

A new index for non-invasive assessment of liver fibrosis

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Abstract

AIM: To construct and evaluate a new non-invasive fibrosis index for assessment of the stage of liver fibrosis.

METHODS: A new fibrosis index (Fibro-Stiffness index) was developed in 165 of 285 patients with chronic hepatitis C, and was validated in the other 120 patients where liver biopsy was performed. Its usefulness was compared with liver stiffness (LS) measured by FibroScan, the aminotransferase-to-platelet ratio index, the Forns index and the FibroIndex.

RESULTS: The Fibro-Stiffness index consists of LS,

platelet count and prothrombin time. The values of the Fibro-Stiffness index differed significantly between neighboring fibrosis stages except F0-F1. The area under the receiver operating characteristics curves of the Fibro-Stiffness index for prediction of $F \geq 2$ (0.90), $F \geq 3$ (0.90) and $F = 4$ (0.92) in the estimation group and those for $F \geq 3$ (0.93) and $F = 4$ (0.97) in the validation group were the highest among the 5 methods examined. The accuracy of the Fibro-Stiffness index had highest values for $F \geq 2$, $F \geq 3$ and $F = 4$ in both the estimation and validation groups. The diagnostic performance for $F = 4$ was improved by a combination of the Fibro-Stiffness index with serum hyaluronic acid level.

CONCLUSION: The Fibro-Stiffness index was constructed and validated. It showed superior diagnostic performance to other indices for $F \geq 2$, 3 and 4.

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Key words: Non-invasive fibrosis index; Fibro-Stiffness index; Chronic hepatitis C; Liver stiffness; Liver fibrosis

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INTRODUCTION

The stage of liver fibrosis is important in the clinical

management of chronic hepatitis C, since the treatment and prognosis of chronic hepatitis depend on the fibrosis stage^[1]. In chronic viral hepatitis, the presence of significant fibrosis ($F \geq 2$) indicates the need for antiviral therapies, and the outcome of therapy should be assessed by the improvement in fibrosis stage. Furthermore, the risk of hepatocellular carcinoma or bleeding from esophageal varices is high in patients with advanced fibrosis^[2,3]. Liver biopsy is the gold standard for the assessment of fibrosis stage in chronic hepatitis. However, liver biopsy is an invasive and expensive procedure, and its accuracy is sometimes questionable because of sampling errors, inadequate specimens and the subjectivity of diagnosis^[4,5].

Non-invasive assessment of liver fibrosis is a major objective that has been encouraging many approaches, such as routine laboratory tests and serum markers of fibrosis^[6-12]. The aminotransferase-to-platelet ratio index (APRI)^[11], the Forns index^[6], the FibroTest^[7] and the FibroIndex^[12] have been proposed for use as non-invasive fibrosis indices. Transient elastography with the use of a new apparatus, FibroScan (EchoSens, Paris, France) for measurement of liver stiffness (LS) has been developed^[13]. LS measured by FibroScan has been reported to correlate with stage of fibrosis in various liver diseases^[13-24]. It was used for assessing the effect of treatment in chronic hepatitis C^[25].

In the present study, we developed a new fibrosis index, the Fibro-Stiffness index, consisting of LS, platelet count and prothrombin time from 165 patients with chronic hepatitis C (estimation group) to improve the diagnostic efficacy of LS. We also tried a combination of Fibro-Stiffness index and routinely available laboratory tests to improve its diagnostic performance. These results in the estimation group were validated in 120 patients with chronic hepatitis C (validation group).

MATERIALS AND METHODS

Patients

In 285 consecutive patients with chronic hepatitis C virus infection, liver biopsy was performed at Fujita Health University Hospital from July 2004 to February 2009 (Table 1).

From July 2004 to September 2007, 165 of these patients (estimation group) were used to develop the Fibro-Stiffness index. From October 2007 to February 2009, the other 120 patients (validation group) were used to validate the diagnostic performance of the Fibro-Stiffness index. The usefulness of the Fibro-Stiffness index was compared with LS, the APRI, the Forns index and the FibroIndex.

Clinical data were collected within 3 d of liver biopsy. Sections were stained with hematoxylin-eosin stain and Azan stain. Liver biopsy specimens were assessed by 2 hepatologists (Yoshioka K and Kawabe N). When fibrosis stages evaluated by 2 hepatologists differed, the higher fibrosis stage was adopted. Fibrosis stage, determined according to the METAVIR score, was classified as F0, no fibrosis; F1, portal fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis.

