Utility of a Discriminant Score for Diagnosing Advanced Fibrosis or Cirrhosis in Patients with Chronic Hepatitis C Virus Infection

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Original contributions

Utility of a Discriminant Score for Diagnosing Advanced Fibrosis or Cirrhosis in Patients with Chronic Hepatitis C Virus Infection

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Objective: **The aim of the study was to assess the utility of a modified three-parameter cirrhosis discriminant score (CDS) for diagnosing advanced fibrosis or cirrhosis in patients with evidence of chronic hepatitis C.** ***Methods:*** **We examined liver tissue from 79 patients. Patients with a histological fibrosis score of 0-2 made up group A, and patients with a score of 3 or 4 (advanced fibrosis or cirrhosis) group B.** ***Results:*** **The modified CDS (possible total score 0-11) was derived from three laboratory parameters: platelets, ALT/AST ratio, and PT. The total score was significantly lower in group A (4.3 ± 2.0) than in group B (7.9 ± 1.4) ($p < 0.0001$). There was a positive correlation between the CDS and histological fibrosis score ($r = 0.64$, $p < 0.0001$). With 8 or above as the cutoff value, the CDS had a sensitivity of 46% and a specificity of 98% for the diagnosis of histological fibrosis scores of 3 or 4.** ***Conclusions:*** **We conclude that a three-parameter CDS is useful for identifying patients with hepatitis C and a high likelihood of cirrhosis. Patients with a CDS $\leq$7 still require histological examination to identify advanced fibrosis or cirrhosis.**

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INTRODUCTION

The diagnosis of cirrhosis in patients with chronic hepatitis C infection is of therapeutic and prognostic importance. The gold standard for the diagnosis of cirrhosis is the histological examination of liver tissue. Recently, Teran and colleagues [1] described a cirrhosis discriminant score (CDS) that appeared useful for diagnosing cirrhosis in nonalcoholic patients with chronic hepatitis. This CDS included four laboratory and two clinical variables, spider angiomas, and ascites [1] . In the present study, we simplified this score by using only laboratory variables for patients with evidence of chronic hepatitis C. We then evaluated its association with the fibrosis score, as defined by liver biopsy.

MATERIALS AND METHODS

We selected 77 consecutive patients *1*) with positive serum anti-HCV antibody by second-generation ELISA, *2*) with elevated transaminase levels, *3*) who had undergone a liver biopsy, and *4*) with available

liver biopsy tissue for review. Two additional patients had well-preserved autopsy tissue. All liver tissue samples were adequate for histological interpretation.

Exclusion criteria were decompensated liver disease (ascites, history of a variceal bleed), positive serum hepatis B surface antigen or evidence of alcoholic liver disease at histology.

All 79 liver histological slides were reviewed by one of us (S.G.) without knowledge of the laboratory data or the modified CDS. The original Histologic Activity Index score assessed the degree of bridging necrosis, intralobular degeneration, portal inflammation, and fibrosis [2] . The first three variables constitute the necroinflammation score, quantified from 0 to 18. Fibrosis is graded as follows: 0 = no fibrosis, 1 = portal fibrosis, 3 = bridging fibrosis, and 4 = cirrhosis. Because a score of 3 encompasses varying degrees of bridging fibrosis, we modified the fibrosis score as follows: 0 = no fibrosis, 1 = portal fibrosis, 2 = portal fibrosis with mild to moderate bridging fibrosis, 3 = advanced bridging fibrosis, and 4 = cirrhosis. In retrospect, all patients classified as 3 had their initial biopsy reading as "bridging fibrosis approaching cirrhosis."

Patients were divided into two groups: group A (n = 51) included patients with chronic hepatitis C virus (HCV) infection and a fibrosis score between 0 and 2 (*i.e.*, no evidence of cirrhosis), and group B (n = 28) included patients with a diagnosis of cirrhosis and a fibrosis score of 3 or 4, according to the above modification of the Histologic Activity Index [2] .

