Predicting Cirrhosis in Patients With Hepatitis C Based on Standard Laboratory Tests: Results of the HALT-C Cohort

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Knowledge of the presence of cirrhosis is important for the management of patients with chronic hepatitis C (CHC). Most models for predicting cirrhosis were derived from small numbers of patients and included subjective variables or laboratory tests that are not readily available. The aim of this study was to develop a predictive model of cirrhosis in patients with CHC based on standard laboratory tests. Data from 1,141 CHC patients including 429 with cirrhosis were analyzed. All biopsies were read by a panel of pathologists (blinded to clinical features), and fibrosis stage was determined by consensus. The cohort was divided into a training set (n = 783) and a validation set (n = 358). Variables that were significantly different between patients with and without cirrhosis in univariate analysis were entered into logistic regression models, and the performance of each model was compared. The area under the receiver-operating characteristic curve of the final model comprising platelet count, AST/ALT ratio, and INR in the training and validation sets was 0.78 and 0.81, respectively. A cutoff of less than 0.2 to exclude cirrhosis would misclassify only 7.8% of patients with cirrhosis, while a cutoff of greater than 0.5 to confirm cirrhosis would misclassify 14.8% of patients without cirrhosis. The model performed equally well in fragmented and nonfragmented biopsies and in biopsies of varying lengths. Use of this model might obviate the requirement for a liver biopsy in 50% of patients with CHC. In conclusion, a model based on standard laboratory test results can be used to predict histological cirrhosis with a high degree of accuracy in 50% of patients with CHC. (HEPATOLOGY **2005;42:282-292.**)

Chronic hepatitis C (CHC) is the most common cause of cirrhosis and the most frequent indication for liver transplantation in the United States.[1] After the onset of hepatitis C virus (HCV) infection, approximately 25% of patients with CHC will progress to cirrhosis over a period of 25 to 30 years.[1] Development of cirrhosis is an important stage in the natural history of CHC, because it heralds significant morbidity and mortality and higher health care costs related to complications of end-stage liver disease. Detection of cirrhosis triggers screening for hepatocellular carcinoma and gastroesophageal varices as well as heightened vigilance for evidence of hepatic decompensation, which may prompt referral for liver transplantation.[2] Moreover, the presence of cirrhosis also influences decisions about antiviral therapy. Patients with cirrhosis have the most urgent need for treatment, yet they have lower response rates, reduced tolerance to therapy, and requirements for close monitoring during treatment.

Liver biopsy is the standard method used for the assessment of cirrhosis. However, biopsy is invasive and costly and is associated with patient discomfort and risk of major complications (0.3%-0.5%), including death (0.03%-0.1%).[3-5] Furthermore, sampling error and intraobserver/interobserver variability may lead to underestimation of underlying cirrhosis,[6] especially when biopsy specimens

Abbreviations: CHC, chronic hepatitis C; HCV, hepatitis C virus; HALT-C Trial, Hepatitis C Antiviral Long-term Treatment Against Cirrhosis Trial; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ROC, receiver-operating characteristic; AUROC, area under the receiver-operating characteristic.

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are small or fragmented.[7] Thus, the need exists for a noninvasive, inexpensive, and accurate method for diagnosing cirrhosis.

A clinical model based on standard laboratory tests that could accurately detect the presence of cirrhosis would be useful and could reduce the requirement for liver biopsy in clinical practice. The ideal model should be developed and validated in a well-characterized cohort, easy to implement, and accurately discriminate between the presence and absence of cirrhosis. Current models to predict cirrhosis have relied upon a combination of clinical features, serum biochemical tests, an array of fibrosis markers, radiological studies, and other measures of hepatic function.[8-22] Most models were derived from small cohorts of patients, some of which included subjective variables or laboratory tests that are costly and not readily available, and very few models have been validated. Thus, all existing clinical models to predict cirrhosis in CHC patients have limitations.

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial is a prospective, randomized, controlled study to determine if long-term pegylated interferon therapy can reduce the risk of progression to cirrhosis, decompensated liver disease, and/or hepatocellular carcinoma in patients with CHC who have advanced fibrosis or cirrhosis.[23,24] The large, well-characterized cohort (>1,000 patients enrolled); central review of liver histology by a committee of hepatic pathologists; and high percentage of patients with cirrhosis provided an ideal setting for the development of a model to distinguish between cirrhosis and fibrosis. The aims of this analysis were to identify demographic, clinical, laboratory, virological, and radiological factors associated with histological cirrhosis and to develop a predictive model based on objective, routinely available laboratory test results.

Patients and Methods

The HALT-C Trial is being conducted in 10 clinical centers in the United States. Details of the trial design and entry criteria have been previously reported.[23,24] The study protocol was approved by the institutional review board of each participating institution, and written consent was obtained from all patients.