Liver stiffness measurement

LS measurement by transient elastography was performed with FibroScan (EchoSens, Paris, France) within a week of liver biopsy. FibroScan is equipped with a probe including an ultrasonic transducer and a vibrator. A vibration of mild amplitude and low frequency is transmitted from the vibrator placed on the body surface toward the liver through the intercostal space. The vibration induces an elastic shear wave that propagates through the liver tissue. The pulse-echo ultrasound acquisitions follow the propagation of the shear wave and determine its velocity. The velocity is directly related to tissue stiffness; the harder the tissue, the faster the shear wave propagates. LS is calculated from velocity and expressed in kilopascals (kPa). Ten successful acquisitions were performed on each measurement, and the median value was adopted as representative of LS.

Statistical analysis

The end point was the discrimination between F0 and F1-4, between F0-1 and F2-4, between F0-2 and F3-4 and between F0-3 and F4, using a combination of LS and relevant biochemical or hematological variables. Variables that correlated significantly with fibrosis stage in the estimation group were identified by univariate analyses (analysis of variance). Then the independent predictors of fibrosis stage were assessed by multiple regression analysis (ordinal logistic regression). A predictive index was constructed by modeling the values of the independent variables and their coefficient of regression. The difference of fibrosis indices between neighboring fibrosis stages were estimated by the Tukey-Kramer test. The optimal discriminate cut-off values of each fibrosis index were assessed from the area under the receiver operating characteristics (ROC) curves (AUCs). The optimal discriminating cut-off values were determined at the maximum total of sensitivity and specificity. The statistical analysis was performed by JMP® (SAS Institute, Cary, NC, USA).

RESULTS

Development of the Fibro-Stiffness Index

LS, platelet count, prothrombin time, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, γ globulin, total cholesterol and hyaluronic acid were significantly correlated with fibrosis stage in the estimation group (Table 2). Among these variables, LS ($P < 0.0001$), platelet count ($P = 0.0408$), and prothrombin time ($P = 0.0066$) were identified as independent predictors of fibrosis stage by multiple regression analysis (Table 3). By multiple regression analysis, the estimated values of LS, platelet count and prothrombin time were calculated as -0.2662, 0.0749 and 0.0560, respectively. The optimum intercept was also calculated as 5.7710. Thus the Fibro-Stiffness index was constructed with these 3 variables: Fibro-Stiffness index = $5.7710 - 0.2662 [\text{LS (kPa)}] + 0.0749 [\text{platelet count } (\times 10^4/\text{mL})] + 0.0560 [\text{prothrombin time (\%)}]$.

Table 1 Characteristics of the 165 patients in the estimation group and the 120 patients in the validation group (mean \pm SD)

	All patients (<i>n</i> = 285)	Estimation group (<i>n</i> = 165)	Validation group (<i>n</i> = 120)	<i>P</i> -value
Male gender, <i>n</i> (%)	149 (52.3)	92 (55.8)	57 (47.5)	NS
Age (yr)	52.4 \pm 13.3	53.2 \pm 12.6	51.5 \pm 14.2	NS
Liver stiffness (kPa)	9.99 \pm 6.99	10.29 \pm 7.33	9.58 \pm 6.51	NS
Platelet count ($\times 10^4$ /mL)	16.54 \pm 5.28	16.53 \pm 5.41	16.57 \pm 5.13	NS
Prothrombin time (%)	9.35 \pm 11.3	92.4 \pm 10.2	95.1 \pm 12.6	NS
AST (IU/L)	52.5 \pm 34.0	53.0 \pm 34.6	51.8 \pm 33.4	NS
ALT (IU/L)	70.8 \pm 52.6	72.4 \pm 54.9	68.7 \pm 49.4	NS
Total protein (g/dL)	7.81 \pm 0.52	7.79 \pm 0.49	7.85 \pm 0.57	NS
Albumin (g/dL)	4.31 \pm 0.34 (<i>n</i> = 283)	4.31 \pm 0.31 (<i>n</i> = 163)	4.31 \pm 0.38	NS
γ -GTP (IU/L)	59.8 \pm 62.0	58.1 \pm 57.9	62.1 \pm 67.5	NS
γ -globulin (g/dL)	1.57 \pm 0.41 (<i>n</i> = 276)	1.54 \pm 0.38 (<i>n</i> = 146)	16.1 \pm 0.44	NS
Total cholesterol (mg/dL)	178.1 \pm 31.9	177.2 \pm 31.1	179.5 \pm 33.0	NS
Hyaluronic acid (ng/mL)	104.1 \pm 128.3 (<i>n</i> = 281)	114.5 \pm 140.0 (<i>n</i> = 161)	90.0 \pm 109.3	NS
Fibrosis stage, <i>n</i> (%)				
F0	28 (9.8)	14 (8.5)	14 (11.7)	
F1	85 (29.8)	52 (31.5)	33 (27.5)	
F2	82 (28.8)	42 (25.5)	40 (33.3)	
F3	53 (18.6)	33 (20.0)	20 (16.7)	
F4	37 (13.0)	24 (14.5)	13 (10.8)	

