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Acta Medica Okayama

Volume 60, *Issue* 2 2006 *Article* 2

APRIL 2006

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Abstract

This study was conducted to develop a simple surrogate index comprised of routinely available laboratory tests to reflect the histological fibrosis stage. Clinical characteristics and laboratory data from 368 and 249 consecutive patients with chronic hepatitis C, a training cohort and a validation cohort, respectively, were retrospectively evaluated. Platelet (Plt) count and albumin (Alb) level contributed to the discrimination of the respective fibrosis stages. We derived the fi brosis index (FI), FI = 8.0-0.01 x Plt (10 multiply 3/microliter) - Alb (g/dl), from a multiple regression model. FI significantly correlated with the histological fibrosis stage in both the initial and validation cohort at p=0.691 and p=0.661, respectively (Spearman's rank correlation coefficient, $p<0.0001$). The sensitivity and positive predictive value of FI at a cutoff value < 2.10 for predicting fibrosis stage F0-1 were 66.8% and 78.8% in the initial cohort and 68.5% and 63.6% in the validation cohort, respectively. Corresponding values of FI at a cutoff value $>$- 3.30 for the prediction of F4 were 67.7% and 75.0% in the initial cohort and 70.8% and 81.0% in the validation cohort. The fibrosis index comprised of platelet count and albumin level reflected the histological fibrosis stage in patients with chronic hepatitis C.

KEYWORDS: albumin level, chronic hepatitis C, fi brosis index, fi brosis stage, platelet count

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*PMID: 16680183 [PubMed - in process]
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Acta Med. Okayama, 2006
Vol. 60, No. 2, pp. 77-84
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Acta Medica Okayama
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Original Article

Simple Surrogate Index of the Fibrosis Stage in Chronic Hepatitis C Patients Using Platelet Count and Serum Albumin Level

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This study was conducted to develop a simple surrogate index comprised of routinely available laboratory tests to reflect the histological fibrosis stage. Clinical characteristics and laboratory data from 368 and 249 consecutive patients with chronic hepatitis C, a training cohort and a validation cohort, respectively, were retrospectively evaluated. Platelet (Plt) count and albumin (Alb) level contributed to the discrimination of the respective fibrosis stages. We derived the fibrosis index (FI), FI = 8.0 − 0.01 × Plt ($10^3/\mu$l) − Alb (g/dl), from a multiple regression model. FI significantly correlated with the histological fibrosis stage in both the initial and validation cohort at ρ=0.691 and ρ=0.661, respectively (Spearman's rank correlation coefficient, p<0.0001). The sensitivity and positive predictive value of FI at a cutoff value < 2.10 for predicting fibrosis stage F0-1 were 66.8% and 78.8% in the initial cohort and 68.5% and 63.6% in the validation cohort, respectively. Corresponding values of FI at a cutoff value ≥ 3.30 for the prediction of F4 were 67.7% and 75.0% in the initial cohort and 70.8% and 81.0% in the validation cohort. The fibrosis index comprised of platelet count and albumin level reflected the histological fibrosis stage in patients with chronic hepatitis C.

Key words: albumin level, chronic hepatitis C, fibrosis index, fibrosis stage, platelet count

Chronic hepatitis C (CHC) is a progressive disease that is linked to cirrhosis and hepatocellular carcinoma (HCC) development. The disease progression from mild chronic hepatitis to cirrhosis is evaluated by histological examination and expressed in terms of the stage of liver fibrosis [1-5]. Knowing the exact stage of liver fibrosis is crucial to making therapeutic decisions and assessing the prognosis of CHC patients. Liver biopsy, however, is costly and presents a small risk for complications. Histological examination, therefore, is rarely performed repeatedly, even when the disease activity is severe and the progression of liver disease is highly suspected.

