The Role of Liver Biopsy in Chronic Hepatitis C

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Hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide, affecting 175 million people globally. Over 80% of acutely infected patients go on to develop chronicity, but only 20% to 25% will develop end-stage liver disease and its complications. The sequelae of HCV-induced chronic liver disease accounts for 8,000 to 10,000 deaths annually in the United States and is currently the leading indication for liver transplantation. To date, there are no accurate noninvasive markers of disease activity and fibrosis. Liver biopsy is indicated to exclude other forms of liver pathologies and to establish the stage of liver disease. In this study, the role of liver biopsy in chronic hepatitis C was evaluated. Additionally, we calculated a discriminant score to predict cirrhosis in chronic hepatitis C infection. Our results showed that additional diagnoses or unsuspected diagnoses are less frequent than clinicians' suspected. We confirmed that the discriminant score for predicting cirrhosis is inferior to liver biopsy. In conclusion, the majority of patients with chronic hepatitis C will require a liver biopsy, which has an important implication on staging of the liver disease, prognosis, and possibly further management options. (HEPATOLOGY 2001;33:196-200.)

The hepatitis C virus (HCV) is a major cause of chronic liver disease in the United States. The prevalence of the HCV antibody in patients in the United States is 1.8% with an estimated 74% with detectable HCV RNA.[1-3] Approximately 60% to 80% of those infected go on to develop chronic hepatitis and 20% to 30% may progress to cirrhosis.[4-6] Because of the high disease burden, health and economic consequences of HCV are significant.[6] Strategies to reduce resource utilization (*e.g.*, liver biopsy) for care of HCV-infected individuals without jeopardizing patients' clinical care and well-being are needed.

HCV infection may be discovered by abnormal serum transaminases but this is not required for the diagnosis. Positive HCV serologies (antibodies or HCV RNA) confirm the diagnosis.[4,7] In the high-risk individual with elevated aminotransferases, anti-HCV tests have a positive predictive value over 95%. These tests can be supplemented with sensitive HCV RNA testing basically establishing the diagnosis of chronic hepatitis C with viremia.[5,7,8] Liver biopsy has been recommended to exclude other liver diseases and to establish the histologic stage of liver disease. This provides an important clue for prognosis and potentially the management of patients with chronic hepatitis C.[4,9-12] Data from studies involving sequential biopsies have provided convincing evidence that the grade of fibrosis and the extent of inflammatory changes in the initial biopsy can predict the likelihood of progression to cirrhosis.[13] Moreover, fibrosis cannot be reliably predicted from currently available laboratory tests.

On the other hand, liver biopsy is an invasive procedure with associated morbidity and mortality. It also carries a significant cost of $1,500 to $2,000 per procedure. Therefore, the role of liver biopsy in patients with chronic HCV infection has increasingly been questioned.[11,14,15]

In this study, we evaluated the utility of liver biopsy in patients with chronic hepatitis C and its role in excluding other forms of liver pathology and in establishing the stage of liver disease. Furthermore, we calculated a cirrhosis discriminant score[16] to predict cirrhosis in patients with chronic hepatitis C infection.

PATIENTS AND METHODS

Patient Selection. All cases of hepatitis C seen at the Cleveland Clinic Department of Gastroenterology between January 31, 1990 and February 1, 1997 were identified. Records of patients infected with HCV who met the following inclusion criteria were reviewed: (1) an abnormal alanine transaminase (ALT) level, defined as a value greater than 40 IU/L on at least 2 separate occasions (values of ALT were not adjusted for sex and body mass index)[17]; (2) positive enzyme-linked immunosorbent assay antibody for HCV confirmed by supplemental testing either by recombinant immunoblot assay (RIBA) or HCV RNA (polymerase chain reaction or branched DNA); and (3) a liver biopsy after serologic testing was performed.

Patients with fulminant hepatic failure or clinically evident cirrhosis (ascites or hepatic encephalopathy) were excluded. Patient records were also excluded from the analysis if the patient had known cirrhosis from prior liver biopsy or was referred for liver transplantation evaluation.

