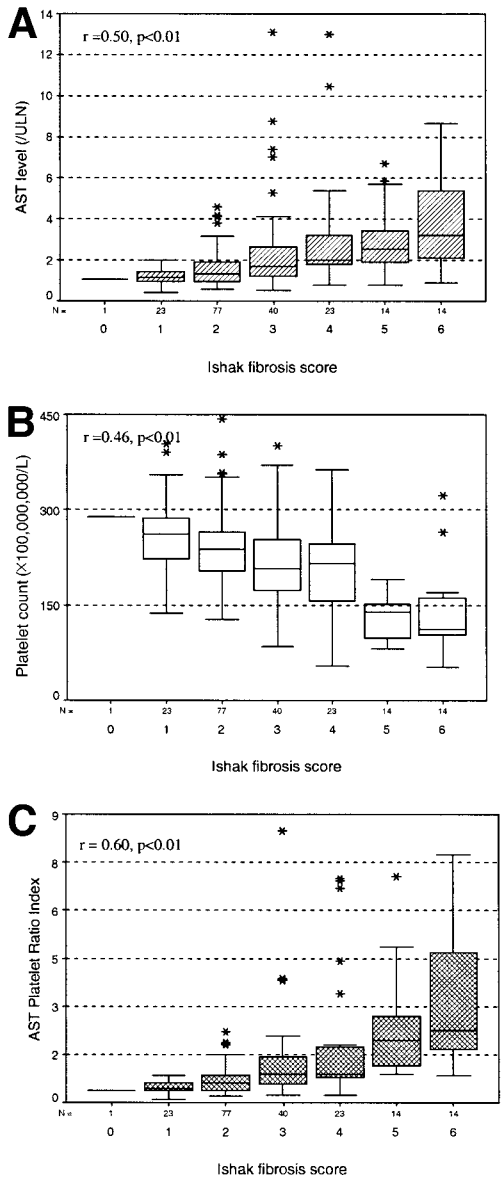

Fig. 1. Box plot of (A) AST, (B) platelet count, and (C) AST platelet ratio index in relation to the Ishak fibrosis score. The box represents the interquartile range. The **whiskers** indicate the highest and lowest values, and the **asterisks** represent outliers. The **line** across the box indicates the median value.

variables (Table 3). Predictive values of the APRI in the validation set were similar to that in the training set. For the prediction of significant fibrosis in the validation set, the positive predictive value and negative predictive value of an APRI of 0.50 were 64% and 90%, and the corresponding values for an APRI of 1.50 were 91% and 65%, respectively. For the prediction of cirrhosis in the validation set, the positive and negative predictive value of an APRI of 1.00 were 35% and 100%, and the corresponding values for APRI of 2.00 were 65% and 95%, respectively.

Finally, we applied the models to the 270 patients from the training and validation sets combined. For the formulas comprising platelet count and AST level, the AUC were 0.82 (95% CI, 0.77-0.87) and 0.92 (95% CI, 0.87-0.96) for prediction of significant fibrosis and cirrhosis, respectively. For APRI, the AUC were 0.83 (95% CI, 0.78-0.88) and 0.90 (95% CI, 0.86-0.94) for prediction of significant fibrosis and cirrhosis, respectively.

To show the use of APRI in predicting fibrosis, for a hypothetical patient with CHC who has a platelet count of 120×10^9/L and an AST level of 90 IU/L (ULN = 45), the APRI could be calculated as follows:

$$\text{APRI} = \frac{\text{AST (/ULN)} \times 100}{\text{Platelet } (10^9/\text{L})} = \frac{2 \times 100}{120} = 1.67 \quad (2)$$

This APRI value is more than 1.5 (the higher cut-off value for significant fibrosis), so the positive predictive value for significant fibrosis is 0.88. The APRI value is less than 2.0