Despite the accuracy of histological examination in diagnosing chronic liver disease, an evaluation of the disease progression based on biochemical and hematological tests is still indispensable as a daily practice for many patients with CHC. Studies have been performed to establish noninvasive laboratory methods that can predict the severity of liver fibrosis [6-13]. While these methods aim to predict either the presence or absence of significant fibrosis and/or

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cirrhosis in patients with chronic liver diseases, none can accurately or reliably reflect the respective fibrosis stage from minimal chronic hepatitis to cirrhosis. A better evaluation of the progression of liver disease is needed for use in the clinical practice of chronic liver diseases. The aim of this study was to develop an index comprised of routinely available laboratory tests to reflect the fibrosis stage and disease progression in patients with CHC.

Patients and Methods

Study Cohorts. Three hundred and sixty-eight consecutive patients with chronic hepatitis C virus (HCV) infection who underwent peritoneoscopic liver biopsy at Okayama University Hospital between January 1995 and December 2003 constituted the training cohort. Two hundred and forty-nine patients with CHC who underwent liver biopsy at affiliated hospitals between January 2002 and December 2003 constituted the validation cohort. Patients with clinically evident liver cirrhosis or decompensated liver disease (ascites, jaundice, variceal bleeding, or encephalopathy) were excluded from the laparoscopic liver biopsy. Patients with a concomitant infection of hepatitis B virus (HBV) and patients with other causes underlying liver disease were also excluded from the study.

CHC was diagnosed if alanine aminotransferase (ALT) was elevated greater than 36 IU/L within at least 6 months of the histological examination and a second-generation anti-HCV test (Abbott Laboratories, Chicago, IL, USA) yielded positive results or HCV-ribonucleic acid (RNA) was present in serum as determined by either reverse transcription-polymerase chain reaction (RT-PCR) or quantitative assay (Amplicor HCV Monitor; Roche Diagnostic Systems, Branchburg, NJ, USA).

Laboratory examination and data collection. Clinical characteristics and laboratory data that were collected within 2 weeks before liver biopsy were retrieved from the liver biopsy databases of the respective hospitals. To identify the laboratory variables capable of predicting the respective fibrosis stages, we chose eleven clinical, biochemical, and hematological variables for the analysis: age, gender, white blood cell (WBC) count, platelet (Plt) count, serum level of albumin (Alb), total bilirubin (T.Bil), aspartate aminotransferase (AST), ALT, lactate dehydrogenase (LDH), total cholesterol (T.Chol), and prothrombin time (measured as a percentage of the daily internal control, PT).

Liver biopsy and histological examination. Once informed consent was obtained from each patient, peritoneoscopic liver biopsies were performed according to a standardized protocol. Biopsy specimens were fixed in formalin, paraffin-embedded, and stained with hematoxylin-eosin, azan stain, and reticulin silver impregnation.

Specimens were reviewed by 2 experienced hepatopathologists who were blinded to the clinical characteristics and laboratory results of the study subjects. The histology of liver biopsy specimens was evaluated for activity grade and fibrosis stage according to the criteria of Desmet *et al.* [3].

Statistical analysis. Unless otherwise stated, the descriptive statistics consisted of median values with the 1st and 3rd quartiles. Spearman's rank correlation coefficient was used to evaluate the significance of the correlation between histological fibrosis stage and the continuous variables. Categorical variables were compared using the chi-square test.

To select the predictive factors contributing to discrimination of the fibrosis stage, we performed univariate and multivariate logistic regression analyses on the variables in F0–1 and F2, F2 and F3, and F3 and F4 patients, respectively. Furthermore, a multiple regression analysis was used for studying the correlation between histological fibrosis stage and the selected variables, as well as for establishing a multiple regression model in which the fibrosis stage was regarded as a continuous variable. From the multiple regression model, a simple index for predicting the fibrosis stage was derived. We then estimated the area under the receiver operating characteristics (ROC) curve to evaluate the diagnostic ability of the established index.

A p value less than 0.05 was considered statistically significant. Statistical analyses were performed using JMP computer software, version 5.01J (SAS Institute Inc., Cary, NC, USA) and Stat View version 5.0 (SAS Institute Inc.).