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ -GTP: γ -glutamyl transpeptidase; NS: Not significant.**Table 2** Variables associated with fibrosis stage in the estimation group (165 patients) in univariate analysis (mean \pm SD)

	F0 (<i>n</i> = 14)	F1 (<i>n</i> = 52)	F2 (<i>n</i> = 42)	F3 (<i>n</i> = 33)	F4 (<i>n</i> = 24)	<i>P</i> -value
Liver stiffness (kPa)	5.58 \pm 1.96	5.76 \pm 1.91	9.02 \pm 4.11	13.40 \pm 4.95	20.77 \pm 10.81	< 0.0001
Platelet count ($\times 10^4$ /mL)	20.80 \pm 4.77	18.79 \pm 5.19	15.66 \pm 4.54	15.72 \pm 5.58	11.75 \pm 2.63	< 0.0001
Prothrombin time (%)	101.8 \pm 10.3	96.1 \pm 7.9	92.5 \pm 7.9	88.7 \pm 10.5	83.6 \pm 9.6	< 0.0001
AST (IU/L)	30.3 \pm 17.3	40.1 \pm 23.7	46.9 \pm 31.8	73.2 \pm 40.3	77.0 \pm 33.3	< 0.0001
ALT (IU/L)	44.4 \pm 34.2	58.1 \pm 47.1	62.5 \pm 42.9	103.0 \pm 72.9	94.6 \pm 47.9	< 0.0001
Total protein (g/dL)	7.61 \pm 0.30	7.78 \pm 0.58	7.74 \pm 0.44	7.83 \pm 0.44	7.91 \pm 0.48	0.4459
Albumin (g/dL)	4.52 \pm 0.26 (<i>n</i> = 13)	4.44 \pm 0.23 (<i>n</i> = 51)	4.32 \pm 0.32	4.15 \pm 0.24	4.12 \pm 0.38	< 0.0001
γ -GTP (IU/L)	40.07 \pm 26.10	57.52 \pm 84.73	49.29 \pm 32.91	75.79 \pm 47.91	61.25 \pm 40.46	0.2409
γ -globulin (g/dL)	1.22 \pm 0.25 (<i>n</i> = 12)	1.44 \pm 0.32 (<i>n</i> = 45)	1.52 \pm 0.33 (<i>n</i> = 36)	1.62 \pm 0.35 (<i>n</i> = 30)	1.83 \pm 0.43 (<i>n</i> = 23)	< 0.0001
Total cholesterol (mg/dL)	179.5 \pm 29.4	186.7 \pm 31.5	173.8 \pm 32.0	176.4 \pm 26.8	162.3 \pm 30.4	0.0251
Hyaluronic acid (ng/mL)	59.6 \pm 83.1	49.64 \pm 41.1 (<i>n</i> = 50)	110.3 \pm 113.3	136.0 \pm 138.4	266.6 \pm 217.9 (<i>n</i> = 23)	< 0.0001

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ -GTP: γ -glutamyl transpeptidase.**Table 3** Multiple regression predicting liver fibrosis stage with liver stiffness and laboratory data in the estimation group

	Estimated value	Standard error	χ^2	<i>P</i> -value
Liver stiffness (<i>n</i> = 165)	-0.2661602	0.0481713	30.53	< 0.0001
Platelet count (<i>n</i> = 165)	0.0748652	0.0366051	4.18	0.0408
Prothrombin time (<i>n</i> = 165)	0.0560460	0.0206514	7.37	0.0066
AST (<i>n</i> = 165)	-0.0093853	0.0100069	0.88	0.3483
ALT (<i>n</i> = 165)	0.0007594	0.0058897	0.02	0.8974
Albumin (<i>n</i> = 163)	-1.1130330	0.7353340	2.29	0.1301
γ -globulin (<i>n</i> = 146)	-0.6349751	0.5201549	1.49	0.2222
Total cholesterol (<i>n</i> = 165)	0.0011393	0.0057519	0.04	0.8430
Hyaluronic acid (<i>n</i> = 161)	-0.0019629	0.0017064	1.32	0.2500