Patient Population. Entry criteria included the presence of antibody to HCV and HCV RNA in serum, failure to respond to the most recent treatment of standard interferon with or without ribavirin, and the demonstration on a liver biopsy performed within 12 months of enrollment of bridging fibrosis or cirrhosis. All the entry biopsies were performed at least 2 months after completion of the prior course of therapy; 79% of the biopsies were performed more than 6 months after discontinuation of treatment. Patients with other co-existent liver disorders and those with hepatic decompensation were excluded.

Baseline Evaluation. Baseline evaluations included a complete history, physical examination, review of historical information regarding prior treatment, assessment of lifetime alcohol consumption using the Skinner survey, an abdominal ultrasound, laboratory tests and a liver biopsy. The possible mode of infection and estimated age at infection were assessed independently by patients and investigators using structured questionnaires.

Baseline laboratory tests included complete blood counts, liver panel, basic metabolic panel, prothrombin time/international normalized ratio (INR), alpha-fetoprotein, HCV genotype, quantitative HCV RNA level, thyroid-stimulating hormone level, and tests to exclude other causes of liver disease. Assays for HCV genotype and HCV RNA were performed by a single laboratory (University of Washington, Seattle, WA), as previously described.[23,24] All other blood tests were performed at the hospital laboratories of the participating clinical centers. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels were expressed as a ratio of the upper limit of normal based on the reference ranges for each laboratory. Abdominal ultrasound examinations were performed in the participating clinical centers and in regional referring hospitals.

Interpretation of Liver Histology. Baseline liver biopsies were reviewed in conference by a committee of hepatic pathologists representing the 10 clinical centers and the data-coordinating center. The panel met at the beginning of the study to decide on the scoring methods used for assessing inflammation, fibrosis, steatosis, and iron staining and went through practice sessions to improve uniformity in interpretation of the scoring systems. The modified histology activity index, also known as the Ishak score, was chosen as the principal scoring system for the trial, because the range of possible scores (0 to 18 for inflammation and 0 to 6 for fibrosis) was larger than that of other published scoring systems.[25] This scoring system would allow fine distinctions, if needed, for any future secondary analyses, while categories could be combined when such fine distinctions were not needed. Fibrosis scores, evaluated with the Masson trichrome stain, were determined by a consensus of the committee members or in cases of divided opinions by a vote of the majority. For the purposes of the present analysis, fibrosis stages 5 (incomplete cirrhosis) and 6 (definite cirrhosis) were combined to comprise the cohort with "cirrhosis," while stages 3 (occasional bridging fibrosis) and 4 (marked bridging fibrosis) were combined to comprise the cohort

with "fibrosis." Ninety-seven patients (8%) with a biopsy showing only stage 2 (fibrosis of most portal areas without septal or bridging fibrosis) were allowed into the study and were included in the fibrosis cohort if a previous biopsy or assessment of sections at the participating center had shown bridging fibrosis. Biopsies were recorded as fragmented when the specimen had broken into numerous small pieces of tissue. The length of each biopsy was determined during the committee review by measuring all pieces of liver tissue or tissue fragments in the section.

External Validation Cohort. Laboratory and histological data from a cohort of treatment-naive CHC patients that were previously studied[15] were used to validate the accuracy of predicting cirrhosis using the best model derived from the HALT-C data. There were 270 patients in the original study; data on INR were missing in 5 patients. Of the remaining 265 patients, 98 (37%) with Ishak fibrosis 0-2, 127 (48%) with Ishak fibrosis 3-4, and 40 (15%) with Ishak fibrosis 5-6 comprised the external validation cohort.

Statistical Analyses. Demographic, clinical, laboratory, and radiological data were entered by study coordinators at each clinical center into a secure Internet-based website maintained by a central data-coordinating center (New England Research Institute, Watertown, MA). Histological data derived from central review of liver biopsies were entered by staff at the data-coordinating center, who presided at pathology review meetings.

Baseline data from all patients enrolled in the lead-in phase of the HALT-C Trial were analyzed using Statistical Analysis Software version 8.2 (SAS Institute, Cary, NC). Patients were randomly divided into two groups: training (2/3) and validation (1/3). Univariate chi-square and *t* test analyses were performed to identify variables that were significantly different between patients with (Ishak fibrosis score 5-6) and without (Ishak fibrosis score 3-4) cirrhosis. All variables that were significant in the univariate analysis were entered in a logistic regression model with backward selection to develop a model for predicting cirrhosis.[26] Variables that remained in the final logistic regression model were used, dropping one variable at a time, to develop several models for prediction of cirrhosis based on data from the training set. Performance of these models was analyzed by constructing receiver-operating characteristic (ROC) curves and comparing the area under these curves.[27] Validity of the eight best models was tested on data from the validation set. To determine the effect of fragmentation and length of the biopsies on the performance of the models, we ran the same models on the fragmented and nonfragmented biopsies and on biopsies of varying lengths. The sensitivity, specificity, and positive and negative predictive values for various values in the final model were calculated to determine the optimal cutoff values that would predict or exclude cirrhosis with confidence. To explore the accuracy of simpler models, we performed logistic regression with cirrhosis as the independent variable and platelet count, AST/ALT ratio, and INR as the dependent variables; predicted probabilities of cirrhosis were calculated based on model estimates at the midpoints of the categories. A P value of less than .05 was considered significant.