Results

Patients' clinical characteristics and laboratory data. Of the 368 patients in the training cohort, 184 (50.0%), 85 (23.1%), 68 (18.5%), and 31 (8.4%) were diagnosed with histological fibrosis stage F0–1, F2, F3, and F4, respectively (Table 1). Of the 11 demographical, hematological, and biochemical variables studied, 9 variables, age, WBC, Plt, Alb, T.Bil, AST, ALT, T.Chol, and PT, correlated with the fibrosis stage ($p<0.05$ by Spearman's rank correlation coefficient).

Selection of variables and construction of a model for predicting fibrosis stage. To select which variables could accurately discern the fibrosis stage of each patient, a logistic regression analysis was performed using the 11 variables in F0–1 and F2, F2 and F3, and F3 and F4 patients, respectively (Table 2). Under this analysis, we found that age, WBC, Plt, Alb, AST, ALT, T.Chol, and PT could discriminate fibrosis stage in F0–1 and F2 patients; Plt, Alb, and PT were significant variables capable of discriminating fibrosis stage in F2 and F3 patients; and WBC, Plt, and Alb were the variables capable of discriminating the proper stage in F3 and F4 patients. From these results, Alb and Plt were identified as the predictive variables common to the discrimination of all categories of

Table 1 Clinical characteristics of chronic hepatitis C patients in the respective fibrosis stages in the training cohort

		Fibrosis stage							
Variables		F0–1		F2		F3		F4	
No. of patients		184		85		68		31	
Age*	(years)	49	(37–58)	55	(49–62)	56	(50–62)	59	(49–63)
Gender	(Male/Female)	110 / 74		51 / 34		43 / 25		19 / 12	
WBC*	($x10^3$ /μl)	5.5	(4.7–6.7)	4.7	(4.2–5.6)	5.5	(4.4–6.7)	4.8	(3.9–5.6)
Plt*	($x10^3$ /μl)	185	(160–220)	151	(132–184)	121	(101–145)	91	(79–100)
Alb*	(g/dl)	4.3	(4.1–4.4)	4.1	(4.0–4.3)	4.0	(3.8–4.2)	3.6	(3.3–3.9)
T.Bil*	(mg/dl)	0.67	(0.53–0.90)	0.75	(0.56–0.93)	0.83	(0.65–1.06)	0.98	(0.64–1.32)
AST*	(IU/l)	36	(28–52)	59	(45–83)	65	(44–84)	68	(52–119)
ALT*	(IU/l)	53	(34–88)	75	(48–117)	82	(51–127)	85	(56–128)
LDH	(IU/l)	336	(293–390)	340	(394–395)	323	(277–387)	361	(283–437)
T.Chol*	(mg/dl)	181	(160–212)	168	(152–191)	167	(154–200)	160	(136–182)
PT*	(%)	100	(88–111)	95	(85–103)	87	(71–96)	77	(69–87)

Data are expressed as the median (the 1st and 3rd quartiles).
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotrabsferase; LDH, lactate dehydrogenase; Plt, platelet; PT, prothrombin time; T.Bil, total bilirubin; T.Cho, total cholesterol; WBC, white blood cell.
*, Nine variables correlate with fibrosis stage ($p<0.05$ by Spearman's rank correlation coefficient).

Table 2 Univariate analysis of variables associated with discriminating between F0–1 and F2 (F0–1/F2), F2 and F3 (F2/F3), and F3 and F4 (F3/F4) patients