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Comparison of Fibro-Stiffness index with LS, the APRI, the Forns index and the FibroIndex in the estimation group

Fibro-Stiffness index was compared with LS, the APRI, the Forns index and the FibroIndex in the estimation group (Figure 1). The values of Fibro-Stiffness index and LS significantly differed between neighboring fibrosis

stages except F0-F1 (Figure 1A and B). The APRI did not significantly differ between any neighboring stages (Figure 1C). The Forns index significantly differed only between F1 and F2 (Figure 1D). The FibroIndex significantly differed between F1 and F2 and between F3 and F4 (Figure 1E).

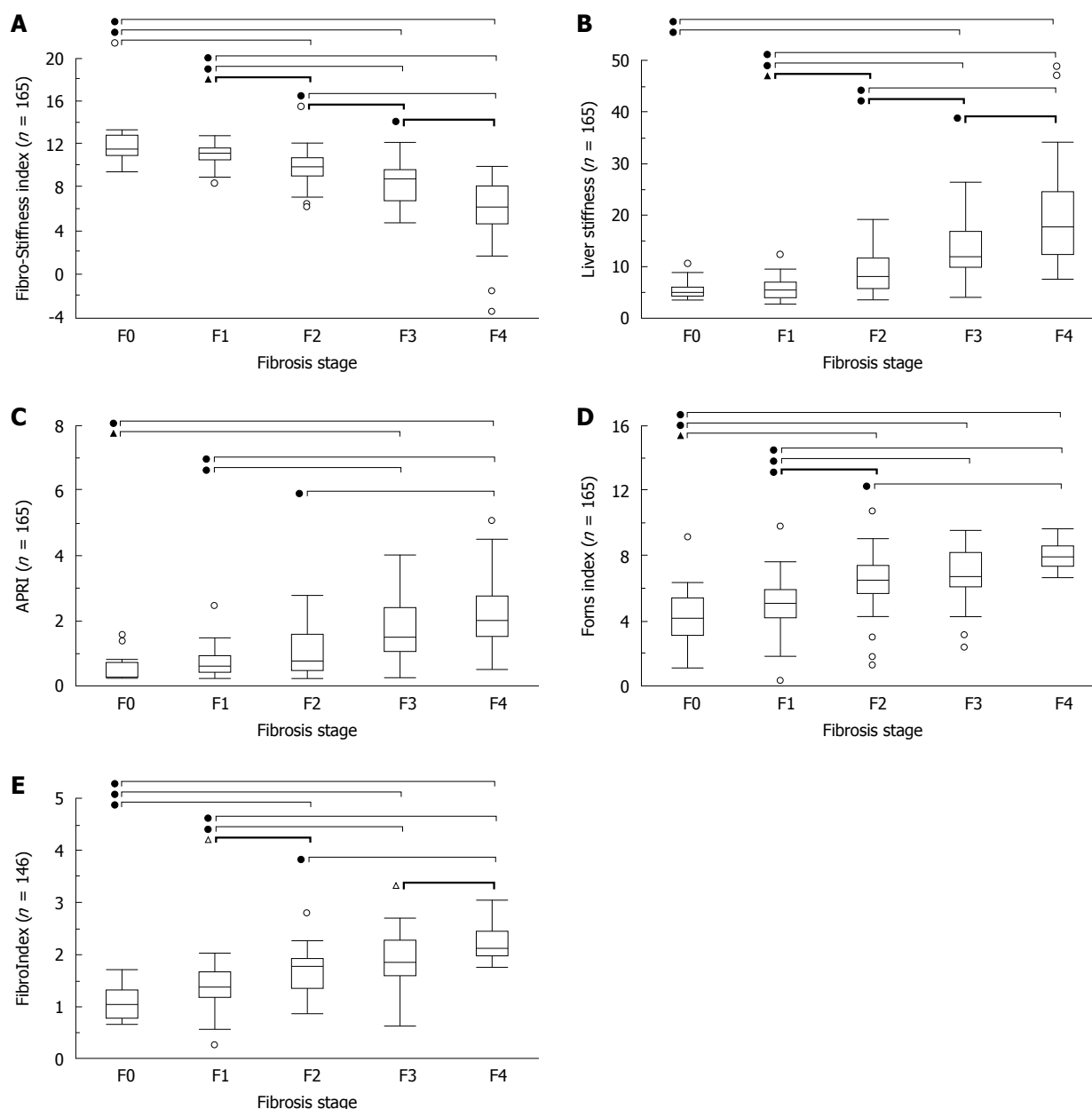


Figure 1 Correlation between 5 noninvasive methods for assessment of fibrosis and stage of fibrosis in the estimation group. A: Fibro-Stiffness index: $\rho = -0.7626$, $P < 0.0001$; B: Liver stiffness measured by FibroScan: $\rho = -0.7340$, $P < 0.0001$; C: Aspartate aminotransferase-to-platelet ratio index (APRI): $\rho = 0.6008$, $P < 0.0001$; D: Forns index: $\rho = 0.6175$, $P < 0.0001$; E: FibroIndex: $\rho = 0.6496$, $P < 0.0001$. The top and bottom of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median, and the error bars indicate the 10th and 90th percentiles. The closed circles, the closed triangles, the open circles and the open triangles indicate P -values of 0.001, 0.005, 0.01 and 0.05, respectively.