Results

A total of 1,145 patients were enrolled; 4 were excluded because their biopsies were considered too small for staging by the panel of pathologists. Of the 1,141 patients included in this analysis, 429 (38%) had cirrhosis. Comparison of the baseline characteristics of the patients with and without cirrhosis is shown in Table 1. No difference in age or duration of infection was apparent between the two groups. Significant differences were found for body mass index, splenomegaly on ultrasound, lifetime alcohol consumption, and all laboratory tests except for the degree of ALT elevation and the proportion with HCV genotype 1. Biopsies from patients with cirrhosis were more often fragmented (33% vs. 19% in patients without cirrhosis; $P < .0001$), but no difference was found in mean total length of the biopsies between patients with and without cirrhosis.

There were 783 patients in the training set and 358 patients in the validation set. Baseline characteristics of the two sets of patients were comparable (Table 2), except that the validation set had a lower mean INR (1.02 vs. 1.04; $P = .003$).

Performance of various logistic regression models in identifying the presence of cirrhosis in the training and validation sets is shown in Table 3. The area under the ROC (AUROC) of the three best models were comparable, ranging from 0.79 to 0.78 in the training set. Examination of the regression formulas revealed that platelet count had the greatest weight, followed by INR and AST/ALT ratio. All the models had similar or slightly better performance in the validation set.

Application of the regression models to fragmented and nonfragmented biopsies and biopsies with total lengths varying from less than 1.5 cm to more than 2.5 cm showed that fragmentation had a greater effect than length on the performance of these models (Table 4). Based on the performance of these models in biopsies of various lengths and fragmentation and ease of use, we selected a final model (model 3) relying on laboratory values that are routinely available in patients with hepatitis C: platelet count, AST/ALT ratio, and INR. Model 1 was abandoned because low white blood cell

Table 1. Characteristics of Patients With and Without Cirrhosis

	Ishak Fibrosis Score 3–4 (n = 712)		Ishak Fibrosis Score 5–6 (n = 429)		
	Mean	**SD**	**Mean**	**SD**	***P* Value**
Demographics					
Age (yrs)	49.6	7.3	50.4	7.2	.070
Female (%)	28		28		.98
Race (%)*					.44
Asian	3		2		
White	75		72		
Hispanic	6		12		
African American	16		14		
Body mass index (kg/m^2)	29.4	5.5	30.1	5.3	.038
Splenomegaly on ultrasound (%)	23		44		<.0001
Duration of infection (yrs)	28	8	29	8	.096
Alcohol					
Duration of consumption (yrs)	20	12	21	12	.21
Total consumption (kg)	17	28	21	34	.024
Average consumption (g/d)	24	38	29	48	.050
Laboratory					
White blood cells ($\times$1,000/mm^3)	6.0	1.9	5.7	2.0	.016
Neutrophils ($\times$1,000/mm^3)	3.3	1.4	3.1	1.3	.007
Hemoglobin (g/dL)	15.2	1.4	14.9	1.3	.0029
Platelets ($\times$1,000/mm^3)	188	61	138	58	<.0001
AST ratio to ULN	1.9	1.3	2.5	1.7	<.0001
ALT ratio to ULN	2.3	1.8	2.4	1.7	.10
AST/ALT ratio	0.78	0.25	0.94	0.33	<.0001
AST/ALT ratio >1.0 (%)	16		31		<.0001
AST ($\times$ULN)/platelets	1.22	1.24	2.26	2.00	<.0001
Alkaline phosphatase ratio to ULN	0.76	0.30	0.93	0.40	<.0001
Total bilirubin (mg/dL)	0.72	0.36	0.90	0.47	<.0001
Albumin (g/dL)	4.0	0.4	3.8	0.4	<.0001
Prothrombin time, INR	1.01	0.10	1.08	0.11	<.0001
Alpha-fetoprotein (ng/mL)	11	19	22	34	<.0001
HCV RNA and genotype					
HCV RNA $\log_{10}$ (IU/mL)	6.5	0.5	6.3	0.6	<.0001
Genotype 1 (%)	88		90		.45
Biopsies					
Fragmented (%)	19		33		<.0001
Length (%)					
<1.5 cm	35		37		.08
1.5–2.5 cm	49		51		
>2.5 cm	16		12		

Abbreviation: ULN, upper limit of normal.

*Comparison of white vs. others.

count had an unexpected paradoxical effect (high white blood cell count appeared to predict cirrhosis). Models 2 and 3 had similar performance that was better than model 4; therefore, model 3 was selected for the sake of simplicity.

