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Discordance Among Transient Elastography, Aspartate Aminotransferase to Platelet Ratio Index, and Histologic Assessments of Liver Fibrosis in Patients With Chronic Hepatitis C

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Abstract

BACKGROUND & AIMS—Liver biopsy is the standard for assessing hepatic fibrosis.

Ultrasound transient elastography (TE) and the aspartate aminotransferase to platelet ratio index (APRI) are validated, noninvasive tests for identifying patients with cirrhosis. We evaluated discordance among TE, APRI, and histology diagnoses of cirrhosis.

METHODS—We analyzed findings from 109 patients with chronic hepatitis C who underwent TE within 6 months of liver biopsy at the US National Institutes of Health from 2006 to 2011. Fibrosis was scored using the Ishak scale (0–6). APRI scores were calculated using data collected on the day of the biopsy. Area under receiver operator characteristic curves for TE and APRI were calculated to distinguish patients with cirrhosis (Ishak scores, 5–6) from those without cirrhosis (Ishak scores, 0–4). The best cut-off value and corresponding positive predictive value (PPV) and negative predictive value (NPV) were selected.

RESULTS—Based on biopsy analysis, 18% of the patients had no fibrosis, 52% had mild fibrosis, 17% had bridging fibrosis, and 13% had cirrhosis. A TE cut-off value of 13.1 kPa identified patients with cirrhosis with the highest level of accuracy (100% sensitivity, 89% specificity, 58% PPV, 100% NPV), as did an APRI cut-off value of 1.0 (79% sensitivity, 78% specificity, 34% PPV, 96% NPV). Results from TE and APRI were discordant for 28% of cases. TE identified all cases of cirrhosis and an additional 10 patients who were not found to have cirrhosis based on histology analysis; 7 of these patients had clinical or radiologic evidence of cirrhosis, indicating that the biopsy sample was not staged correctly.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2012.10.044>.

Conflicts of interest

The authors disclose the following: all authors are employees of the US government.

CONCLUSIONS—TE increases the accuracies of biopsy and APRI analyses in identifying patients with cirrhosis. TE also might be used to screen patients for cirrhosis and identify those who should be followed up for development of hepatocellular carcinoma and varices.

Keywords

HCV; Liver Disease; Cancer Risk; AUROC

Assessment of hepatic fibrosis is important for making decisions regarding whether to initiate therapy, for advising patients of their long-term prognosis, and for instituting surveillance for complications of cirrhosis. At present, liver biopsy is considered the gold standard for assessment of the degree of fibrosis in chronic hepatitis C.^{1–3} However, liver biopsy has many limitations. It is an invasive procedure that is expensive and not without complications. It has poor overall patient acceptance,⁴ sampling error may lead to inaccurate staging of liver fibrosis in 10% to 15% of cases,^{5–7} and interpretation is affected by interobserver variability.⁸

In the past few years, there has been growing interest in developing noninvasive alternatives to liver biopsy to stage liver fibrosis.⁹ These alternatives include imaging devices, serum fibrosis markers, and a number of clinical scoring systems using laboratory results to detect advanced fibrosis or cirrhosis. Fibroscan (Echosens, Paris, France) is a noninvasive method that uses ultrasound transient elastography (TE) to indirectly estimate liver fibrosis. A recent meta-analysis consisting of 9 studies showed a sensitivity of 87% and a specificity of 91% in predicting cirrhosis.¹⁰ Most of the data evaluating the performance characteristics of TE have come from European and Asian populations and have shown geographic variation. There are only a few studies from a North American population and these studies were either conducted on subjects with chronic liver disease of multiple etiologies or in human immunodeficiency virus–hepatitis C virus (HCV) co-infected subjects.^{11–14}

The aspartate aminotransferase to platelet ratio index (APRI) uses 2 readily available laboratory indexes to determine the presence or absence of cirrhosis.¹⁵ A meta-analysis showed that an APRI threshold of greater than 1.0 had an estimated sensitivity and specificity of 76% and 72%, respectively, for detection of cirrhosis.¹⁰

Both TE and APRI are useful modalities to assess fibrosis in patients with chronic hepatitis C but the correlation between the gold standard (ie, liver biopsy) and these noninvasive tools is imperfect. In clinical practice, it is important to identify patients with advanced fibrosis to implement screening for complications of cirrhosis and to guide treatment decisions. Importantly, if these tests are to be used as screening tools in patients with chronic hepatitis C, it will be critical to understand the factors associated with accuracy and discordance when compared with liver biopsy in this population. The aim of this study was to evaluate prospectively the optimal cut-off values to predict advanced fibrosis and cirrhosis from mild liver disease and to understand the discordance among TE, APRI, and histologic diagnosis of cirrhosis in North American patients with chronic hepatitis C.