ROC analysis for comparison of diagnostic performance of the Fibro-Stiffness index with LS, the APRI, the Forns index and the FibroIndex in the estimation group

The ROC analysis of the Fibro-Stiffness index, LS, the APRI, the Forns index and the FibroIndex was performed to discriminate between fibrosis stages (Table 4). The AUC of the Fibro-Stiffness index was the highest for discriminating $F \geq 2$, $F \geq 3$ and $F = 4$ among the 5 examined methods. The AUC of the FibroIndex was the highest for discriminating $F \geq 1$.

Optimal discriminating cut-off values of the Fibro-Stiffness index, LS, the APRI, the Forns index and the FibroIndex were determined by ROC analysis. The cut-

off values of the Fibro-Stiffness index for $F \geq 1$, $F \geq 2$, $F \geq 3$ and $F = 4$ were 11.09, 10.12, 9.87 and 8.51, respectively (Table 4). The diagnostic performance was assessed by sensitivity, specificity, accuracy, positive and negative predictive values, and likelihood ratio. Regarding accuracy, the values of the Fibro-Stiffness index for $F \geq 2$, $F \geq 3$ and $F = 4$ were the highest among the 5 examined methods. The value of the APRI was the highest for $F \geq 1$.

Improvement of diagnostic performance by combination of the Fibro-Stiffness index with laboratory tests

The negative predictive value for $F \geq 1$ and the positive

Table 4 Assessment of liver fibrosis stages classification by liver fibrosis indices