		F0–1 / F2			F2 / F3			F3 / F4		
Variables		OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value
Age	(years)	1.06	(1.03–1.09)	< 0.0001	1.01	(0.97–1.04)	0.798	1.03	(0.98–1.08)	0.292
Gender	(Male)	1.01	(0.60–1.71)	0.973	1.15	(0.60–2.21)	0.683	0.92	(0.38–2.21)	0.853
WBC	($x10^3$/μl)	0.68	(0.55–0.84)	0.0003	1.24	(0.98–1.55)	0.071	0.70	(0.49–0.99)	0.042
Plt	($x10^3$/μl)	0.98	(0.98–0.99)	< 0.0001	0.98	(0.97–0.99)	< 0.0001	0.95	(0.93–0.98)	< 0.0001
Alb	(g/dl)	0.10	(0.04–0.30)	< 0.0001	0.22	(0.07–0.76)	0.016	0.02	(0.00–0.11)	< 0.0001
T.Bil	(mg/dl)	1.05	(0.52–2.11)	0.889	3.06	(0.89–10.6)	0.077	1.17	(0.67–2.05)	0.589
AST	(IU/l)	1.02	(1.01–1.03)	< 0.0001	1.00	(1.00–1.01)	0.439	1.01	(1.00–1.02)	0.217
ALT	(IU/l)	1.01	(1.00–1.01)	0.014	1.00	(1.00–1.01)	0.818	1.00	(0.99–1.01)	0.817
LDH	(IU/l)	1.00	(1.00–1.00)	0.687	1.00	(0.99–1.01)	0.489	1.00	(1.00–1.01)	0.145
T.Chol	(mg/dl)	0.99	(0.98–1.00)	0.003	1.01	(0.99–1.02)	0.310	0.99	(0.97–1.00)	0.059
PT	(%)	0.98	(0.97–0.99)	0.005	0.98	(0.96–0.99)	0.016	0.98	(0.95–1.00)	0.080

OR, odds ratio; CI, confidence interval.
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, lactate dehydrogenase; Plt, platelet; Pt, prothrombin time; T.Bil, total bilirubin; T.Chol, total cholesterol; WBC, white blood cell.

Table 3 Multivariate analysis of platelet count (Plt) and serum albumin level (Alb) for discriminating between F0–1 and F2 (F0–1/F2), F2 and F3 (F2/F3), and F3 and F4 (F3/F4) patients

		F0–1 / F2			F2 / F3			F3 / F4		
Variables		OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value
Plt	($x10^3/\mu l$)	0.98	(0.98–0.99)	< 0.0001	0.98	(0.97–0.99)	< 0.0001	0.95	(0.92–0.98)	0.0005
Alb	(g/dl)	0.14	(0.05–0.45)	0.0008	0.22	(0.06–0.82)	0.024	0.01	(0.00–0.10)	< 0.0001

OR, odds ratio; CI, confidence interval.
Alb, albumin; Plt, platelet.

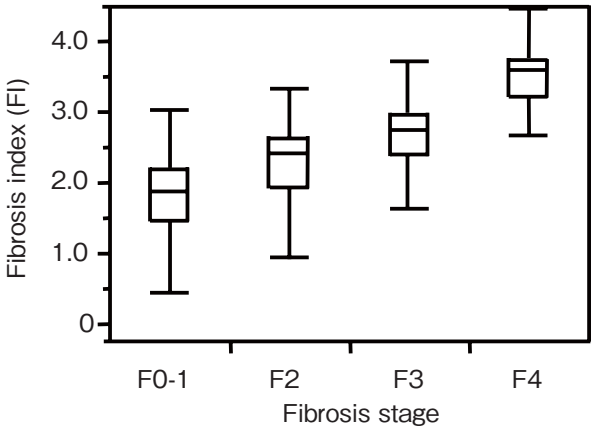

Fig. 1 Box plot of the fibrosis index (FI) for each fibrosis stage in the training cohort. The top and bottom of boxes represent the 25th and 75th percentiles, respectively. The entire box in each case thus represents the interquartiles range (IQR). The upper error bar is the largest observation in the <75th percentile plus 1.5 IQR, and the lower error bar is the smallest observation in the >25th percentile minus 1.5 IQR.

patients, and multivariate logistic regression analysis revealed them to be independent variables as well (Table 3).

