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Predicting Clinical and Histological Outcomes Based on Standard Laboratory Tests In Advanced Chronic Hepatitis C

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Abstract

Background & Aims—Predictors of clinical outcomes and histological progression among patients with chronic hepatitis C and advanced fibrosis are poorly defined. We developed statistical models to predict clinical and histological outcomes in such patients.

Methods—Baseline demographic, clinical, and histological data from Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial participants were subjected to multivariate analyses to determine their ability to predict clinical outcomes (ascites, spontaneous bacterial peritonitis, Child-Turcotte-Pugh score ≥ 7 on two consecutive visits, variceal bleeding, hepatic encephalopathy, and liver-related death) and histological outcome (≥ 2 -point increase in Ishak fibrosis stage) during the 3.5 years of the trial.

Results—Of 1,050 randomized patients, 135 had one or more clinical outcomes a median of 23 (range 1–45) months after randomization. Factors associated with a clinical outcome in multivariate analyses were higher AST/ALT ratio, lower albumin, lower platelet count, higher total bilirubin, and more advanced Ishak fibrosis score ($p < 0.0001$). The cumulative 3.5-year incidence of a clinical outcome was 2% in the lowest and 65% in the highest risk group. Of 547 patients without cirrhosis at baseline and at least one follow-up biopsy, 152 had a histological outcome. Independent variables associated with a histological outcome were higher body mass index, lower platelet count, and greater hepatic steatosis ($p < 0.0001$).

Conclusion—In patients with chronic hepatitis C and advanced fibrosis, risk of clinical complications and fibrosis progression during 3.5 years can be predicted using baseline laboratory tests and histological data. Our models may be useful in counseling patients and determining the frequency of monitoring.

Keywords

Chronic hepatitis C; Clinical outcome; Histological outcome

INTRODUCTION

Chronic hepatitis C is an important cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC)¹ and the leading indication for liver transplantation in adults worldwide. Wise et al.² reported an increase in premature death related to chronic hepatitis C during the decade spanning 1995–2004, and mathematical models predict that the number of deaths related to chronic hepatitis C will more than double in the next decade.³ Among patients with chronic hepatitis C, estimates suggest that cirrhosis will develop in 10% to 25% and HCC in 1% to 5% over a period of 20–30 years.⁴ A reliable estimate of the likelihood of disease progression is important for advising patients of their prognosis, including risk of hepatic decompensation, HCC, and death. Because surveillance for gastroesophageal varices and HCC are indicated in patients with advanced liver disease, and because cirrhotic patients merit more intensive monitoring to ensure timely referral for liver transplantation, clinicians require tests that can reliably predict clinical decompensation and histological progression of liver disease.

No tests are currently available to predict risk of decompensation in patients with chronic hepatitis C who have advanced fibrosis or cirrhosis. The Child-Turcotte-Pugh (CTP) score and the model for end-stage liver disease (MELD) are frequently used to assess this risk. However,

the CTP score which was developed originally to predict operative risk of mortality associated with surgical portosystemic shunt surgery,⁵ was never validated for the purpose of predicting nonoperative survival or clinical outcome. Similarly, MELD which was designed to predict the survival of patients undergoing a transjugular intrahepatic portosystemic shunt, is used primarily to predict 90-day mortality of patients awaiting liver transplantation.⁶ The results of some studies suggest a poor correlation between MELD score and the development of late complications of cirrhosis, such as ascites and hepatic encephalopathy.^{7, 8}

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial was a randomized, controlled study to determine if long-term peginterferon therapy could reduce the risk of progression to cirrhosis, decompensated liver disease, and/or HCC in patients with chronic hepatitis C who had advanced fibrosis or cirrhosis.⁹ This large, prospectively followed cohort provided an ideal setting for the derivation of a model to predict clinical outcomes and progression to cirrhosis. The aims of this analysis were to identify baseline demographic, clinical, laboratory, virological, and histological factors associated with clinical outcomes and histological progression to cirrhosis and to develop models that predict clinical decompensation or progression of fibrosis based on demographic, histological and routinely available laboratory tests.