	AUCs (95% CI)	Optimal cutoff value	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio
F ≥ 1 (F0 vs F1-2-3-4)								
Fibro-Stiffness index	0.82 (0.715-0.928)	11.07	77.5	78.6	77.6	97.5	24.4	3.62
Fibro-Stiffness index and AST	Non	11.07 and 51 (IU/L)	85.4	78.6	84.8	97.7	33.3	3.99
Liver stiffness	0.77 (0.666-0.867)	6.6 (kPa)	64.2	85.7	66.1	97.8	18.2	4.49
APRI	0.81 (0.680-0.934)	0.44	88.1	64.3	86.1	96.4	33.3	2.47
Forns index	0.77 (0.640-0.908)	4.72	82.1	71.4	81.2	96.9	27.0	2.87
FibroIndex	0.85 (0.757-0.932)	1.19	82.1	75.0	81.5	97.3	27.3	3.28
F ≥ 2 (F0-1 vs F2-3-4)								
Fibro-Stiffness index	0.90 (0.847-0.943)	10.12	78.8	89.4	83.0	91.8	73.8	7.43
Liver stiffness	0.88 (0.826-0.929)	7.1 (kPa)	80.8	80.3	80.6	86.0	73.6	4.10
APRI	0.78 (0.714-0.851)	1.06	64.6	84.8	72.7	86.5	61.5	4.27
Forns index	0.82 (0.757-0.890)	6.22	76.8	83.3	79.4	87.4	70.5	4.61
FibroIndex	0.82 (0.754-0.888)	17.00	74.2	80.7	76.7	85.7	66.7	3.84
F ≥ 3 (F0-2 vs F3-4)								
Fibro-Stiffness index	0.90 (0.851-0.953)	9.87	93.0	79.6	84.2	70.7	96.7	4.56
Liver stiffness	0.90 (0.856-0.952)	9.6 (kPa)	87.7	82.4	84.2	72.5	92.7	4.98
APRI	0.84 (0.767-0.904)	1.13	80.7	80.6	80.6	68.7	88.8	4.15
Forns index	0.80 (0.732-0.874)	6.36	82.5	70.4	74.5	59.5	88.4	2.78
FibroIndex	0.85 (0.749-0.901)	1.85	73.6	80.6	81.4	68.4	84.3	3.80
F = 4 (F0-1-2-3 vs F4)								
Fibro-Stiffness index	0.92 (0.871-0.965)	8.51	91.7	83.7	84.8	48.9	98.3	5.62
Fibro-Stiffness index and HA	Non	8.51 and 68 (ng/mL)	91.3	87.9	88.4	55.3	98.4	7.26
Liver stiffness	0.90 (0.844-0.957)	11.6 (kPa)	91.7	78.0	80.0	41.5	98.2	4.17
APRI	0.84 (0.759-0.915)	1.30	91.7	74.5	77.0	37.9	98.1	3.59
Forns index	0.87 (0.816-0.923)	7.07	95.8	75.9	78.8	40.4	99.1	3.97
FibroIndex	0.89 (0.830-0.943)	1.90	91.3	78.0	80.1	43.8	98.0	4.16

AUCs: Area under the receiver operating characteristics; CI: Confidence interval; HA: Hyaluronic acid; AST: Aspartate aminotransferase; APRI: Amino-transferase-to-platelet ratio index.

predictive value for F4 with the Fibro-Stiffness index were rather low. Thus a combination of the Fibro-Stiffness index with AST, ALT, albumin, γ globulin, total cholesterol and hyaluronic acid, which were correlated with fibrosis stages and not included in the Fibro-Stiffness index was examined to improve diagnostic performance in each fibrosis stage. Optimal discriminating cut-off values of these laboratory tests for $F \geq 1$ and $F = 4$ were calculated by ROC analysis (not shown). In $F \geq 1$, the best combination for improvement of diagnostic performance was the Fibro-Stiffness index ≤ 10.09 or AST ≥ 51 IU/L. The negative predictive value for $F \geq 1$ was improved by this combination compared to the Fibro-Stiffness index alone, although it was same as that of the APRI (Table 4). The combination of the Fibro-Stiffness index ≤ 8.51 and serum hyaluronic acid ≥ 68 ng/mL was the best combination for $F = 4$. The negative predictive value for F4 was improved by this combination, and was the highest among the 6 examined methods.

Validation of performance of the Fibro-Stiffness index, its combination with AST for $F \geq 1$, and its combination with hyaluronic acid for F4

The results in the estimation group were validated in the validation group of 120 patients with chronic hepatitis C (Table 5). The AUC of the Fibro-Stiffness index was the highest for $F \geq 3$ and $F = 4$ among the 5 examined methods. The AUC of the FibroIndex was the highest for $F \geq 1$ and that of LS was the highest for $F \geq 2$.

The accuracy of the Fibro-Stiffness index for $F \geq 3$ and $F = 4$ was 86.7% and 85.8%, respectively, similar to the values in estimation group, and the highest value among all the 5 methods. For $F \geq 1$, the accuracy of the FibroIndex was the highest. For $F \geq 2$, the accuracy of LS was the highest.

The combination of the Fibro-Stiffness index and AST for $F \geq 1$ improved the negative predictive value, although it was lower than that of the FibroIndex, and the accuracy was lower than those of the APRI and the FibroIndex. The combination of the Fibro-Stiffness index and hyaluronic acid for $F = 4$ improved the positive predictive value, and its accuracy and positive predictive value were the highest among all the 6 examined methods.