Data Collection. Clinical and demographic data, laboratory data, and the clinicians' prebiopsy diagnosis (primary diagnosis and additional diagnoses) as well as clinical suspicion for cirrhosis were recorded. Prebiopsy suspicion of cirrhosis required one or more of the following: reduced platelet or white blood cell counts, prothrombin time elevation, prominent abdominal venous collaterals, and history of ascites, esophageal varices, or hepatic encephalopathy. Suspected additional diagnoses included alcohol-induced liver disease, hepatitis B, iron-induced liver disease, autoimmune disease, and nonalcoholic fatty liver disease. Information regarding former or current use of alcohol at the time of biopsy was abstracted. Up to 3 months before the liver biopsy, laboratory data were collected, which included measurements of white blood cell count, platelet count, prothrombin time, and international normalized ratio of the prothrombin time (INR), ALT/aspartate transaminase (AST) ratio, hepatitis A and B

Abbreviations: HCV, hepatitis C virus; INR, international normalized ratio; ALT, alanine transaminase; AST, aspartate transaminase; NASH, nonalcoholic steatohepatitis.

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Received April 7, 2000; accepted September 26, 2000.

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0270-9139/01/3301-0025$3.00/0
doi:10.1053/jhep.2001.20534

serologies, smooth muscle antibody titer, anti-nuclear antibody titer, anti-mitochondrial antibody titer, serum iron, ferritin, total iron binding capacity, α1 antitrypsin, ceruloplasmin, bilirubin, lactate dehydrogenase, and alkaline phosphatase levels. Physical findings and signs of cirrhosis (ascites, hepatosplenomegaly, spider angiomata) were also recorded, using a standardized liver-specific physical examination form.

A cirrhosis discriminant score based on the platelet count, ALT/AST ratio, and INR was calculated using Bonacini's method (Table 1C).[16]

The presence or absence of fibrosis and or cirrhosis in the liver biopsy specimens was recorded. All liver biopsy specimens were reviewed by experienced hepatopathologists and were scored using the histologic activity index, developed by Knodell et al.[18] This included the presence of portal and/or parenchymal inflammation, bile duct damage, steatosis, fibrosis, and cirrhosis.

Alternative and additional diagnoses that were discovered by liver biopsy were recorded. Liver biopsy was performed uniformly using a lateral intercostal approach as an outpatient procedure in a single gastrointestinal laboratory. A standard protocol was used by all operators. We used the percussion technique utilizing Tru-Cut needles (Baxter Healthcare Corp, Deerfield, IL) prior to June, 1995. After June, 1995, an ultrasound machine was introduced, and the biopsy site was selected with ultrasound guidance in conjunction with the percussion technique using Bard Monopty needles (C. R. Bard Inc, Billerica, MA). This was also used uniformly by all operators. Early and late complications of liver biopsy were recorded using a standardized nursing protocol and divided into minor complications (pain, vasovagal reaction) and major complications (clinically significant hemorrhage, bowel perforation, pneumothorax, symptoms requiring admission, and death). All patients returned for outpatient follow-up, and so major delayed complications occurring after discharge from our gastrointestinal laboratory were captured.

Statistical Analysis. Descriptive statistics were expressed as mean, median and standard deviation for continuous variables or as frequency counts and percentages for discrete data. Comparisons between cirrhotic patients and noncirrhotic patients were made using the Wilcoxon rank-sum test for continuous variables and using a χ^2 test or Fisher's exact test for categorical data. Multivariate logistic regression with forward and backward stepwise variable selection was used to examine joint effects of prognostic factors on risk of cirrhosis. Factors used in logistic regression analysis were limited to platelet count, ALT/AST ratio, and INR to avoid overfitting of the model. The odds ratio and its 95% confidence interval were calculated for each factor in the presence of the others in the final model. The Hosmer-Lemeshow χ^2 statistic was used to assess the fit of the final estimated logistic regression model relative to the observed outcome data. Receiver operating characteristic curves were used to summarize the accuracy of the logistic regression model and the clinical Bonacini score without having to choose a specific cut-off point.

RESULTS

Of all potential patients with chronic HCV who were identified from our database, 126 patients met inclusion criteria and were enrolled in the study.

Men were more frequently represented in this study (74.6%). Thirty-seven patients (29.4%) had histologic cirrhosis (Table 2). Cirrhotic patients were older than noncirrhotic patients (mean difference, 6.8 years). Race and gender data were similar between the 2 groups. Of the noncirrhotic patients, 39 of 89 (43.8%) showed chronic hepatitis alone, whereas the rest, 50 of 89 patients (56.2%), had chronic hepatitis with fibrosis. Prebiopsy prediction of cirrhosis had a sensitivity of 32.4% (12 of 37). Prebiopsy prediction of no cirrhosis had a specificity of 96.5% (82 of 85). A determination of the clinicians' suspicion of cirrhosis could not be made in 4 cases (Table 3).