The regression formula for model 3 is as follows: log odds (predicting cirrhosis) = $-5.56 - 0.0089 \times$ platelet ($\times 10^3$/mm^3) + $1.26 \times$ AST/ALT ratio + $5.27 \times$ INR. The formula to calculate predicted probability is: exp (logodds)/(1+exp(logodds)). Access to this formula and its computation is available through the HALT-C Trial website (http://www.haltctrial.org). The ROC curves of this model for the training and validation sets are illustrated in Fig. 1, and Table 5 shows how patients with and without cirrhosis would be classified in the final model. A cutoff predicted value of less than 0.2 to exclude cirrhosis would misclassify only 7.8% (24 of 309) of patients with cirrhosis (negative predictive value of 86%), while a cutoff predicted value of more than 0.5 to identify patients with cirrhosis would misclassify 14.8% (70 of 474) of patients without cirrhosis (positive predictive value of 75%). Approximately half (48.5%) of the patients fell between the two cutoff values and could not be classified accurately. A cutoff of 0.6 would misclassify just 8.0% (38 of 474) of patients without cirrhosis as having cirrhosis, but would increase the proportion of patients that would not be classifiable to 59.3%. Examples of three patients with predicted values of 0.15 to 0.70 are shown in Table 5.

Table 2. Characteristics of Patients in Training and Validation Sets

	Training Set (n = 783)		Validation Set (n = 358)		
	Mean	SD	Mean	SD	*P* Value
Demographics					
Age (yrs)	50.1	7.2	49.6	7.6	.36
Female (%)	28		27		.54
Race (%)*					.11
Asian	3		2		
White	75		71		
Hispanic	8		9		
African American	14		18		
Body mass index (kg/m^2)	29.7	5.5	29.8	5.3	.79
Splenomegaly on ultrasound (%)	32		29		.31
Duration of infection (yrs)	28	8	28	8	.70
Alcohol					
Duration of consumption (yrs)	21	12	21	12	.95
Total consumption (kg)	18	31	18	29	.95
Average consumption (g/d)	26	40	27	45	.74
Laboratory					
White blood cells ($\times$1,000/mm^3)	5.9	1.9	5.9	1.9	.98
Neutrophils ($\times$1,000/mm^3)	3.2	1.3	3.2	1.4	.83
Hemoglobin (g/dL)	15.1	1.4	15.0	1.3	.26
Platelets ($\times$1,000/mm^3)	168	65	171	64	.60
AST ratio to ULN	2.1	1.5	2.3	1.6	.055
ALT ratio to ULN	2.3	1.8	2.5	1.7	.068
AST/ALT	0.85	0.30	0.83	0.28	.35
AST/ALT ratio $>$1.0 (%)	22		22		.97
AST ($\times$ULN)/platelets	1.56	1.54	1.72	1.86	.13
Alkaline phosphatase ratio to ULN	0.83	0.35	0.82	0.35	.77
Total bilirubin (mg/dL)	0.80	0.42	0.76	0.39	.16
Albumin (g/dL)	3.9	0.4	3.9	0.4	.63
Prothrombin time (INR)	1.04	0.11	1.02	0.10	.0033
Alpha-fetoprotein (ng/mL)	16	27	15	23	.42
HCV RNA and genotype					
HCV RNA log (IU/mL)	6.4	0.5	6.4	0.5	.96
Genotype 1 (%)	90		87		.16
Biopsies					
Fragmented (%)	25		23		.67
Length					
$<$1.5 cm (%)	35		36		
1.5–2.5 cm, (%)	51		50		
$>$2.5 cm (%)	14		15		.90
Ishak fibrosis 5–6 (%)	39		34		.054

Abbreviation: ULN, upper limit of normal.
*Comparison of white vs. others.

To better understand the basis for the discordant cases, the liver biopsy findings and clinical data from these cases were compared with those from the concordant cases (Table 6). Among patients with cirrhosis read on biopsy, those who also had predicted cirrhosis were more likely to have other evidence of advanced liver disease (splenomegaly, esophageal varices, and hypoalbuminemia) than patients predicted not to have cirrhosis. Likewise, among patients without cirrhosis on biopsy, those who had predicted cirrhosis were more likely to have other evidence of advanced liver disease than patients predicted not to have cirrhosis.

To explore the accuracy of our suggested formula to detect cirrhosis, we examined the predicted probability of

Table 3. Logistic Regression Models Predicting Cirrhosis

	Training Set	Validation Set
Number of patients	783	358
Number of patients with cirrhosis	309	120
Variables in the models, AUROC (95% CI)		
WBCs, platelets, AST/ALT ratio, AP, INR	0.790 (0.75–0.83)	0.822 (0.77–0.88)
Platelets, AST/ALT ratio, AP, INR	0.787 (0.75–0.82)	0.809 (0.75–0.86)
Platelets, AST/ALT ratio, INR	0.776 (0.74–0.81)	0.808 (0.75–0.86)
Platelets, AST/ALT ratio	0.745 (0.71–0.78)	0.798 (0.74–0.85)
Platelets, INR	0.761 (0.72–0.80)	0.797 (0.74–0.85)
Platelets	0.730 (0.69–0.77)	0.779 (0.72–0.84)
AST ($\times$ULN)/platelet ratio	0.705 (0.66–0.75)	0.792 (0.74–0.85)
AST/ALT	0.658 (0.62–0.70)	0.644 (0.57–0.71)

Abbreviations: WBCs, white blood cells; AP, alkaline phosphatase; ULN, upper limit of normal.