Methods

Patients and Methods

The study was conducted at the Clinical Center of the National Institutes of Health (Bethesda, MD) between 2006 and 2011 in a clinical research protocol approved by the Institutional Review Board. All patients provided written, informed consent. Ultrasound TE using a medium probe was offered to all patients with chronic hepatitis C who were scheduled to undergo liver biopsy or who previously had undergone liver biopsy within a 6-

month period of performing TE. TE measured liver stiffness expressed in kilopascals. TE was performed by junior and senior hepatologists of the Liver Diseases Branch at the National Institutes of Health, all of whom were trained in the technique by the manufacturer of the device. Hepatic fibrosis was scored by a single hepatopathologist using the Ishak staging scale of 0 to 6 (0 = no fibrosis, 6 = cirrhosis).¹⁶ Hepatic necroinflammation was scored using the modified histology activity index scoring system, which has a range of 0 to 18. Demographic, clinical, and laboratory values were recorded from the day of the liver biopsy. A valid TE (liver stiffness) score consisted of the median of 10 individual stiffness measurements obtained from a single site, expressed in kilopascals. APRI was calculated by dividing the aspartate aminotransferase (AST), expressed as a multiple of the upper limit of the normal range, by the platelet count, expressed as platelets per microliter divided by 100,000 using laboratory values from the day of the liver biopsy: $APRI = [(AST/\text{upper limit of the normal range})/(\text{platelet count } (10^9/L))] \times 100$.

Two analyses were performed: the first was performed to distinguish advanced fibrosis (Ishak, 3–6) from mild fibrosis (Ishak, 0–2) and the second was performed to differentiate cirrhosis (Ishak, 5–6) from no cirrhosis (Ishak, 0–4). Area under the receiver operating characteristic curves (AUROCs) were calculated and 3 curves were constructed using the TE score, APRI values, and TE + APRI as individual variables. The best cut-off values to predict advanced fibrosis or cirrhosis and corresponding positive predictive value (PPV) and negative predictive value (NPV) were selected based on AUROCs.

Cases in which TE and APRI were not in agreement with the histologic diagnosis were evaluated further.

Statistical Analysis

Descriptive analyses of data were expressed as mean $\pm$ standard deviation unless otherwise specified. Comparisons of continuous variables were tested using either the Student *t* test for normally distributed variables or the Wilcoxon rank test for skewed variables. A 2-sided *P* value of less than .05 was considered statistically significant. The diagnostic performance of noninvasive biomarkers (ie, TE, APRI, and their combinations) was assessed by using logistic regression and receiver operating characteristic analysis. A subject was identified as positive or negative according to whether the noninvasive biomarker was greater than or less than the cut-off value of interest. The AUROC was used as an index of the accuracy of the biomarker, with an AUROC close to unity indicating high diagnostic accuracy. The optimal cut-off values for TE or APRI were chosen to maximize the sum of the sensitivity and specificity. All the analyses were performed using SPSS 19.0 (SPSS, Inc, Chicago, IL), SAS 9.1 (SAS Institute, Inc, Cary, NC), and JMP 8.0 (SAS Institute, Inc).