PATIENTS AND METHODS

The design of the HALT-C Trial has been described previously.⁹ Briefly, patients with previous nonresponse to standard interferon therapies who had advanced hepatic fibrosis on liver biopsy (Ishak fibrosis score ≥ 3)¹⁰ and no history of hepatic decompensation or HCC were treated with peginterferon alfa-2a (180 μ g weekly) and ribavirin (1–1.2 g/day) (*lead-in patients*). Patients who had detectable serum HCV RNA at treatment week 20 met the definition of nonresponders and were randomized at week 24 to maintenance therapy (peginterferon alfa-2a 90 μ g weekly) or no treatment for the next 3.5 years. Patients in whom serum HCV RNA was undetectable at week 20 met the definition of responders and continued combination therapy for a total of 48 weeks; however, “responder” patients in whom detectable HCV RNA appeared during treatment (*breakthrough*) or after stopping treatment (*relapse*) were offered enrollment into the randomized trial. “Express” patients were nonresponders to peginterferon/ribavirin who received therapy outside the HALT-C Trial, i.e., were not enrolled in the lead-in phase of the trial, and were enrolled directly into the randomized phase (Figure 1).

For lead-in patients, the baseline liver biopsy was performed at least 2 months following the last course of interferon therapy and within 12 months of enrollment. For express patients, a liver biopsy must have been performed within 18 months before randomization and at least 8 weeks after the end of the previous course of peginterferon and ribavirin. Liver biopsies were repeated 1.5 and 3.5 years after randomization. All biopsies were reviewed for inflammation, fibrosis, and other histological features, including steatosis, by a panel of hepatic pathologists. Inflammation was graded according to an 18-point histology activity index (HAI), and fibrosis was staged according to a 7-point scale as proposed by Ishak.¹⁰ Hepatic steatosis was graded based on the percentage of hepatocytes with fat as 0 (<1%), 1 (1%–5%), 2 (5%–33%), 3, (33%–67%), and 4 (>67%). The mean time from baseline laboratory tests to randomization was 162 days for lead-in patients, 516 days for breakthrough/relapse patients, and 7 days for express patients.

Assessment of clinical and histological outcomes

Patients were evaluated every 3 months during the 3.5 years of the randomized trial. Blood counts, liver blood test panel, and serum alpha fetoprotein (AFP) were tested at the local clinical center at each visit. Lead-in patients had an ultrasound examination of the liver 20 weeks and 12 months after enrollment and then every 12 months. Express patients had ultrasounds 6

months after enrollment and then every 12 months. Randomized subjects underwent esophagogastroduodenoscopy at the time of randomization and again at 1.5 years if they had varices or at 3.5 years if they did not have varices on the baseline endoscopy. For this analysis, treated and untreated patients from the randomized phase of the trial were combined, because the results of the trial showed that maintenance, low-dose peginterferon had no significant effect on clinical outcomes or histological progression.¹¹

Pre-defined clinical outcomes included an increase in CTP score to ≥ 7 on two consecutive occasions 3 months apart, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and/or death. For this analysis, HCC was excluded as a clinical outcome; our intent was to identify a model that would predict disease progression, but the pathogenesis of HCC was felt to be different from that of the other assessed clinical outcomes. Furthermore, because HCC can occur in the absence of cirrhosis or decompensated liver disease, the timing of its occurrence can be independent of disease progression.^{12–14} Diagnostic criteria were established for each of the clinical outcomes, and an Outcomes Review Panel of three rotating investigators from the 10 HALT-C Trial clinical centers reviewed all outcome reports. Only clinical outcomes deemed to have met the predefined criteria were included in this analysis.

The trial was designed to enroll patients with Ishak fibrosis stage 3; however, in 72 patients, a biopsy taken near the time of enrollment was interpreted to show Ishak stage 2, despite the fact that they had had an earlier biopsy showing Ishak fibrosis stage ≥ 3 . Histological outcome was defined as an increase in Ishak fibrosis score by ≥ 2 points on at least one of the follow-up biopsies 1.5 or 3.5 years after randomization (from stage 2 to 4–6, stage 3 to 5–6, or stage 4 to 6). Patients in whom a biopsy pair was not available were excluded from this analysis ($n=75$). The mean biopsy length was 1.8 cm (median 1.6, range 0.4 to 3.4 cm), and 13% were fragmented.

Statistical Analyses

We used multivariable time-to-event analytic methods to explore factors associated with time to the first clinical outcome and time to histological outcome as indicated by a ≥ 2 -point increase in Ishak fibrosis score, which was coded as a continuous variable (2, 3, 4, 5, 6). First, individual factors were explored in relation to each outcome. For multivariable models, factors that were associated with the outcome on bivariate analysis with a p value < 0.1 and factors previously reported to be associated with outcomes (age, race, gender and BMI) were included in the initial multivariable analysis, as was treatment assignment. Variables that were no longer statistically significant in the multivariate analyses were deleted to create the final models.