Table 4. Application of Logistic Regression Models

	Fragmented Biopsies	Nonfragmented Biopsies
Number of patients	277	864
Number of patients with cirrhosis	141	288
Variables in the models, AUROC (95% CI)		
WBCs, platelets, AST/ALT ratio, AP, INR	0.735 (0.68–0.79)	0.812 (0.78–0.85)
Platelets, AST/ALT ratio, AP, INR	0.727 (0.67–0.79)	0.805 (0.77–0.84)
Platelets, AST/ALT ratio, INR	0.717 (0.66–0.78)	0.795 (0.76–0.83)
Platelets, AST/ALT ratio	0.674 (0.61–0.74)	0.774 (0.74–0.81)
Platelets, INR	0.719 (0.66–0.78)	0.777 (0.74–0.82)
Platelets	0.675 (0.61–0.74)	0.752 (0.71–0.79)
AST (×ULN)/platelet ratio	0.700 (0.64–0.76)	0.729 (0.69–0.77)
AST/ALT ratio	0.596 (0.53–0.66)	0.669 (0.63–0.71)

	Biopsy Length <1.5 cm	Biopsy Length 1.5–2.5 cm	Biopsy Length >2.5 cm
Number of patients	406	570	165
Number of patients with cirrhosis	160	219	50
Variables in the models, AUROC (95% CI)			
WBCs, platelets, AST/ALT ratio, AP, INR	0.776 (0.73–0.83)	0.811 (0.77–0.85)	0.856 (0.76–0.92)
Platelets, AST/ALT ratio, AP, INR	0.772 (0.72–0.82)	0.803 (0.76–0.84)	0.780 (0.74–0.91)
Platelets, AST/ALT ratio, INR	0.767 (0.72–0.82)	0.799 (0.76–0.84)	0.787 (0.70–0.88)
Platelets, AST/ALT ratio	0.744 (0.69–0.80)	0.773 (0.73–0.82)	0.764 (0.67–0.86)
Platelets, INR	0.759 (0.71–0.81)	0.778 (0.73–0.82)	0.787 (0.70–0.88)
Platelets	0.735 (0.68–0.79)	0.749 (0.70–0.79)	0.758 (0.66–0.84)
AST (×ULN)/platelet ratio	0.735 (0.68–0.79)	0.741 (0.70–0.79)	0.671 (0.57–0.78)
AST/ALT ratio	0.638 (0.58–0.70)	0.662 (0.61–0.71)	0.642 (0.54–0.76)

Abbreviations: WBCs, white blood cells; AP, alkaline phosphatase; ULN, upper limit of normal.

cirrhosis versus the actual prevalence of cirrhosis for various clinically relevant levels of platelet count, AST/ALT ratio, and INR. As shown in Table 7, cirrhosis can be predicted with a high degree of accuracy with standard laboratory tests. For example, patients with CHC who have a platelet count less than $100 \times 10^3/mm^3$, an AST/ALT ratio of 1 or more, and an INR more than 1 had a predicted probability of cirrhosis of 73% and an observed prevalence of cirrhosis of 79%. Similarly, patients with CHC who had a platelet count more than $200 \times 10^3/mm^3$, an AST/ALT ratio less than 1, and an INR of 1 or less had a predicted probability of cirrhosis of 19% and an observed prevalence of cirrhosis of 12%.

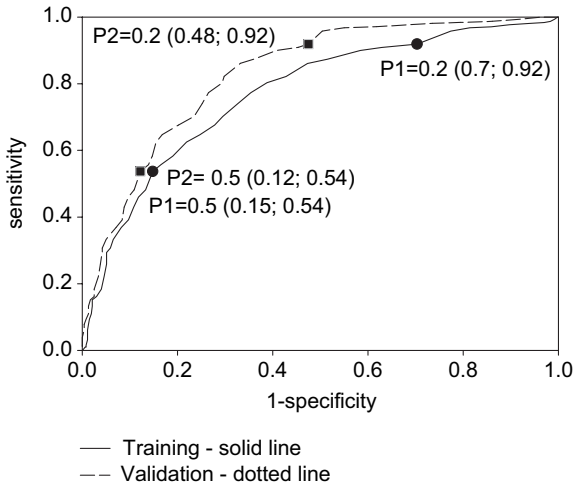

Fig. 1. Comparison of ROC curves of the final model that comprised platelet, AST/ALT ratio, and INR using data from the training set (solid line) and validation set (dotted line). Predicted values (P1 = training set, P2 = validation set) of 0.2 and 0.5 are marked on the curves. Numbers in parentheses correspond to 1-specificity and sensitivity for each point on the curve.