Step-wise multiple regression analysis, which was used to formulate a suitable multivariable model for the correlation between laboratory variables and the fibrosis stage, revealed that Plt and Alb also independently correlated with histological fibrosis stage (F), R^2=0.498. The contribution of Plt and Alb to R^2 was 0.384 and 0.114, respectively. The final multiple regression model incorporating both Plt and Alb was:

$F=8.28 - 0.01 \times Plt\ (10^3/\mu l) - 1.08 \times Alb\ (g/dl)$.

Development of fibrosis index (FI) and its diagnostic accuracy. Based on the multiple regression model described above, we derived a novel index defined by Plt and Alb, called the fibrosis index (FI), to reflect the fibrosis stage:

$FI = 8.0 - 0.01 \times Plt\ (10^3/\mu l) - Alb\ (g/dl)$.

The FI distribution for patients in the respective fibrosis stage is depicted in Fig. 1. The median values for FI in F0–1, F2, F3, and F4 patients were

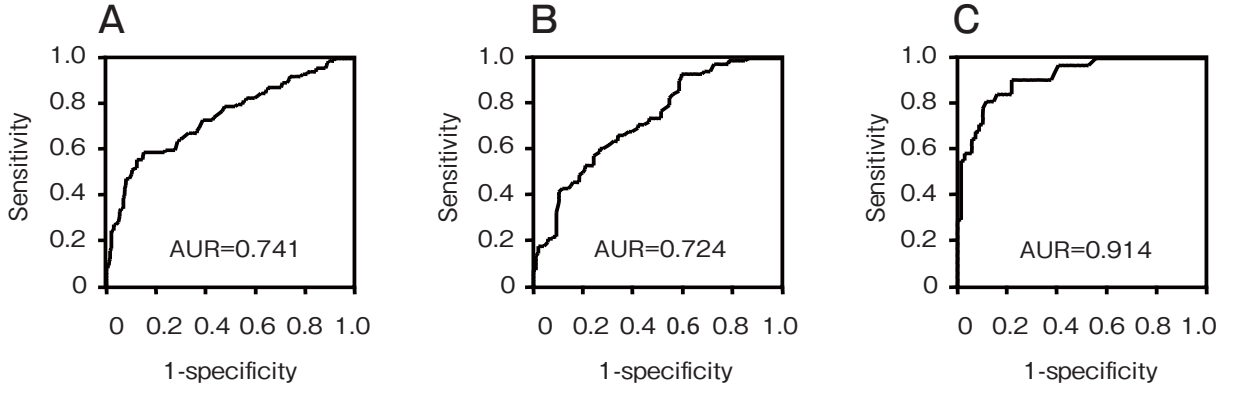

Fig. 2 Receiver operating characteristic curves generated by the fibrosis index (FI) used for discriminating between patients in fibrosis stage (**A**) F0–1 and F2, (**B**) F2 and F3, and (**C**) F3 and F4 in the training cohort.

1.88 (the 1st and 3rd quartiles, 1.44–2.23), 2.44 (1.92–2.67), 2.74 (2.40–3.01), and 3.60 (3.23–3.77), respectively. FI significantly correlated with the histological fibrosis stage (Spearman's rank correlation coefficient, ρ=0.691, p<0.0001).

The diagnostic values of FI in the discrimination between F0–1 and F2, F2 and F3, and F3 and F4 patients were evaluated using the area under the ROC curve (AUR) (Fig. 2). The AUC for FI was 0.741, 0.724, and 0.914 in F0–1 and F2, F2 and F3, and F3 and F4 patients, respectively. The cutoff values obtained from the respective ROC curves were 2.10, 2.60, and 3.30 in discriminating between F0–1 and F2, between F2 and F3, and between F3 and F4 patients, respectively.