For time to first clinical outcome, we used Cox proportional hazards regression analysis. Data were censored at the patient's last follow-up visit or at 1400 days (3.8 years) after randomization, whichever occurred first. The 3.8 rather than 3.5 year mark provided a window period for performance of the 3.5 year liver biopsy and for confirming a CTP score ≥ 7 that first occurred at the 3.5 year visit. We used the resulting individual estimates of the final model to divide the sample into four risk groups. Cumulative incidence rates of clinical outcomes among these groups were determined by Kaplan Meier analysis. For time to histological progression, we used the complementary log-log regression analysis since the time-to-event analysis was grouped (1.5 and 3.5 years of follow-up). All analyses were performed at the Data Coordinating Center (New England Research Institutes, Watertown, MA) with SAS statistical software release 9.1 (SAS Institute, Cary, NC).

RESULTS

Clinical Outcome

A total of 1,050 patients with chronic hepatitis C and advanced fibrosis or cirrhosis were followed for predefined clinical outcomes reflecting the presence of decompensated liver disease over the 3.5 years of the randomized phase of the HALT-C Trial, and, in 135 (13%), a clinical outcome developed. An increase in CTP score to ≥ 7 on two successive study visits was the most frequently observed initial outcome, accounting for two-thirds of the clinical outcomes (Table 1). In 48% of patients with a CTP score ≥ 7 as their first outcome, at least one event representing hepatic decompensation (death, ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy) developed subsequently a median of 8.2 (range 0.6–37.7) months after first achieving an increase in CTP score to >7 . The most frequent initial decompensation event was the development of ascites, accounting for 16% of outcomes.

Baseline demographic, laboratory, and liver histology data and univariate hazard ratios for the 135 patients who had a clinical outcome and the 915 patients who did not are shown in Table 2. On univariate analysis clinical and laboratory measures associated with subsequent hepatic decompensation ($p < 0.05$) included higher body mass index (BMI), lower cigarette consumption, treatment stratification (being a lead-in and express patients versus breakthrough/relapser) and the following laboratory results: increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST/ALT ratio, total bilirubin, International Normalized Ratio (INR) of prothrombin time, AFP, iron saturation, and ferritin; and lower HCV RNA, albumin, platelets, creatinine, and white blood cell count (WBC). For histological and endoscopic variables, periportal inflammation, composite histological activity index (HAI) scores, Ishak fibrosis scores, and the presence of esophageal varices were associated with decompensation. Treatment assignment was not associated with a clinical outcome.

To determine which variables were independent predictors of clinical outcomes, we first included baseline laboratory variables from the univariate analysis, omitting histological or endoscopic variables. Higher AST/ALT ratio, higher total bilirubin concentration, lower albumin concentration, and lower platelet count were associated with increased risk in a multivariate Cox proportional hazards model (Table 3, Model a). With the addition of histological and endoscopic information, we found that only Ishak fibrosis score was associated with risk of clinical outcome. The inclusion of the Ishak fibrosis score led to a modest attenuation of the $\log_{10}$ AST/ALT ratio HR (from 3.34 to 3.06) and had no effect on the association with the other laboratory measures (Table 3, Model b).

Breakthrough/relapser patients may have benefited from a longer duration of combination therapy prior to randomization (48 weeks compared to 24 weeks for lead-in and express patients). To address this issue we performed a second analysis controlling for enrollment status (breakthrough/relapser versus lead-in and express patients). Breakthrough/relapser was significant in model a (HR 0.41, p -value 0.02) but not model b. All the other previously identified variables remained significant in both models with minor changes in the HR (data not shown). If breakthrough/relapsers were excluded from the analysis, the previously identified variables in model a remained unchanged but the HR for $\log$ AST/ALT decreased from 3.34 to 3.0 and for total bilirubin increased from 1.82 to 2.13; the HRs for the other variables remained the same (Table 3). Interestingly, in model b, Ishak fibrosis was just below statistical significance ($p = .06$, HR decreased from 1.31 to 1.18) when breakthrough/relapsers were excluded.

We found a significant interaction between treatment (treatment group versus control group) and total bilirubin on the association with clinical outcome in both models a and b. Total

bilirubin had a stronger effect in the control group compared to the treatment group with a hazard ratio of 3.12 in the control group and 1.29 in the treatment group (model a) and 3.05 in the control group and 1.41 in the treatment group (model b). Separating the groups into either fibrosis/cirrhosis strata or including patients with HCC as the first primary outcome (n=27) resulted in only minor differences of the variables associated with clinical decompensation in univariate analysis (data not shown). Inclusion of patients whose first primary outcome was HCC had a minimal effect on hazard ratios in the multivariate analysis (log AST/ALT HR decreased from 3.34 to 2.36, total bilirubin decreased from 1.82 to 1.79, while HR for albumin 0.20 to 0.21 and platelets 0.59 to 0.59 were unchanged).