Table 8 shows the applicability of our model in an external validation cohort of treatment-naive CHC patients with a broad range of liver fibrosis. Using a cutoff of less than 0.2 to exclude cirrhosis, only 1 (2.5%) of 40 patients with cirrhosis would have been misclassified. With a cutoff of greater than 0.5, only 12 (5.3%) of 225 patients without cirrhosis would be mistakenly predicted to have cirrhosis. With these cutoff values, cirrhosis can be confidently excluded or diagnosed without resorting to a liver biopsy in 58% of the patients. The AUROC of model 3 when applied to this external cohort was 0.906 (95% CI, 0.84-0.97).

Discussion

In this study of 1,141 well-characterized patients with CHC, we developed clinical models that can reliably predict the histological presence of cirrhosis. Of the three models with the highest AUROC based on data from the training set, we chose a final model comprising three variables: platelet count, AST/ALT ratio, and INR. Our

Table 5. Application of the Final Model in Predicting Cirrhosis in Training Set

Predicted Values	No. of Patients	No. (%) With Cirrhosis	No. (%) Without Cirrhosis	Sensitivity*	Specificity*	PPV*	NPV*
<0.1	36	6 (17%)	30 (83%)	98%	6%	41%	83%
0.1–0.2	130	18 (14%)	112 (86%)	92%	30%	46%	86%
0.2–0.3	159	29 (18%)	130 (82%)	83%	57%	56%	84%
0.3–0.4	116	45 (39%)	71 (61%)	68%	72%	62%	78%
0.4–0.5	105	44 (42%)	61 (58%)	54%	85%	70%	74%
0.5–0.6	84	52 (62%)	32 (38%)	37%	92%	75%	69%
0.6–0.7	60	44 (73%)	16 (26%)	23%	95%	76%	66%
0.7–0.8	50	36 (72%)	14 (28%)	11%	98%	81%	63%
0.8–0.9	29	25 (86%)	4 (14%)	3%	99%	71%	61%
>0.9	14	10 (71%)	4 (29%)				
Total	783	309 (39%)	474 (61%)				

NOTE. Predicted values of 3 patients with laboratory values are as follows. (1) AST 70, ALT 100, platelet 200,000, INR 0.9: 0.15 (fewer than 8% of patients with cirrhosis scored at this level or lower). (2) AST 90, ALT 100, platelet 125,000, INR 1.0: 0.43. (3) AST 120, ALT 100, platelet 100,000, INR 1.1: 0.70 (2% of patients without cirrhosis scored at this level or higher).

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

*Sensitivity, specificity, positive predictive value, and negative predictive value for a cutoff of < compared with =.

model performed well in the objective of predicting cirrhosis. Using a predicted cutoff value of less than 0.2 to exclude cirrhosis, we would have misclassified only 7.8% of patients with cirrhosis, and, relying on a cutoff value of greater than 0.5 to diagnose cirrhosis, we would have misclassified 14.8% of patients without cirrhosis as actually having cirrhosis.

In the past 10 years, several studies on models to predict cirrhosis have been published.[8-22] Our model has several notable advantages over those published previously. Our model was based on prospectively collected data from more than 1,100 well-characterized patients; the large number of patients with histologically proven cirrhosis (n = 429) permitted a robust analysis with multiple variables. Moreover, the inclusion of patients from 10 centers around the country, with 15% African Americans and 8% Hispanics, renders our results more generalizable to other populations with CHC. A unique aspect of this study was the fact that all liver biopsies were scored by a panel of expert pathologists who determined fibrosis stage

Table 6. Comparison of Clinical Characteristics and Quality of Liver Biopsies of Concordant and Discordant Cases