A total of 111 patient records (88.1%) contained the data required to generate a cirrhosis discriminant score (Table 1B). The mean discriminant score for noncirrhotic patients was 3.4 ± 1.5, and for cirrhotic patients, 5.5 ± 1.9 (Table 1A). None of the patients without cirrhosis had a discriminant score greater than 7. Using a discriminant score greater than 7 as a threshold, the sensitivity of detecting cirrhosis was only 14.7%, but the specificity was 100%. A score of ≤3 carried a sensitivity of 85.3% and a specificity of 58.4% for the absence of cirrhosis.

Table 4 provides descriptive statistics by diagnosis for age, platelets, white blood cell count, INR, albumin, bilirubin, AST, ALT, ALT/AST ratio, γ-glutamyl transferase, ferritin, and iron. Differences between cirrhotic and noncirrhotic patients were significant for all measurements except white blood cell count and ALT.

Possible additional diagnoses were suspected prebiopsy in 47 patients. These included alcohol-induced liver disease, hepatitis B, hemochromatosis, nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, medication-induced disease, and other miscellaneous causes including graft-versus-host disease, malignancy, granulomatous disease, and cytomegalovirus hepatitis. Additional suspected diagnoses were confirmed in 3 of 47 patients (6.4%): these included hereditary hemochromatosis (n = 1), steatohepatitis (n = 1), and hepatitis B (n = 1). Unsuspected additional diagnoses were discovered by the liver biopsy in only 3 patients: NASH (n = 2) and steatosis alone (n = 1). Two of these patients were obese and 1 was also diabetic. Only 1 had no obvious risk factors for NASH.[19]

TABLE 1A. Descriptive Statistics for Bonacini Scores

Cirrhosis	n	Mean Score	SD	Median	*P* Value
Yes	34	5.5	1.9	6.0	<.001
No	77	3.4	1.5	3.0	

TABLE 1B. Summary of Discriminant Scores

Discriminant Score	Frequency	Percent of Patients
<3	21	18.9%
3-7	85	76.6%
>7	5	4.5%

TABLE 1C. Discriminant Score Calculation

Laboratory Parameter	Score						
	0	1	2	3	4	5	6
INR	<1.1	1.1–1.4	>1.4				
ALT/AST ratio	>1.7	1.2–1.7	0.6–1.19	<0.6			
Platelets 1,000/mm^3	>340	280–340	220–279	160–219	100–159	40–99	<40

TABLE 2. Patient Demographics

	Cirrhosis (n = 37)	Noncirrhotic Patients (n = 89)	P Value
Age mean ± SD	48.8 ± 9.6	42 ± 9.0	<.001
Men (%)	31 (83.8)	63 (70.8)	=.18
Race (%):			=.74
Caucasian	29 (78.4)	74 (84.1)	
African-American	6 (16.2)	11 (12.5)	
Others	2 (5.4)	3 (3.4)	
Unknown	0 (0.0)	1 (1.1)	

TABLE 3. Clinical and Histologic Diagnosis of Cirrhosis

Histologic Cirrhosis	Clinical Suspicion* of Cirrhosis	Frequency	Percent
Yes	Yes	12	9.8%
Yes	No	25	20.5%
No	Yes	3	2.5%
No	No	82	67.2%

NOTE. Sensitivity, 32.4%; specificity, 96.5%; positive predictive value, 80.0%; negative predictive value, 76.6%.
*Indeterminate in 4 patients.

Possible hemochromatosis was suspected in 7 patients based on abnormal iron studies including elevation of the transferrin saturation or serum ferritin, but was confirmed in only 1 patient. In these patients liver biopsy with iron staining and determination of a hepatic iron index were necessary to confirm or exclude the diagnosis. Newer serologic testing (HFE gene mutations) for detection of genetic hemochromatosis was not available for these patients.[20] Possible hepatitis B coinfection was suspected in 5 but confirmed in only 1 by histologic diagnosis. This patient had serologic testing that indicated resolving infection.