DISCUSSION

In the present study, we constructed a new fibrosis index for non-invasive assessment of liver fibrosis, the Fibro-Stiffness index, using LS, platelet count and prothrombin time. LS measured by FibroScan has been reported to correlate with stage of liver fibrosis in various liver diseases^[13-24]. Previous studies also confirmed that platelet count and prothrombin time also correlated with stage of liver fibrosis^[6,11,26-29]. A decrease in the platelet count is caused by splenomegaly and reduced production of thrombopoietin, accompanied by the advance of liver fibrosis. Prolongation of prothrombin time is caused by reduced production of coagulation factors by the liver

Table 5 Validation of liver fibrosis stages classification by liver fibrosis indices

	AUCs (95% CI)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio
F ≥ 1 (F0 vs F1-2-3-4)							
Fibro-Stiffness index	0.80 (0.712-0.878)	73.6	78.6	74.2	94.0	27.7	3.52
Fibro-Stiffness index and AST	Non	78.3	78.6	78.3	96.5	32.4	3.64
Liver stiffness	0.82 (0.727-0.907)	63.2	85.7	65.8	97.1	23.5	4.42
APRI	0.80 (0.704-0.899)	87.7	35.7	81.7	91.2	27.8	1.36
Forns index	0.77 (0.659-0.880)	72.4	71.4	72.3	95.0	25.6	2.53
FibroIndex	0.83 (0.723-0.937)	89.6	50.5	85.8	93.1	38.9	1.79
F ≥ 2 (F0-1 vs F2-3-4)							
Fibro-Stiffness index	0.82 (0.750-0.898)	65.7	96.6	76.7	90.6	63.8	10.31
Liver stiffness	0.85 (0.787-0.920)	76.7	83.0	79.2	87.5	69.6	4.51
APRI	0.82 (0.741-0.893)	50.7	89.4	65.8	88.1	53.8	4.76
Forns index	0.78 (0.700-0.864)	58.3	80.9	67.2	82.4	55.9	3.05
FibroIndex	0.79 (0.713-0.875)	69.5	83.0	74.2	86.2	62.9	4.02
F ≥ 3 (F0-2 vs F3-4)							
Fibro-Stiffness index	0.93 (0.876-0.986)	93.9	83.9	86.7	68.9	97.3	5.84
Liver stiffness	0.92 (0.871-0.977)	81.8	82.8	82.5	64.3	92.3	4.75
APRI	0.83 (0.753-0.922)	75.8	81.6	80.0	61.0	89.9	4.12
Forns index	0.84 (0.759-0.912)	78.1	71.3	73.1	50.0	90.0	2.72
FibroIndex	0.85 (0.772-0.928)	76.6	80.5	80.0	60.5	90.9	4.03
F = 4 (F0-1-2-3 vs F4)							
Fibro-Stiffness index	0.97 (0.934-0.997)	100	84.1	85.8	43.3	100	6.29
Fibro-Stiffness index and HA	Non	100	86.9	88.3	48.1	100	7.63
Liver stiffness	0.97 (0.942-0.999)	100	83.2	85.0	41.9	100	5.94
APRI	0.92 (0.867-0.972)	100	75.7	78.3	33.3	100	4.12
Forns index	0.88 (0.798-0.968)	83.3	72.9	73.9	25.6	97.5	3.07
FibroIndex	0.92 (0.874-0.971)	100	77.6	80.0	35.0	100	4.46

AUCs: Area under the receiver operating characteristics; CI: Confidence interval; HA: Hyaluronic acid; AST: Aspartate aminotransferase; APRI: Amino-transferase-to-platelet ratio index.

with advanced fibrosis. The Fibro-Stiffness index, which combines these 3 factors, was shown to be a highly accurate index to estimate fibrosis stage in chronic hepatitis C.

So far, several non-invasive fibrosis indices such as the APRI^[11], the Forns index^[6], the FibroIndex^[12], and the FibroTest^[7] have been developed. The Fibro-Stiffness index showed its superior correlation with fibrosis stage compared with the APRI, the Forns index and the Fibro-Index. The Fibro-Stiffness index and LS showed a significant difference between neighboring fibrosis stages except between F0 and F1 in the estimation group. The AUC of the Fibro-Stiffness index was the highest among the 5 examined methods for $F \geq 2$, $F \geq 3$ and $F = 4$ in the estimation group, and for $F \geq 3$ and $F = 4$ in the validation group. The AUCs of the APRI, the Forns index and the FibroIndex for predicting F4 in the present study were similar to the values reported in their respective original manuscripts (APRI, 0.88; Forns index, 0.81; FibroIndex, 0.86)^[6,11]. Therefore, the results of the present study can be considered to be appropriate. The superiority of the Fibro-Stiffness index was further demonstrated by the accuracy values. The accuracy of the Fibro-Stiffness index was highest for $F \geq 2$, $F \geq 3$ and $F = 4$ in both the estimation group and validation group.