	Biopsy Read as Cirrhosis			Biopsy Read as No Cirrhosis		
	Model Predicts No Cirrhosis (N = 24)	Model Predicts Cirrhosis (N = 167)	*P* Value	Model Predicts No Cirrhosis (N = 142)	Model Predicts Cirrhosis (N = 70)	*P* Value
Fragmented biopsy, n (%)	7 (29)	62 (37)	.45	18 (13)	24 (34)	.0002
Length, n (%)						
<1.5 cm	8 (33)	70 (42)		42 (30)	37 (53)	
1.5–2.5 cm	12 (50)	82 (49)		70 (49)	28 (40)	
>2.5 cm	4 (17)	15 (9)	.24	30 (21)	5 (7)	.0003
Splenomegaly (ultrasound), n (%)	3 (13)	91 (55)			35 (52)	<.0001
Albumin, mean (SD)	4.0 (0.4)	3.6 (0.4)	.0002	4.0 (0.4)	3.8 (0.4)	.0005
Esophageal varices on EGD, n (%)	3 (17)	69 (59)	.0008	4 (5)	19 (33)	<.0001
Platelets, n (%)						
>199	19 (79)	3 (2)		126 (89)	1 (1)	
151–199	5 (21)	18 (11)		14 (10)	9 (13)	
101–150	0 (0)	63 (38)		2 (1)	31 (44)	
<101	0 (0)	83 (50)	<.0001	0 (0)	29 (41)	<.0001
Mean (SD)	253 (73)	108 (35)	<.0001	247 (51)	112 (34)	<.0001
AST/ALT ratio, n (%)						
1	22 (92)	90 (54)		131 (92)	38 (54)	
>1	2 (8)	77 (46)	.0004	11 (8)	32 (46)	<.0001
INR, n (%)						
1	23 (96)	18 (11)		140 (99)	17 (24)	
						<.0001
>1	1 (4)	149 (89)	<.0001	2 (1)	53 (76)	

Abbreviation: EGD, esophago-gastroduodenoscopy.

Table 7. Prediction of Histological Cirrhosis

Platelets	AST/ALT = 1 and INR = 1	AST/ALT = 1 and INR >1	AST/ALT = 1 and INR = 1	AST/ALT >1 and INR >1
100				
N	33	63	21	58
% Cirrhosis	61	83	52	79
Predicted probability (%)*	47	60	61	73
101–150				
N	110	122	34	31
% Cirrhosis	37	59	44	74
Predicted probability (%)	38	51	53	65
151–200				
N	195	72	29	21
% Cirrhosis	19	43	31	71
Predicted probability (%)	29	40	42	55
>200				
N	238	60	48	6
% Cirrhosis	12	22	25	50
Predicted probability (%)	19	28	30	42

*Based on a logistic regression with platelets, AST/ALT, and INR.

by consensus. Furthermore, the final model included only biologically plausible variables. Platelet count, the variable with the largest impact on the model, is known to correlate with the degree of portal hypertension and, to a lesser extent, with hepatic function and reduced thrombopoietin synthesis.[28-30] Similarly, INR, directly related to hepatic synthetic function, worsens with progression of fibrosis and loss of hepatocyte mass. An AST/ALT ratio above 1 has been demonstrated in many studies to correlate with the presence of cirrhosis, perhaps as a result of delayed AST clearance relative to ALT[31] or of mitochondrial injury associated with advanced liver disease, resulting in more marked release of AST than ALT.[32] Adding to the value of our model was the reliance exclusively on objective laboratory tests routinely available in patients with CHC. Inclusion of subjective variables such as spleen size and alcohol history did not enhance the performance of the model. Our robust model, based on a large number of biopsies, performed equally well in the training and validation sets and was independent of biopsy length and fragmentation, which have been shown to influence histological assessment of fibrosis.[7] Finally, the accuracy of our model in predicting cirrhosis was higher in an external validation cohort, indicating its use in treatment-naive CHC patients and in CHC patients with less advanced liver disease.

Our model should perform well in clinical practice; however, the formula is complex, requiring access to a calculator or computer, which might not be available in a busy clinic. Thus we have also included the model prediction according to convenient levels of platelet count, AST/ALT ratio, and INR. The resulting table (Table 7) provided predicted probabilities of cirrhosis that were close to the observed prevalence. Thus these simple algorithms could be applied with a fair degree of accuracy in practice to make informed decisions regarding the need for a liver biopsy.

Our model performed better than or as well as other previously reported models in predicting cirrhosis. An AST/ALT ratio of 1 or more has been reported to have 100% specificity and 100% positive predictive value in detecting cirrhosis but a sensitivity of only 53%.[8] This model also performed poorly in our database and was much less accurate in other reports.[10,18,22] Similarly, the AST-to-platelet ratio index, proposed recently to predict accurately (AUROC of 0.89-0.94) the presence of cirrhosis,[15] was derived in a study that included only 41 patients with cirrhosis, and was validated in some[33] but not all cohorts,[34] including our training set. Other models have included subjective variables that have not been validated by others[13]; incorporated less readily available laboratory

Table 8. Application of the Final Model in Predicting Cirrhosis to the External Validation Cohort

Predicted Values	No. of Patients	No. (%) With Cirrhosis	No. (%) Without Cirrhosis	Sensitivity*	Specificity*	PPV*	NPV*
<0.1	41	1 (2%)	40 (98%)	98%	18%	17%	98%
0.1–0.2	79	0 (0%)	79 (100%)	98%	53%	27%	99%
0.2–0.3	66	4 (6%)	62 (91%)	88%	80%	44%	97%
0.3–0.4	25	7 (28%)	18 (72%)	70%	88%	52%	94%
0.4–0.5	21	7 (33%)	14 (67%)	53%	95%	64%	92%
0.5–0.6	14	5 (36%)	9 (64%)	40%	99%	84%	90%
0.6–0.7	6	4 (67%)	2 (33%)	30%	99%	92%	89%
0.7–0.8	7	6 (86%)	1 (14%)	15%	100%	100%	87%
0.8–0.9	2	2 (100%)	0 (0%)	10%	100%	100%	86%
>0.9	4	4 (100%)	0 (0%)	0%	100%		85%
Total	265	40 (15%)	225 (85%)				

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

*Sensitivity, specificity, positive predictive value, and negative predictive value for a cutoff of < compared with =.

tests such as serum hyaluronate, procollagen peptide III, and YKL-40; or required complicated analytical tools such as artificial neural network analysis. None of these methods has been validated.