For the same subjects in the initial cohort, the AUC of FI for the discrimination between mild fibrosis (F0–1) and significant fibrosis or cirrhosis (F2, F3, F4), and between non-cirrhosis (F0–1, F2, F3) and cirrhosis (F4) were 0.850 and 0.976, respectively (Fig. 3). Table 4 illustrates the diagnostic accuracy of FI at discriminating between mild fibrosis (F0–1) and significant fibrosis (F2, F3, or F4), and between non-cirrhosis (F0–1, F2, F3) and cirrhosis (F4). Using a cutoff value of <2.10, FI had a sensitivity of 66.8%, a positive predictive value (PPV) of 78.8% with a specificity of 82.1%, and a negative predictive value (NPV) of 71.2% for the prediction of F0–1. On the other hand, at a cutoff value of 3.30 and more, FI had a sensitivity of 67.7%, a PPV of 75.0% with a specificity of 97.9%, and a NPV of 97.1% for the prediction of cirrhosis (F4).

Testing the validity of FI. FI was applied to the validation cohort comprised of 249 patients (F0–1, 92; F2, 84; F3, 49; F4, 24) to test its accuracy and reproducibility. The median of FI was 1.92 (the 1st and 3rd quartiles, 1.59–2.26), 2.33 (1.87–2.79), 2.78 (2.40–3.12), and 3.61 (3.21–3.82) in the F0–1, F2, F3, and F4 patients of the validation cohort, respectively (Fig. 4). FI correlated with histological fibrosis stage in the validation cohort (Spearman's rank correlation coefficient, ρ=0.661, p<0.0001). Table 5 illustrates the diagnostic accuracy of FI in the validation cohort for discriminating mild fibrosis (F0–1) from significant fibrosis (F2, F3, or F4), and cirrhosis (F4) from non-cirrhosis (F0–1, F2, or F3). At FI <2.10, FI had a sensitivity of 68.5% and PPV of 63.6% with a specificity of 77.1%, and a NPV of 80.7% for predicting F0–1. At FI ≥ 3.30, FI had a sensitivity of 70.8% and PPV of 81.0%, with a high specificity of 98.2%, and a NPV of 96.9% for predicting F4.

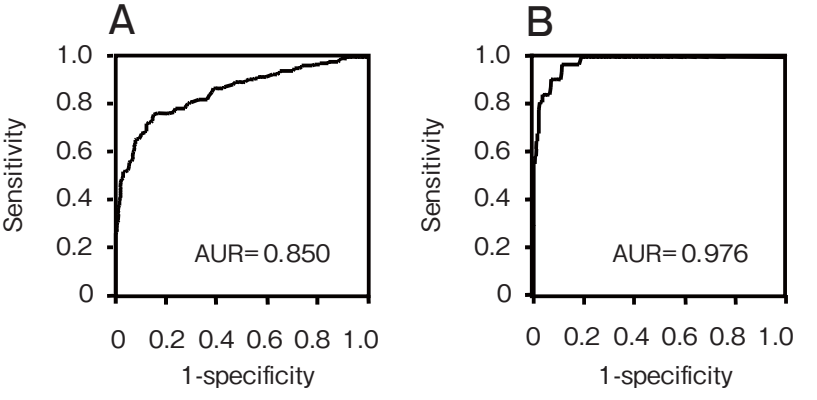

Fig. 3 Receiver operating characteristic curves generated by the fibrosis index (FI) for discriminating between (**A**) patients in the mild fibrosis stage of F0–1 and patients in the significant fibrosis stages of F2, F3, or F4, and (**B**) non-cirrhotic F0-1, F2, or F3 patients and cirrhotic F4 patients.

Table 4 Diagnostic accuracy of the fibrosis index (FI) for the prediction of mild fibrosis (F0–1) or liver cirrhosis (F4) in the training cohort

FI Cutoff value	Interpretation	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR	Accuracy (%)
< 2.1	F0–1	66.8	82.1	78.8	71.2	3.73	74.5
≥ 2.1	F2, F3, F4	82.1	66.8	71.2	78.8	2.48	74.5
< 3.3	F0–1, F2, F3	97.9	67.7	97.1	75.0	2.36	95.4
≥ 3.3	F4	67.7	97.9	75.0	97.1	32.61	95.4

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

Discussion

The progression of chronic liver disease from mild chronic hepatitis to cirrhosis is expressed according to histological fibrosis stage [1–5]. In this study, we present a simple, novel index called the fibrosis index (FI) that uses platelet count and serum albumin level to reflect the disease progression associated with the development of fibrosis stage in CHC patients.