The model to predict clinical outcome using only baseline laboratory variables (Model a) is represented by $R_a = 1.21 \cdot \log_{10}(\text{AST/ALT}) + 0.60 \cdot \text{total bilirubin (mg/dl)} - 1.60 \cdot \text{albumin (g/dl)} - 0.52 \cdot \text{platelets (per mm}^3\text{)}/50$, where R denotes the linear predictor portion of the equation. Ranges of R within a risk group for this model and for Model b (including the Ishak fibrosis score) are provided in Table 4. The lowest risk group (lowest 50% of patients) was associated with a risk of decompensation of 2%, while the highest risk group (top 10% of patients) was associated with a risk of hepatic decompensation of 65% over 3.5 years (Table 4, Model a, Figure 2). An example of the use of the model is provided as a footnote to Table 4.

Histological Outcome (≥ 2 -point increase in Ishak fibrosis score)

A second analysis was performed to determine clinical predictors of a ≥ 2 -point increase in Ishak fibrosis score among patients without cirrhosis (Ishak fibrosis score < 5) at baseline. For this analysis, 72 patients with Ishak stage 2, 315 with Ishak stage 3, and 160 with Ishak stage 4 at baseline who had at least one of the two subsequent protocol biopsies were included. Of these 547 patients, 529 underwent liver biopsy at 1.5 years, 460 underwent liver biopsy at 3.5 years and 443 had both follow-up biopsies. One hundred and fifty-two (28%) patients experienced a ≥ 2 -point increase in Ishak fibrosis score. Baseline data in the 152 patients who had a ≥ 2 -point increase in Ishak fibrosis score and those who did not are shown in Table 5. Features associated with a histological outcome on univariate analysis were higher BMI; higher ALT, AST, AST/ALT ratio, alkaline phosphatase, total bilirubin, INR, iron saturation, ferritin, and AFP; as well as lower albumin, platelet count, and WBC count. In addition, less portal inflammation and greater steatosis on baseline liver biopsy and the presence of esophageal varices were associated in the univariate analysis with ≥ 2 -point increases in fibrosis score. On multivariate analysis, high BMI and low platelet count were the only noninvasive measures that were associated with a ≥ 2 -point increase in Ishak fibrosis score (Table 6). No evidence of interaction between these variables and treatment assignment was observed. With the addition of findings from invasive testing, only hepatic steatosis was associated with a ≥ 2 -point increase in Ishak fibrosis score (Table 6). Inclusion of hepatic steatosis attenuated the effect of BMI in the multivariate model (data not shown).

Platelet count had a nonlinear relationship with a ≥ 2 -point increase in Ishak fibrosis score, such that including a quadratic term for platelets (platelet count squared) provided a better indication of the effect of platelet count than platelet count itself. This relationship is demonstrated in Table 7, in which we found a strong association of platelet count with subsequent ≥ 2 -point increase in Ishak fibrosis score for platelet counts less than $150,000/\text{mm}^3$, but no association for platelet count $> 150,000/\text{mm}^3$. The final model to predict the risk of a ≥ 2 -point increase in Ishak fibrosis score is shown in Table 6. Patients with a low platelet count may have been understaged on the initial liver biopsy. To address the issue of sampling error, we excluded patients with a baseline platelet count $< 100 \text{ K}/\text{mm}^3$ (n=35) from the analysis. This had no effect on the variables identified in the univariate analysis and in the multivariate model to predict a two-point increase in Ishak fibrosis score. The HR remained almost unchanged for all the

variables (BMI 1.03 to 1.03, platelets/50K/mm³ 0.26 to 0.23, hepatic steatosis 1.37 to 1.35 and platelets/50K/mm³ squared 1.12 to 1.14)

DISCUSSION

Clinical outcomes developed in 13% and histological outcomes in 28% of subjects with advanced chronic hepatitis C followed in the HALT-C Trial for 3.5 years. Based upon baseline data obtained from these patients, we developed separate models to predict clinical and histological outcomes. The best model to predict clinical outcomes consisted of 4 variables: log₁₀ AST/ALT ratio, platelet count, total bilirubin, and albumin. The model to predict histological outcome included baseline BMI, platelet count, and hepatic steatosis.