Several models have also been developed to predict advanced fibrosis among patients with hepatitis C. A model based on age, γ-glutamyl transpeptidase, platelet count, cholesterol, and prothrombin time accurately excluded F2-F4 fibrosis but would have avoided liver biopsy in less than 40% of patients.[16] Another model to identify fibrosis scores of 3 or more by incorporating platelet count, ALT/AST ratio, and prothrombin time in a discriminant score was specific but insensitive and was based on only 79 study subjects, a quarter of whom were coinfected with HIV.[12] A "fibrosis index" proposed by Imbert-Bismut et al.[11] consisting of five biochemical markers (α2-macroglobulin, haptoglobin, γ-glutamyl transpeptidase, total bilirubin, and apolipoprotein A1) has been studied extensively. Based on an original training cohort of 205 patients and a validation set of 134, this index predicted advanced fibrosis (Metavir F2-F4) accurately (AUROC 0.84-0.87), with 100% specificity and 90% sensitivity but with more than half of the patients falling in an indeterminate zone. Unlike our model, this fibrosis index requires costly, nonstandard laboratory tests; correlates poorly with histological fibrosis in biopsies less than 1.5 cm in length[35]; and does not discriminate cirrhosis (F4) from stages F2 and F3. The discriminatory value of this fibrosis index has been confirmed by some but not all investigators.[33,36,37]

All models are hampered somewhat by the inherent inaccuracy of needle liver biopsies as the standard for assessing cirrhosis. The distribution of fibrosis is patchy, not uniform, and subject to sampling error, particularly in smaller and fragmented specimens.[6] In addition, all models assume that the clinical findings associated with cirrhosis have a linear relationship to the degree of fibrosis. However, clinical features such as thrombocytopenia are more closely associated with the presence of portal hypertension, which is not necessarily synonymous with the anatomical lesion of cirrhosis. Finally, it is difficult to assess the actual number of false positive and false negative liver biopsies in the absence of an alternate gold standard. For patients whose biopsies were read as no cirrhosis but were predicted to have cirrhosis, the biopsies were more likely to be smaller and fragmented than in patients who were predicted not to have cirrhosis. These patients were also more likely to have other evidence of advanced liver disease, including low albumin, splenomegaly, and esophageal varices. Therefore, some of these patients who appeared to have been misclassified by the model may have cirrhosis that was not diagnosed because of sampling error or inadequate quality of the biopsies. Nonetheless, the number of misclassified biopsies in this study is likely to be small, because the degree of improvement in the ability of our model to detect cirrhosis in better quality biopsies was limited (Table 4).

Our study had a number of other potential limitations. The HALT-C Trial was not designed specifically to identify predictors of cirrhosis, and our cohort consisted of patients with advanced fibrosis who had already undergone at least one course of antiviral therapy and were seen in tertiary care referral centers. The task undertaken in this study of using commonly available laboratory values to discriminate between cirrhosis and advanced fibrosis is more difficult than discrimination between cirrhosis and minimal fibrosis, as demonstrated by a higher accuracy of our model when applied to the external validation cohort, which included patients with less advanced fibrosis. It should also be emphasized that noninvasive models to predict liver fibrosis or cirrhosis carry the implicit assumption that, in patients with CHC, the only value of a liver biopsy is in distinguishing between patients with and without advanced fibrosis or cirrhosis. Much more information can be gleaned from a liver biopsy, including histological activity, finer gradations of histologic fibrosis, architecture of the hepatic lobules, and presence of steatosis.

In conclusion, we demonstrated that a model based on a few standard laboratory tests can be used to predict histological cirrhosis with a high degree of accuracy in patients with CHC and advanced fibrosis. Relying on cutoff values of less than 0.2 and more than 0.5, we could have distinguished between the presence and absence of cirrhosis with sufficient reliability to avoid a liver biopsy in half of our patients. Theoretically, application of this model in practice could be cost-saving and helpful in identifying patients with CHC who require surveillance for hepatocellular carcinoma and varices as well as closer monitoring during antiviral therapy. Clearly, our model needs to be validated by other investigators. Our results and those of similar studies underscore the need for development of noninvasive methods that reflect histological findings in patients with all forms of chronic liver disease.

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