Results

Patient Characteristics

A total of 134 patients underwent both TE and liver biopsy during the study period, but 14 patients (10%) were excluded because the time between the 2 procedures exceeded 6 months. Among 120 patients who underwent both TE and liver biopsy within 6 months of each other, 92 (77%) were performed on the same day. On liver biopsy, 22 patients (18%) had no fibrosis (Ishak, 0), 63 patients (52%) had portal fibrosis only (Ishak, 1–2), 19 patients (16%) had bridging fibrosis (Ishak, 3–4), and 16 patients (13%) had cirrhosis (Ishak, 5–6). The baseline characteristics of the study population by fibrosis group are shown in Table 1. The overall mean age was 52 years, 57% were male, 63% were Caucasian, and the mean body mass index (BMI) was 28. AST values ranged from 19 to 334 U/L (mean, 59 U/L), and platelet counts ranged from 66,000 to 476,000/ μ L (mean, 206,000/ μ L). The mean biopsy

specimen length was 13.4 mm (range, 3–42 mm), and the mean number of portal areas per biopsy was 13 (range, 2–46). Patients with cirrhosis were more likely to have higher serum AST values, alkaline phosphatase values, and lower platelet counts and serum albumin level compared with those without cirrhosis.

Among the 120 patients, TE was unsuccessful in 11 (9%) despite attempts by different operators. These patients were similar to the cohort in whom TE was successful in all regards except body weight. Thus, their mean age was 49 years, AST level was 61 U/L, platelet count was 227,000/ μ L, and 2 patients had bridging fibrosis and 2 patients had cirrhosis. The average BMI in this group, however, was 35.7 kg/m² compared with 27.6 kg/m² in the analysis cohort ($P = .0001$).

Among the 109 patients in whom TE was successful, liver stiffness values ranged from 2.7 to 69.1 kPa (median, 7.8 kPa). The average liver stiffness values increased with higher Ishak fibrosis stage, but there was considerable overlap among Ishak stages 0 to 3 (Figure 1A). APRI scores also ranged widely, from 0.18 to 6.91 (median, 0.66), and increased with worsening fibrosis (Figure 1B).

Performance of Transient Elastography and Aspartate Aminotransferase to Platelet Ratio Index for Predicting Advanced Fibrosis (Ishak 3–6)

TE scores were significantly higher in patients with advanced liver fibrosis (Ishak, 3–6) than in those with mild fibrosis (Ishak, 0–2) (median value, 16.9 vs 6.8 kPa, respectively; $P < .0001$), yielding an AUROC of 0.91 (95% confidence interval [CI], 0.85–0.97). A TE cut-off score of 8.9 kPa was optimal in separating mild from advanced fibrosis (sensitivity, 0.90; specificity, 0.78; PPV, 0.62; NPV, 0.95). Forty-one percent (45 of 109) of patients had a TE score of 8.9 kPa or greater.

APRI also was significantly higher in patients with advanced liver fibrosis than in those with mild fibrosis (median value, 1.5 vs 0.5; $P = .0003$), yielding an AUROC of 0.86 (95% CI, 0.78–0.93). The optimal APRI for separating mild from advanced fibrosis was 0.8 (sensitivity, 0.81; specificity, 0.76; PPV, 0.57; NPV, 0.91). Forty-two percent (46 of 109) of patients had an APRI of 0.8 or greater. Including both TE and APRI in logistic regression analysis did not improve the AUROC of either test alone significantly (AUROC, 0.92; 95% CI, 0.87–0.97) (Figure 2A).

Performance of Transient Elastography and Aspartate Aminotransferase to Platelet Ratio Index for Predicting Cirrhosis (Ishak 5–6)

TE scores were significantly higher in patients with cirrhosis than in those without cirrhosis (median value, 20.2 vs 7.0 kPa; $P < .0001$), yielding an AUROC of 0.96 (95% CI, 0.92–0.99). A TE score of 13.1 kPa had the best accuracy in separating patients with cirrhosis from those without cirrhosis (sensitivity, 1.0; specificity, 0.89; PPV, 0.58; NPV, 1.0). Twenty-two percent (24 of 109) of patients had a TE score of 13.1 kPa or greater.

APRI also was higher among patients with cirrhosis compared with those without cirrhosis (median, 1.65 vs 0.57; $P = .0009$), yielding an AUROC of 0.84 (95% CI, 0.73–0.94). For APRI, a cut-off value of 1.0 was most accurate in detecting cirrhosis (sensitivity, 0.79; specificity, 0.78; PPV, 0.34; NPV, 0.96). Thirty percent (33 of 109) of patients had an APRI of 1.0 or greater. Combining TE and APRI did not improve diagnostic accuracy over TE alone, the AUROC being 0.96 (95% CI, 0.93–0.99) (Figure 2B).