No major biopsy complications were reported from the liver biopsies performed. Minor complications included pain not requiring medication in 12 (9.5%), pain requiring medication in 19 (15.1%), hypotension/vasovagal reaction in 2 (1.6%), and admission to an emergency room or hospital in 4 (3.2%). There was no difference related to the method used for liver biopsy.

Table 5 provides the results from the logistic regression analysis, which contains 3 significant factors and fits the data well (goodness-of-fit P value .72; $P < .05$ indicates a poor fit). As judged by the receiver operating characteristic analyses (Fig. 1), the clinical score model performs as well as the logistic model for cirrhosis diagnosis, with the area under the curves for the logistic and clinical score models at 0.84 and 0.80, respectively. The clinical score that yielded the largest combined sensitivity and specificity was a clinical score of 3.

DISCUSSION

Liver biopsy is of unquestioned value in patients with chronic liver disease. Our study suggests that after serum-based testing indicates HCV infection, liver biopsy continues to play an important role in establishing the stage of liver disease. Our data showed that no alternative diagnoses (0 of 126) and few additional diagnoses (3 of 126), all of which consisted of variants of NASH, were provided by liver biopsy. None of these would preclude interferon-based antiviral therapy for hepatitis C.

The rate of progression of chronic HCV infection remains controversial. As recently reported, liver-related mortality in some HCV patients (especially those acquiring the infection at a young age) may be rather low.[21,22] In contrast, earlier data indicated that a large number of patients with chronic HCV hepatitis followed-up for 10 to 15 years could develop cirrho-

TABLE 4. Descriptive Statistics for Liver Biopsy Study (n = 126)

Variable	Cirrhosis Diagnosis	n	Mean	SD	Median	P Value
Age (years)	Yes	37	48.8	9.6	50.0	<.001
	No	89	42.0	9.0	40.0	
Platelet count	Yes	36	160	67	160	<.001
	No	82	222	69	218	
White blood cells	Yes	36	6.13	1.71	5.90	NS
	No	79	6.73	2.75	6.50	
INR	Yes	35	1.19	0.21	1.14	<.001
	No	83	1.03	0.10	1.01	
Albumin	Yes	35	4.1	0.5	4.2	<.001
	No	82	4.4	0.4	4.4	
Bilirubin	Yes	36	1.0	0.7	0.9	.006
	No	85	1.2	4.1	0.6	
AST	Yes	35	123	68	107	<.001
	No	85	93	81	68	
ALT	Yes	35	153	93	141	NS
	No	85	156	153	106	
ALT/AST ratio	Yes	34	1.30	0.49	1.32	<.001
	No	85	1.66	0.49	1.63	
GGT	Yes	26	134	100	109	.05
	No	58	102	112	63	
Ferritin	Yes	25	597	602	426	.03
	No	49	296	281	209	
Iron	Yes	23	144	51	136	.006
	No	53	109	52	105	

Abbreviation: NS, not significant.

TABLE 5. Multivariate Analysis of Factors Associated With a Diagnosis of Cirrhosis Among 111 Patients Undergoing Liver Biopsy

Factor	Parameter Estimate	SE Parameter Estimate	*P* Value	Adjusted Odds Ratio	95% Confidence Interval for Adjusted Odds Ratio
Platelet count (per 50 cells mm^3 decrease)	−0.382	0.190	.04	1.47	1.01, 2.12
ALT/AST ratio (per 0.5 unit decrease)	−0.640	0.268	.02	1.90	1.12, 3.21
INR (per 0.1 unit increase)	0.629	0.204	.002	1.88	1.25, 2.80

sis.[23] Age, degree of histologic inflammation, and presence of septal fibrosis with incomplete nodular regeneration were all important factors affecting the cumulative rate of progression to cirrhosis. Others have confirmed the evolution from fibrosis to cirrhosis in chronic HCV patients, particularly in patients older than 50 and in those consuming excessive alcohol (>50 g/d).[24] Although cirrhotic patients in our study were older, the exact interaction between age and fibrosis remains unclear. In addition to longer duration of infection, older patients acquiring HCV may have a more aggressive course.