Several studies have described methods for predicting the presence or absence of significant fibrosis and/or cirrhosis using noninvasive markers [6–13]. In a recent study, Imberti-Bismut and the MULTIVIRC group reported that a combination of 5 biochemical markers (Fibrotest) can be useful in discriminating between early and more advanced liver fibrosis [10]. However, the Fibrotest is somewhat difficult to use in clinical practice, since this assay utilizes less common biochemical markers such as α_2-macroglobulin, haptoglobin, and apolipoprotein A_1, and also requires use of a special computer program to perform the calculations.

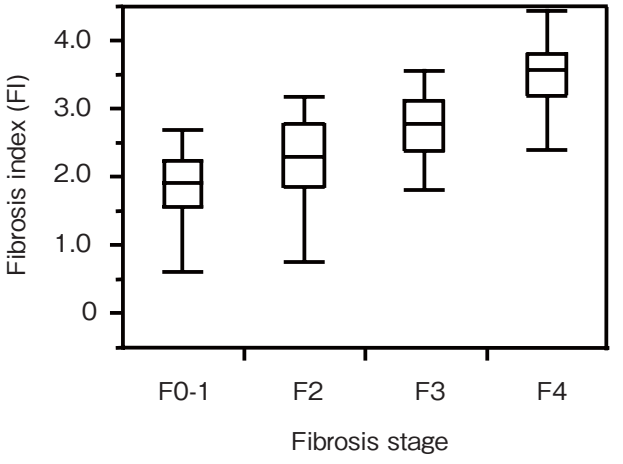

Fig. 4 Box plot of the fibrosis index (FI) for each fibrosis stage in the validation cohort. The top and bottom of boxes represent the 25th and 75th percentiles, respectively. The entire box thus represents the interquartiles range (IQR). The upper error bar is the largest observation in the <75th percentile plus 1.5 IQR. The lower error bar is the smallest observation in the >25th percentile minus 1.5 IQR.

Laboratory variables used for discriminant functions or scores must be more readily measurable, steady, and cheap to obtain, as well as contribute significantly toward the discrimination of patients with significant fibrosis and/or liver cirrhosis. In this study, platelet count and albumin level were identified as independent predictive variables contributing to the discrimination of patients in the respective fibrosis stages. These 2 independent variables also correlated with histological fibrosis stage in the multiple regression analysis. It is well documented that Plt count decreases along with liver disease progression and adversely correlates with the fibrosis stage [14–16], and a value for Plt count as a marker of liver fibrosis has already been assigned [7–9, 11–13]. Serum albumin level also decreases in cases of liver cirrhosis and has been adopted into the Child-Turcotte classification [17] and Child-Pugh classification [18], both of which express the grade of liver cirrhosis. Thus, both Plt count and Alb level are easily measurable in daily practice for many CH-C patients, and both meet the requirements described above.

Other variables such as age, PT, or T.Chol may play a role in the discrimination function and have been found useful in patients with significant fibrosis or cirrhosis [7, 11, 12]. However, compared to Plt and Alb, these other variables correlate with the histological fibrosis stage at a much smaller coefficient of determination (R^2) in the multiple

Table 5 Diagnostic accuracy of the fibrosis index (FI) for the prediction of mild fibrosis (F0–1) or liver cirrhosis (F4) in the validation cohort

FI Cutoff value	Interpretation	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR	Accuracy (%)
< 2.1	F0–1	68.5	77.1	63.6	80.7	2.99	73.9
≥ 2.1	F2, F3, F4	77.1	68.5	80.7	63.6	2.44	73.9
< 3.3	F0–1, F2, F3	98.2	70.8	96.9	81.0	3.37	95.6
≥ 3.3	F4	70.8	98.2	81.0	96.9	39.8	95.6

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

regression analysis in our cases. On the other hand, since Wai suggested that 2 variables can be practically used in a prediction index [13], we decided to construct a simple function using Plt and Alb because of their convenience of application in general practice.