Three laboratory parameters were scored as follows: *1*) Platelets (×1000/mm ^{3}): >340 = 0, 280-339 = 1, 220-279 = 2, 160-219 = 3, 100-159 = 4, 40-99 = 5, and <40 = 6. *2*) ALT/AST ratio: >1.7 = 0, 1.2-1.7 = 1, 0.6-1.19 = 2, and <0.6 = 3. *3*) PT: <1.1 INR = 0, 1.1-1.4 INR = 1, and >1.4 INR = 2. The sum of the above

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TABLE 1 -- Comparison of Laboratory Data from Group A (Fibrosis Score 0-2) and Group B (Fibrosis Score 3 or 4)

	Group A (n = 51)	Group B (n = 28)	*p* Value
Total score	4.3 ± 2.0	7.9 ± 1.4	<0.0001
Platelet score	2.6 ± 1.3	4.0 ± 0.8	<0.0001
ALT/AST ratio	1.2 ± 0.9	2.2 ± 0.7	<0.0001
PT score	0.6 ± 0.6	1.4 ± 0.5	<0.0001

Data presented as means ± SD.

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represented the total modified CDS score with a possible numerical value of 0 to 11.

Statistics

The Student's *t* test was used for all comparisons between groups. Spearman's correlation coefficient was calculated for correlations between the modified CDS and necroinflammation and fibrosis score.

RESULTS

Seventy-nine patients with HCV infection and no evidence of alcoholic liver disease on biopsy were evaluated. Eighteen patients (22%) were also positive for antibodies to HIV. The exclusion of this subgroup did not change the results substantially. The analysis of four laboratory variables generated CDS values that ranged from 1 to 10.

Although each component of the modified CDS was statistically different in group A *versus* group B patients, the total score was the most distinct: 4.3 ± 2.0 *versus* 7.9 ± 1.4, respectively ($p < 0.0001$) (Table 1) .

Fifty of the 51 patients in group A (98%) had a modified CDS value 7. Thirteen of the 28 patients in group B (46%) had a score ≥8. Therefore, with 8 as the cutoff value above which advanced fibrosis or cirrhosis is diagnosed, the modified CDS had a sensitivity of 46% and a specificity of 98%. If a cutoff value of 7 was used, the score had a sensitivity of 86% and a specificity of 84%.

When the ALT/AST ratio alone was used to separate patients with cirrhosis from those without, a cutoff of 1 had a sensitivity of 83% and a specificity of 75% for the diagnosis of cirrhosis.

There was also a clear-cut association between the modified CDS score and the degree of fibrosis estimated at liver biopsy ($r = 0.64$, $p < 0.0001$). Higher CDS scores correlated with advanced fibrosis and cirrhosis (Fig. 1) .

On the other hand, there was no correlation between the necroinflammation score and the modified CDS.

The 28 patients with advanced fibrosis or cirrhosis (group B) were divided according to their CDS (≤7 *vs* ≥8). In the 15 patients with scores ≤7, the platelet score was significantly lower than in the 13 patients with scores ≥8 ($p < 0.001$). Although the ALT/AST ratio and PT score were also different, this difference was less marked (Table 2)

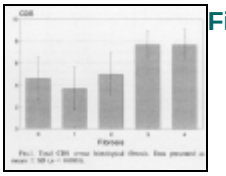

Figure 1. Total CDS *versus* histological fibrosis. Data presented as means ± SD ($p < 0.0001$).

TABLE 2 -- Comparison of Patients with Advanced Fibrosis or Cirrhosis (Fibrosis Score 3 or 4) with CDS ≤7 and Patients with Advanced Fibrosis or Cirrhosis with CDS ≤8

	Patients with CDS 0-7 (n = 15)	Patients with CDS 8-11 (n = 13)	*p* Value
Platelet score	3.5 ± 0.7	4.7 ± 0.5	<0.001
ALT/AST ratio	0.9 ± 0.4	0.6 ± 0.2	<0.01
PT score	1.2 ± 0.4	1.7 ± 0.5	<0.05

Data presented as means ± SD.