A cirrhosis discriminant score can predict cirrhosis without a liver biopsy in a minority of HCV-infected patients.[16,25] A discriminant score of greater than 7 predicts cirrhosis and less than 3 predicts no cirrhosis. By using this score in our patients, liver biopsy could have been avoided in approximately 23% of patients (26 of 111). However, for the larger group (>75% [85 of 111]) with a discriminant score of 3 to 7, a liver biopsy was required to define the stage of their liver disease and to establish the presence or absence of cirrhosis. This finding has an important prognostic implication and can influence further management options of patients with chronic hepatitis C. In a recent study reported by Poynard et al.,[12] the lack of fibrosis or fibrosis limited to the portal tract was associated with favorable outcome and sustained virologic response to antiviral therapy. In this regard, discriminant score analysis is inferior to liver biopsy in establishing the presence or absence of fibrosis and/or cirrhosis, and its role in the clinical management of these patients remains limited.

Our data reaffirm the overall safety of liver biopsy in patients with hepatitis C. The most frequent complication was pain in 24.6%, which was generally mild. This rate was comparable with the expected rate of approximately 33%.[11,26-28] The fact that no serious complications were seen is likely a function of the limited number of patients enrolled in our study.

In summary, our study shows that in patients with chronic HCV, liver biopsy provides important information about the stage of liver disease. Additional diagnoses are less common than clinicians suspect. Unsuspected additional diagnoses were rare and consisted only of fatty liver disease. Only in 23%, the presence or absence of cirrhosis could reliably be predicted by the use of a clinical discriminant score. However, the majority of HCV-infected patients with a score of 3 to 7 (>75%) will still benefit from the important information contained in a liver biopsy with important implications for staging their liver disease. Additionally, the role of sequential liver biopsy in clinical research in assessing the natural history of HCV infection or the impact of therapy on the rate of progression of fibrosis remains important. In the future, development of accurate indirect markers of fibrosis (procollagen peptide III, hyaluronidase, etc.) may further refine our ability to detect fibrosis or cirrhosis without a liver biopsy. Until these markers are developed and validated, liver biopsy remains important in the majority of patients with HCV.

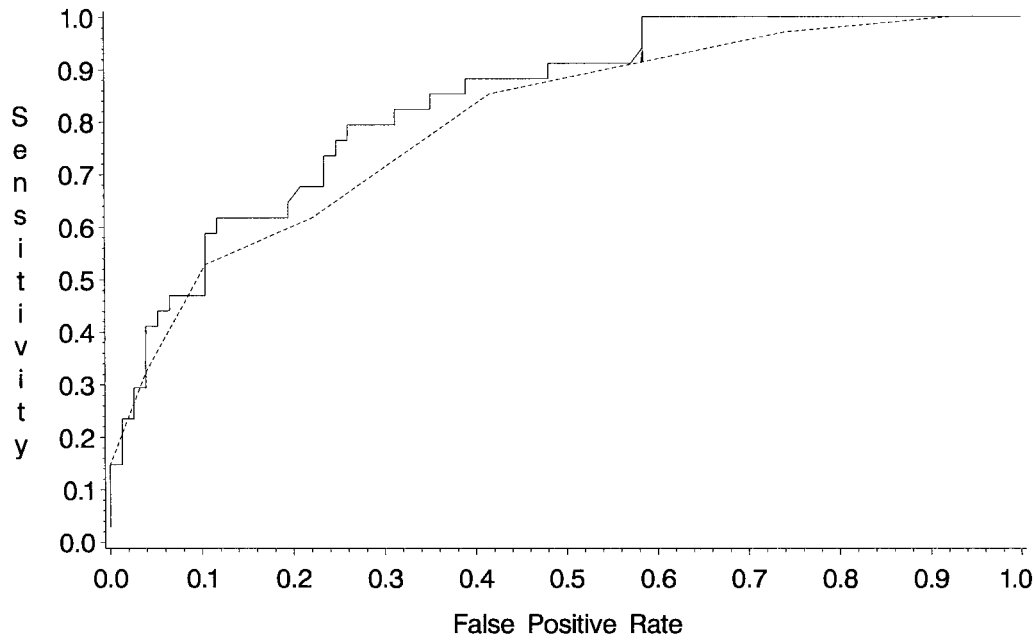

FIG. 1. Receiver operating curves for chronic hepatitis C patients. Logistic regression (*solid line*) and Bonacini score (*dotted line*) in 34 patients with cirrhosis and 77 without cirrhosis.

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