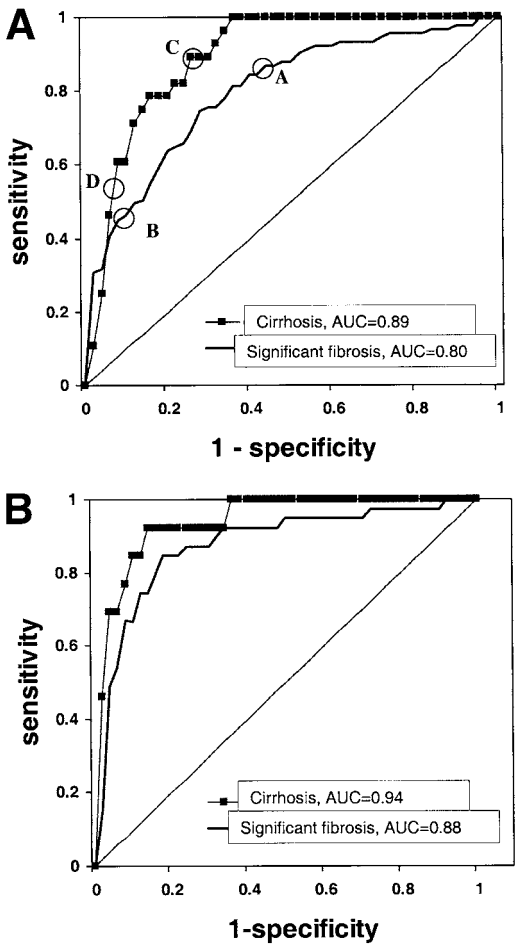

Fig. 2. ROC curves of APRI in the prediction of significant fibrosis and cirrhosis in the (A) training set and (B) validation set. An AUC of 1.0 is characteristic of an ideal test, whereas an AUC of 0.5 or less indicates a test of no diagnostic value.

Table 4. Accuracy of APRI in Predicting Significant Fibrosis and Cirrhosis in the Training Set

APRI	All Patients (n = 192) n (%)	Actual Fibrosis: Stage 0-2 (n = 101) n (%)	Actual Fibrosis: Stage 3-6 (n = 91) n (%)	Sensitivity %	Specificity %	PPV %	NPV %
For prediction of significant fibrosis							
≤0.50	55 (29)	47 (47)	8 (9)	91	47	61	86
>0.50	137 (71)	54 (53)	83 (91)				
≤1.50	150 (78)	96 (95)	54 (59)	41	95	88	64
>1.50	42 (22)	5 (5)	37 (41)				
		Actual Fibrosis: Stage 0-4 (n = 164)	Actual Fibrosis: Stage 5-6 (n = 28)				
For prediction of cirrhosis							
≤1.00	126 (66)	123 (75)	3 (11)	89	75	38	98
>1.00	66 (34)	41 (25)	25 (89)				
≤2.00	164 (85)	152 (93)	12 (43)	57	93	57	93
>2.00	28 (15)	12 (7)	16 (57)				

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

(the higher cut-off level for cirrhosis), so the negative predictive value for cirrhosis is 0.93. Hence, this patient is likely to have significant fibrosis but not cirrhosis.

Discussion

In this study, we attempted to develop a single model using routinely available laboratory test results to predict significant fibrosis and cirrhosis in a consecutive series of treatment-naive CHC patients. We found that platelet count, AST level, and ALP level were the independent predictors for significant fibrosis, whereas platelet and white cell count, AST and ALP levels, as well as AST/ALT ratio, were the independent predictors for cirrhosis. Our findings echoed results from many previous studies, which showed that platelet count, AST level, and AST/ALT ratio were important predictors of either significant fibrosis or cirrhosis.[17-27] To amplify the opposite relationship between the stage of fibrosis and AST level and platelet count, we devised a novel index, the APRI, which was simple to use and had comparable accuracy with models that comprised 3 or more variables in predicting both significant fibrosis and cirrhosis. The performance of APRI in predicting significant fibrosis and cirrhosis was validated in a subsequent set of patients with similar accuracy.

Many studies on prediction of significant fibrosis and cirrhosis among CHC patients have been published in the past few years.[13-27] Our study has several unique features. First, we recruited consecutive patients undergoing percutaneous liver biopsies at our medical center who met eligibility criteria. Many prior studies have recruited only patients enrolled in treatment trials,[18,32] which may have introduced selection bias. Our study included treatment-naive patients only because several studies have shown that liver histology may improve even among nonresponders to interferon-based therapy.[33-35]

Secondly, our study included a sufficient proportion of patients with significant fibrosis (47%) and cirrhosis (15%), thus allowing us to study variables that could predict both of the study endpoints within the same patient population. Although the overall study population only included 270 patients, and differences in race and mode of infection were present between the training and validation sets, the accuracy of APRI was validated in a sequential cohort of CHC patients undergoing a liver biopsy at our institution. This suggests that the model is robust and accurate.