Concordance Between Diagnostic Modalities for Diagnosis of Cirrhosis

By using the cut-off values obtained in AUROC analysis, TE was in agreement with liver biopsy assessment of fibrosis in 99 patients (91%), whereas APRI was in agreement in only 84 patients (77%). TE yielded liver stiffness scores suggestive of cirrhosis in all 14 patients diagnosed with cirrhosis histologically, but also in 7 of 17 (41%) patients with bridging fibrosis and 3 of 78 (4%) patients with no or portal fibrosis only. Thus, the sensitivity and NPV of a TE score of 13.1 kPa or greater in this cohort was 100%, but the PPV was only 58%, indicating that TE tended to overdiagnose cirrhosis. The APRI performed less well (79% sensitivity, 77% specificity, 33% PPV, 96% NPV), indicating that it missed the diagnosis of cirrhosis in 21% and also was more likely to overdiagnose cirrhosis than TE.

The 10 subjects with a TE score of 13.1 kPa or greater but without cirrhosis on liver biopsy were analyzed in further detail (Table 2, Supplementary Table 1). Overall, these patients more closely resembled patients with cirrhosis than those with no or minimal fibrosis, in mean age (59 vs 55 years in those with cirrhosis and 51 years in those without), AST levels (75 vs 86 U/L and 52 U/L), alkaline phosphatase (94 vs 112 U/L and 70 U/L), albumin levels (3.7 vs 3.6 g/L and 3.9 g/L), and platelet counts (150,000 vs 121,000/ μ L and 224,000/ μ L). Indeed, 7 of the 10 patients had other clinical and laboratory evidence suggestive of having cirrhosis or portal hypertension (low platelet count in 6 patients, APRI $\geq$ 1.0 in 5 patients, decreased albumin in 3 patients, hyperbilirubinemia in 1 patient, and splenomegaly in 4 patients).

Discussion

The current study summarizes results of a prospective evaluation of the performance of 2 noninvasive tests for the diagnosis of HCV-related cirrhosis at a single North American center in 109 patients who underwent liver biopsy for chronic hepatitis C. The results showed that both TE and APRI accurately diagnosed advanced fibrosis and cirrhosis in a majority of patients with chronic hepatitis C. Overall, TE had a better sensitivity and specificity compared with APRI. TE scores were in disagreement with liver biopsy interpretation in 9% of cases whereas APRI disagreed with biopsy in 23%.

These results are in agreement with previous studies on the sensitivity and specificity of TE for prediction of cirrhosis in other populations.^{17,18} In this study, a TE cut-off value of 8.9 kPa was most reliable for predicting advanced fibrosis (sensitivity, 0.90; specificity, 0.785) and a cut-off value of 13.1 kPa for cirrhosis (sensitivity, 1.0; specificity, 0.89). A recent meta-analysis of 50 studies analyzing the performance of TE for the staging of liver fibrosis using the Metavir staging system in a variety of liver diseases reported a mean AUROC for diagnosis of severe fibrosis (Metavir stage 3–4) of 0.89 (95% CI 0.88–0.91) and cirrhosis (Metavir stage 4) of 0.94 (95% CI 0.93–0.94); when adjusted for biopsy quality, the adjusted AUROC was 0.99.¹⁸ The current study, which used the Ishak staging system for liver fibrosis, yielded similar performance characteristics.

From a clinical and screening perspective, overdiagnosis of cirrhosis (false-positive results) is less problematic than underdiagnosis and missing cases (false-negative results). Thus, a screening test with high sensitivity is desirable. In this study, TE performed better than APRI when using a histologic diagnosis of cirrhosis as the gold standard, diagnosing all cases whereas APRI missed 3 cases. Both TE and APRI had false-positive results for cirrhosis, but the rate of false-positive results was higher with APRI (23%) than TE (10.5%). Furthermore, careful analysis of individual cases of apparent false-positive results of cirrhosis by TE suggested that most had at least bridging fibrosis and most had laboratory features suggestive of portal hypertension or actual cirrhosis. These findings suggest that the gold standard of liver biopsy histology is not always reliable, perhaps because of sampling

error, the subjective nature of the reading, liver biopsy size, and fragmentation.⁴⁻⁶ The diagnosis of cirrhosis sometimes can be made based on clinical or laboratory features alone. This and other studies indicate that TE can improve on this diagnosis and, in some instances, may outperform liver biopsy. TE was less reliable in separating early from advanced fibrosis without cirrhosis, although it often was supportive and provided confirmation of biopsy findings.