Although the Fibro-Stiffness index was shown to be a highly accurate index, the positive predictive value was rather low for F4. A combination of the Fibro-Stiffness index and hyaluronic acid was shown to improve the diagnostic performance. Serum hyaluronic acid has been

reported to be useful for diagnosis of liver fibrosis and cirrhosis^[8,30]. In the estimation group and in the validation group, both the accuracy and positive predictive value of the combination of the Fibro-Stiffness index and hyaluronic acid were higher than those of the Fibro-Stiffness index alone, and were the highest among all the 6 examined methods. The fact that a combination of the Fibro-Stiffness index and hyaluronic acid enables us to diagnose F4 with a sensitivity of 91%-100% and positive predictive value of 48%-57% is important, because the risk of hepatocellular carcinoma or bleeding from esophageal varices is high in patients with F4^[2,3].

For predicting $F \geq 1$, the Fibro-Stiffness index was inferior to the other fibrosis indices in terms of sensitivity, accuracy and negative predictive value. The combination of Fibro-Stiffness index with AST improved sensitivity, accuracy and negative predictive value in both the estimation group and the validation group. However, the combination of Fibro-Stiffness index with AST was still inferior to the APRI in the estimation group, and inferior to the FibroIndex and the APRI in the validation group. Further investigation is necessary to improve the diagnostic efficiency of the Fibro-Stiffness index for $F \geq 1$.

In chronic viral hepatitis, the presence of significant fibrosis ($F \geq 2$) indicates the need for antiviral therapies. The Fibro-Stiffness index showed a highly accurate diagnostic performance for $F \geq 2$ in both the estimation group and validation group. Thus the patients with a Fibro-Stiffness index of ≥ 10.12 which indicate $F \geq 2$

will be candidates for liver biopsy or interferon treatment.

In conclusion, a new fibrosis index for non-invasive assessment of liver fibrosis, the Fibro-Stiffness index, was constructed using LS measured by FibroScan, platelet count and prothrombin time and was validated. The Fibro-Stiffness index demonstrated superior diagnostic performance to LS alone, the APRI, the Forns index and the FibroIndex for $F \geq 2$, $F \geq 3$ and $F = 4$. The diagnostic performance of the Fibro-Stiffness index for F4 was further improved by combination with hyaluronic acid levels.

COMMENTS

Background

The stage of liver fibrosis is important for clinical management of chronic hepatitis C, since the treatment and prognosis of chronic hepatitis depend on the fibrosis stage. Liver biopsy is the gold standard for the assessment of fibrosis stage. However, it is an invasive and expensive procedure, and its accuracy is sometimes questionable.

Research frontiers

A number of non-invasive fibrosis indices, such as the aminotransferase-to-platelet ratio index (APRI), the Forns index and the FibroIndex have been proposed for assessment of liver fibrosis. Transient elastography with the use of a new apparatus, FibroScan, for measurement of liver stiffness (LS) was developed. LS has been reported to correlate with liver fibrosis in various liver diseases. So far no fibrosis indices incorporating LS have been reported. In the present study, we developed a new non-invasive fibrosis index, the Fibro-Stiffness index, which incorporated LS.

Innovations and breakthroughs

The Fibro-Stiffness index consists of LS, platelet count and prothrombin time. In the present study, its usefulness was compared with LS, the APRI, the Forns index and the FibroIndex. The diagnostic performance of the Fibro-Stiffness index was superior to other indices. Furthermore, the diagnostic performance of the Fibro-Stiffness index for F4 was further improved by combination with hyaluronic acid.

Applications

Using the Fibro-Stiffness index, it is possible to assess the stage of liver fibrosis of patients with chronic hepatitis C non-invasively, accurately and quantitatively. Therefore, the Fibro-Stiffness index is useful not only for the diagnosis of stage of liver fibrosis but also for the assessment of regression of liver fibrosis by interferon treatment in patients with chronic hepatitis C.

Terminology

Fibro-Stiffness index: a new non-invasive fibrosis index which we developed in the present study and consists of LS, platelet count and prothrombin time. Its diagnostic performance is superior to other indices.

Peer review

The authors proposed a novel index for non-invasive assessment of hepatic fibrosis. Its reliability was validated on another group of patients. I think the index is clinically useful and significant.

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