Most of the noninvasive diagnosis methods reported previously have focused on predicting either the presence or absence of significant fibrosis and/or cirrhosis. For example, the index of Forns [12], which aims at predicting the absence of significant fibrosis, can detect patients without significant fibrosis (F0–F1) at a sensitivity of 51% and PPV of 96% (specificity of 94%, NPV 41%) at the lower cutoff value; in patients with significant fibrosis and/or liver cirrhosis (F2–F4) there is a low sensitivity of 30% and PPV of 66% at the higher cutoff value. The Fibrotest of the MULTIVIR group predicts significant fibrosis (F2–F4) at a sensitivity of 50% and PPV of 79% (specificity 91%, NPV of 73%) at the cutoff value of 0.60 [19]. The index of Wai predicts significant fibrosis and/or cirrhosis (Ishak score 3–6) with a sensitivity of 41% and PPV of 88 % (specificity 95%, NPV 64%) at the cutoff value of 1.5, and cirrhosis (Ishak score 5–6) with a sensitivity of 57% and PPV of 57% (specificity 93%, NPV 93%) at the cutoff value of 2.0 [13]. While these noninvasive tests are available for predicting either the presence or absence of significant fibrosis and/or cirrhosis, as pointed out elsewhere [20], they cannot truly distinguish between the respective histological fibrosis stages. On the other hand, the purpose of our study was to adequately reflect each respective fibrosis stage from mild fibrosis (F0–1) to cirrhosis (F4). FI was derived from the multiple regression model, in which the correlation between histological fibrosis stage and the selected variables of Plt and Alb were studied. FI correlated with the histological fibrosis stage, and the values of FI approximately corresponded to the fibrosis stage. FI could discriminate between mild fibrosis (F0–1) and significant fibrosis (F2, F3, and F4) with an AUR of 0.850, a value comparable to that of Forns' index [12], the index of Wai [13], or Fibrotest [19]. FI could also distinguish cirrhosis from non-cirrhosis with an AUR of 0.976, which means that FI could reflect the respective fibrosis stages from mild fibrosis (F1) to cirrhosis (F4) with acceptable accuracy.

In previous reports, the lack of fibrosis or fibrosis limited to the portal tract is associated with favorable outcome and sustained virological response to interferon therapy [21, 22]. Advanced liver fibrosis has been revealed to be more likely to develop hepatocellular carcinoma [23, 24]. These findings show that the evaluation of histological fibrosis stage is especially important in the management of patients with CHC. However, the histological examination is rarely performed repeatedly. Therefore, in general practice, physicians may be able to use FI instead of histological examination to decide whether to initiate or continue interferon therapy and to assess the progression of liver disease and the risk of hepatocarcinogenesis in patients with CHC. On the other hand, since FI was generated from the data of HCV-related chronic liver disease, we do not yet know whether FI is suitable for the evaluation of the fibrosis stage in HBV-related chronic liver disease. To examine this issue, other studies must be performed.

Since chronic hepatitis in the advanced stage sometimes shows transitional histological findings from mild to moderate chronic hepatitis, moderate to severe chronic hepatitis, and severe chronic hepatitis to liver cirrhosis, even a pathological examination cannot always clearly discriminate between the various fibrosis stages [25]. Discrimination analysis, therefore, has a fundamental limitation in establishing complete differentiation of the continuous disease entities. With these limitations under consideration, FI shows acceptable accuracy in the evaluation of CHC disease progression in connection with the development of histological fibrosis stage.

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