These results and the results of several meta-analyses support the role of TE and APRI for the diagnosis of HCV-related cirrhosis.^{10,17,18} APRI did not appear to add to the reliability of TE in assessing cirrhosis but usually was confirmatory. Both TE and APRI are easy to use, reproducible, and can be repeated frequently and at regular intervals over time. Future studies are needed to show the reliability of repeated measures of APRI and TE in showing progression of fibrosis or early detection of cirrhosis.

Our study supports the use of TE as a screening tool for the diagnosis of cirrhosis. It might be used to decide when to implement surveillance for hepatocellular carcinoma and the need for endoscopy to evaluate varices. Indeed, several studies have indicated that TE may be useful in monitoring worsening portal hypertension¹⁹⁻²² and may be predictive of development of hepatocellular carcinoma^{23,24} and the presence of esophageal varices.^{25,26}

A potential limitation of TE as a screening tool is a failure rate (defined as no valid measurements) of approximately 3% to 10% and unreliable results (defined as fewer than 10 valid shots, an interquartile range/liver stiffness measurement greater than 30%, or a success rate less than 60%) in approximately 16% of subjects, respectively.²⁷⁻²⁹ A BMI greater than 30 kg/m² is the strongest predictor of failure and unreliability; subject age older than 52 years, surgeon inexperience (<500 examinations performed), and presence of type 2 diabetes mellitus were additional factors.²⁷ The recent development of an XL probe may address some of these limitations. Several studies have compared the performance of the M probe with the XL in overweight and obese subjects. Overall, these studies have shown a lower failure rate with the XL probe vs the M probe, 1% vs 16%, and a higher reliability rate, 73% vs 50%, respectively, in one notable study.³⁰⁻³³ In general, the probes have similar accuracy but liver stiffness measurements tended to be lower with the XL probe among a variety of chronic liver diseases.^{30,32} Therefore, the optimal diagnostic cut-off values derived with the M probe may not be applicable to the XL probe and future studies will have to define the appropriate cut-off values associated with the XL probe.

In conclusion, TE is a reliable screening tool for the diagnosis of cirrhosis in a North American population. It may be useful in identifying patients who should undergo screening and surveillance for hepatocellular carcinoma without the need for a liver biopsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
AUROC	area under the receiver operating characteristic curve
BMI	body mass index
CI	confidence interval
HCV	hepatitis C virus
NPV	negative predictive value
PPV	positive predictive value
TE	transient elastography.

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Figure 1.

(A) TE stiffness scores stratified by Ishak fibrosis stage. Median TE stiffness scores for Ishak stages 0, 1, 2, 3, 4, 5, and 6 were 5.4, 6.7, 7.8, 9.8, 13.5, 29.6, and 18.3 kPa, respectively. The *dotted line* represents the best cut-off level (13.1 kPa) to distinguish patients with cirrhosis (Ishak, 5–6) from those without cirrhosis (Ishak, 0–4). (B) APRI values stratified by Ishak fibrosis score. Median APRI values for Ishak stages 0, 1, 2, 3, 4, 5, and 6 were 0.38, 0.57, 0.54, 1.11, 1.45, 1.56, and 1.64, respectively. The *dotted line* represents the best cut-off level (1.0) to distinguish patients with cirrhosis (Ishak, 5–6) from those without cirrhosis (Ishak, 0–4).

Figure 2.

(A) AUROC for TE (0.91), APRI, (0.86), and the combination of both (0.92) for discriminating between Ishak 0 to 2 vs 3 to 6 fibrosis. (B) AUROC for TE (0.96), APRI (0.84), and the combination of both (0.96) for discriminating between Ishak 0 to 4 vs 5 to 6 fibrosis.