Most importantly, our predictive model consists of objective and readily available laboratory variables. Both platelet count and AST level are routine tests performed in CHC patients in clinical practice, so no additional tests are needed. The finding of decreased platelet count and increased AST level with progression of liver fibrosis has been reported in many studies. With increasing fibrosis and worsening portal hypertension, there is increased sequestration and destruction of platelets in the enlarging spleen.[36] In addition, studies in liver transplant patients showed that progression of liver fibrosis is associated with decreased production of thrombopoietin by hepatocytes, and hence reduced platelet production.[37,38] Progression of liver fibrosis may reduce the clearance of AST,[39] leading to increased serum AST levels. In addition, advanced liver disease may be associated with mitochondrial injury, resulting in more marked release of AST, which is present in mitochondria and cytoplasm, relative to ALT.[40,41]

To amplify the difference in AST and platelet values among patients with different stages of fibrosis, we devised a novel index, the APRI. The concept of a ratio of 2 important variables in prediction of significant fibrosis is not new. In the study by Williams and Hoofnagle,[32] the investigators observed that as patients with chronic liver disease progressed, AST levels increased more than ALT levels. The investigators exploited the difference between these 2 factors and devised the AST/ALT ratio for prediction of cirrhosis. Although several investigators have confirmed the value of AST/ALT ratio in predicting cirrhosis,[22-25] its accuracy varies widely among studies, with positive predictive values ranging from 0.64 to 1.00, and negative predictive values ranging from 0.72 to 0.88, respectively. In this study, although AST/ALT ratio was 1 of the 5 independent predictors of cirrhosis, it alone was insufficient for accurate prediction of cirrhosis. In addition, AST/ALT ratio alone has not been shown to be useful in predicting significant fibrosis.[17-21]

The APRI was accurate in predicting both significant fibrosis and cirrhosis, with area under ROC of 0.80 and 0.89 in the training set, and 0.88 and 0.94 in the validation set, respectively. Although we could not define one single cut-off value to predict either study endpoint, using values below the lower cut-off level or above the higher cut-off level, a prediction of absence or presence of cirrhosis could be made in 81% of patients. Similarly, a prediction of absence or presence of significant fibrosis could be made in 51% of patients. Our index compared favorably with results from other studies. Forns et al.[21] could predict significant fibrosis in 51% of patients using 4 factors (platelet count, γ-glutamyltransferase level, age, and cholesterol), with an AUC of 0.94. The fibrosis index from the MULTIVIRC group could predict significant fibrosis in 46% of patients by using a combination of 6 markers (α_2 macroglobulin, haptoglobin, γ globulin, apolipoptotein A_1, γ glutamyl-transpeptidase, and total bilirubin), with an AUC of 0.84.[15] Although the value of the index of Forns et al.[21] in predicting the absence of significant fibrosis was better than the APRI, it involved a complicated formula. The major advantage of the APRI is its simplicity. APRI can be determined in the clinic or bedside without the help of a calculator. Moreover, the APRI allows clinicians to use one formula to predict significant fibrosis as well as cirrhosis.

Although our study was retrospective in design, we took all the necessary measures to maximize the accuracy of our data collection. To ensure consistency in data extraction, a predetermined set of criteria for all subjective variables was established before the medical records were reviewed, and all data extraction was performed by one investigator (C.T.W.). The key variables in our study were objective laboratory results, most of which were available in the hospital computer system. All histologic slides were retrieved and re-read by one liver pathologist (J.K.G.) to avoid interobserver discrepancy. In addition, all the slides were re-read over a 12-week period to minimize intraobserver variability.

We acknowledge that there are limitations to our study. Our study included patients from a university hepatology clinic, half of whom had significant fibrosis on histology and none had prior antiviral treatment. Whether our results can be generalized to community-based practice in which patients may have milder disease, or to patients who failed prior antiviral therapy remain to be determined. Despite the simplicity and accuracy of the APRI, there was overlap among patients with different stages of fibrosis. Thus, the use of APRI in the prediction of fibrosis in individual patients with CHC must be confirmed in prospective studies. Finally, our study is based on the premise that liver biopsy is the gold standard for assessing hepatic fibrosis, but sampling error as well as intra- and interobserver variability can complicate the correlations between histology and noninvasive markers of hepatic fibrosis.

In conclusion, we showed that a simple index, the APRI, consisting of 2 readily available laboratory results (AST level and platelet count), can predict significant fibrosis and cirrhosis in treatment-naive CHC patients with a very high degree of accuracy. Our results were validated in a subsequent cohort of CHC patients at our institute. The APRI can be determined in the clinic or at the bedside. Using one simple formula, significant fibrosis and cirrhosis can be predicted accurately in 51% and 81% of treatment-naive CHC patients, respectively, potentially avoiding the need for liver biopsies in these patients. Further prospective studies are needed to validate the APRI in a larger number of CHC patients in other institutes, in particular, community-based practices where the prevalence of significant fibrosis and cirrhosis may be lower, and in patients who had received antiviral therapy previously.

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