DISCUSSION

The diagnosis of cirrhosis in patients with chronic viral hepatitis is of therapeutic and prognostic importance. Patients with chronic hepatitis C without cirrhosis are the best candidates for interferon therapy, with a long-term response rate in the range of 20-25%. The presence of cirrhosis, however, inversely affects the response rate, which decreases to approximately 5% [3] . In addition, cirrhosis associated with hepatitis C is linked with an estimated 2-6% yearly rate of development of hepatocellular carcinoma [4] . Therefore, it would be useful to be able to distinguish chronic viral hepatitis without cirrhosis from chronic hepatitis with cirrhosis based on noninvasive tests. Our study modified a published CDS [1] , using only laboratory variables to generate the discriminant score. The authors of the original CDS included clinical features of liver cirrhosis, such as the presence or absence of ascites and vascular spiders, in their scoring system. However, vascular spiders are not always well formed and therefore represent a subjective criterion. The presence of ascites on physical examination, in the setting of chronic liver disease, is a strong indicator of portal hypertension and most likely liver cirrhosis. The presence of ascites, regardless of any score, would indicate cirrhosis and in general contraindicate the use of interferon as a therapeutic agent. Inversely, small amounts of ascites can be overlooked, and analogous to the

inclusion of vascular spiders, the use of ascites adds a strong element of subjectivity to the CDS as previously published [1] .

The above reasons served as the rationale for our using only the objective laboratory data, keeping unchanged the original relative scoring weight [1] . We also excluded patients with previous variceal bleeding, because this finding is a strong argument for the presence of cirrhosis. We demonstrated that high modified CDS scores ($\geq$8) predict with confidence the presence of severe fibrosis or cirrhosis (98% specificity). In addition, there was a very good correlation between the modified CDS and the degree of fibrosis at histology (Fig. 1) . The histological fibrosis scoring system we used, *i.e.*, from 0 to 4, closely parallels the recently published METAVIR system [5] . On the other hand, low scores do not rule out necessarily the presence of cirrhosis (48% sensitivity). Patients with CDS values <8 still require a liver biopsy to determine the presence of cirrhosis.

When we examined the entire cohort with advanced fibrosis or cirrhosis (group B), we found that patients with cirrhosis and scores <8 had significantly lower platelet scores (*i.e.*, higher platelet counts) than patients with cirrhosis and a higher CDS. The reason for this is unclear. We speculate that this finding might be due to a greater degree of hypersplenism. Other parameters, such as ALT/AST ratio and PT, were less dramatically different. These findings have two possible implications. First, in patients with cirrhosis and a score $\leq$8, portal hypertension may be less pronounced. Second, a higher platelet level may make these patients more suitable candidates for interferon therapy.

Interestingly, a recent abstract [6] showed that an AST/ALT ratio > 1 (in our study, an ALT/AST ratio < 1) was a good predictor of cirrhosis in patients with chronic hepatitis C. However, using our patients' data, we found 12 cases with an ALT/AST ratio < 1 and a fibrosis score $\leq$2; *i.e.*, this ratio had a specificity of 75%.

The finding of an association between an ALT/AST ratio < 1 and liver cirrhosis is not new, given that this association was found to have a 35% sensitivity and 97% specificity for the diagnosis of cirrhosis in nonalcoholic patients with chronic hepatitis B virus infection [7] . This change seems to occur because of a concomitant decline in serum ALT levels and increase in serum AST levels during the progression of chronic hepatitis [7] .

In summary, a three-parameter CDS using an ALT/AST ratio, PT, and platelet count correlated well with the degree of hepatic fibrosis at liver biopsy in patients with HCV infection. A score $\geq$8 may be useful in identifying advanced fibrosis or cirrhosis in patients with chronic HCV infection and has a specificity of 98%. This may obviate the need for liver biopsy in these patients, who have more abnormal coagulation parameters, thus making it possible to avoid the potential complications of this procedure. Patients with scores $\leq$7 still require histological examination of the liver to identify advanced fibrosis or cirrhosis.

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