Table 1

Baseline Demographic and Clinical Characteristics of the Cohort

Variable	Total (N = 120)	Ishak 0-2 (n = 85)	Ishak 3-4 (n = 19)	Ishak 5-6 (n = 16)	P value
Sex, n (%)					.07 (B)
Female	52 (43)	36 (42)	12 (63)	4 (25)	
Male	68 (57)	49 (58)	7 (37)	12 (75)	
Age, y	52 ± 9	51 ± 9	55 ± 10	54 ± 7	.23 (A)
Race, n (%)					.69 (B)
Black	26 (22)	18 (21)	6 (32)	2 (13)	
Other	18 (15)	13 (15)	3 (16)	2 (13)	
White	76 (63)	54 (64)	10 (53)	12 (75)	
BMI, kg/m ²	28.3 ± 5.0	28.0 ± 4.5	28.3 ± 7.4	29.7 ± 4.3	.48 (A)
AST, U/L	59 ± 46	50 ± 42	75 ± 41	85 ± 62	.005 (A)
ALT, U/L	77 ± 60	71 ± 62	92 ± 47	89 ± 63	.29 (A)
Alk P, U/L	77 ± 35	69 ± 20	85 ± 31	110 ± 69	<.0001 (A)
Platelet, k/uL	206 ± 78	228 ± 72	178 ± 75	123 ± 34	<.0001 (A)
Albumin, g/dL	3.8 ± 0.4	3.9 ± 0.3	3.6 ± 0.5	3.5 ± 0.5	<.0001 (A)
Total bilirubin, mg/dL	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.5	0.8 ± 0.5	.97 (A)
Direct bilirubin, mg/dL	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.2	0.3 ± 0.2	.01 (A)
Liver biopsy length, mm	13.4 ± 6.8	13.1 ± 6.4	16.5 ± 8.6	11.3 ± 5.6	.05 (A)
Number of portal areas per biopsy	13 ± 7	13 ± 6	18 ± 8	12 ± 8	.01 (A)
Histology activity index	7 ± 3	7 ± 3	9 ± 2	8 ± 3	.03 (A)
Periportal score	2 ± 1	2 ± 1	3 ± 2	3 ± 3	.01 (A)
Lobular score	3 ± 1	3 ± 1	4 ± 1	3 ± 1	.06 (A)
Portal score	2 ± 1	2 ± 1	2 ± 1	2 ± 1	.42 (A)

NOTE. Results are means ± SD or n (%). (A), 1-way analysis of variance; (B), χ^2 test.

Alk P, alkaline phosphatase; ALT, alanine aminotransferase.

Table 2
Clinical Features of Patients With TE of 13.1 kPa or Greater but With No Cirrhosis by Liver Biopsy

Patient	TE, kPa	APRI	Platelets, K/ μ L	HAI	Ishak fibrosis	AST, U/L	Albumin, g/dL	Bilirubin mg/dL	INR	Spleen, cm ^a
1	13.3	0.47	207	7	2	33	4.3	0.5	0.94	13
2	13.5	0.90	82	3	4	25	4.0	0.7	1.03	15
3	14.0	4.15	127	10	4	179	3.2	1.0	1.09	9
4	15.3	0.54	159	1	2	29	3.7	0.6	1.08	10
5	15.9	0.89	216	8	3	65	4.4	0.8	1.07	10
6	17.6	2.11	134	8	3	96	4.8	0.8	1.07	13
7	22.0	1.45	120	14	4	59	3.1	0.8	1.12	16
8	30.8	1.50	171	6	4	87	3.9	1.1	1.13	15
9	35.3	0.32	202	7	2	22	4.2	0.6	1.04	8
10	38.6	5.45	82	5	3	152	3.1	1.9	1.13	15
Mean ($\pm$ SD)	21.6 ($\pm$ 9.7)	1.78 ($\pm$ 1.71)	150 ($\pm$ 49)	7 ($\pm$ 4)	3 ($\pm$ 1)	75 ($\pm$ 55)	3.7 ($\pm$ 0.5)	0.9 ($\pm$ 0.4)	1.07 ($\pm$ 0.05)	12 ($\pm$ 3)

NOTE. Values suggestive of cirrhosis or portal hypertension are set in bold.
HAI, histology activity index; INR, international normalized ratio (of prothrombin time).

^aBy ultrasonography (normal, 13 cm).