In several studies, prognostic factors for hepatic decompensation (excluding HCC) have been examined in patients with HCV-related cirrhosis. Independent factors associated with decompensation in these studies included older age at infection, higher baseline bilirubin level, lower albumin level, lower platelet count, stigmata of chronic liver disease on physical examination, the presence of esophageal varices and absence of interferon therapy.^{15–20} Differences in predictive factors identified in our prospective study (higher baseline log₁₀ AST/ALT ratio, total bilirubin, lower platelet count, and lower albumin) compared to the other studies may have resulted from use of different definitions of hepatic decompensation, from the limitations of mostly retrospective studies, and from differences in patient populations between other studies and ours. For example, the HALT-C Trial population included participants with advanced fibrosis or cirrhosis but no patients with earlier histological stages, while some of the previous studies did include patients with less advanced histological disease.

Interestingly, despite dissimilarities among previous studies and this one, baseline serum bilirubin, albumin, and platelet count were identified consistently as independent factors associated with hepatic decompensation or the development of HCC. These variables are recognized surrogate markers of disease severity, reflecting either derangements in hepatic synthetic (albumin) and excretory (bilirubin) function or severity of portal hypertension (platelet count). Although previously shown to be useful in the diagnosis of cirrhosis,^{21, 22} AST/ALT ratio has not been reported previously to be predictive of clinical decompensation. Disease modifying variables, e.g., age and alcohol use were not identified in the model, probably because they were outweighed by variables that were associated with disease severity, the age range of the HALT-C cohort was narrow, and few individuals continued to drink alcohol after enrollment into the study. The addition of endoscopic data (i.e., presence of esophageal varices) and of liver biopsy data did not improve significantly the accuracy of the model to predict a clinical outcome. Failure of liver fibrosis to predict clinical outcome may reflect sampling error associated with liver biopsy, suggesting that laboratory tests may be more reliable than histology for predicting clinical outcomes.

This clinical model could prove useful in determining how to allocate resources for patient monitoring. Because the prognosis of patients with HCV-related compensated cirrhosis is so variable—excellent in some studies (80% 10-year survival¹⁵) and poor in others such as ours, (in which decompensation occurred in approximately a third of patients followed prospectively for 3.5 years¹¹) potentially those at highest risk of decompensation could be monitored more intensively, while those with lower risk scores could undergo less frequent monitoring.

Previous cross-sectional liver-biopsy studies (in which a single liver biopsy is correlated with laboratory features) have identified male gender, alcohol consumption >50g per day, and age >40 years as significant correlates of advanced fibrosis,^{23, 24} while paired liver-biopsy studies (in which histology is assessed at two points in time) have identified older age, higher serum ALT, more severe necroinflammatory activity, and higher baseline fibrosis stage as predictors

of progression of fibrosis. None of these variables, however, predicted histological outcome in the present analysis.^{25, 26} Instead, higher baseline BMI, lower platelet count, and greater hepatic steatosis were independent predictors of a >2-point increase in liver fibrosis during the observation period in this trial. The difference between our findings and those in other studies may be related to how histological outcome was assessed in the HALT-C Trial (≥ 2 increase in Ishak fibrosis stage) compared to the approach in other studies (1-point increase in fibrosis stage). Furthermore, other studies included patients with a spectrum of fibrosis stages, as opposed to the HALT-C Trial, which was confined to patients with more advanced liver disease. Finally, not all previous studies examined BMI or steatosis.

Obesity has been associated with more rapid fibrosis progression. Obesity may promote fibrogenesis via proinflammatory cytokines,²⁷ insulin resistance, or hepatic steatosis.^{28–32} In a separate analysis of weight related features (including glucose and insulin levels, BMI, and histological features of fatty liver) among the HALT-C Trial cohort, we showed that hepatic steatosis was associated with an increased rate of outcomes among patients with bridging fibrosis but not cirrhosis.³³ This analysis extends those findings by demonstrating that hepatic steatosis was a predictor of fibrosis progression independent of laboratory markers for liver disease severity. Together, the results of the HALT-C Trial add to the growing evidence that obesity and hepatic steatosis are linked to disease progression.^{31, 34–38} These findings raise the question of whether weight loss might slow fibrosis progression, which merits confirmation in prospective studies.

Low baseline platelet count was the only predictive variable present in both clinical and histological progression models, probably because thrombocytopenia is such a dominant indicator of advanced disease, reflecting both portal hypertension (splenic sequestration) and decreased hepatic synthetic function (thrombopoietin production). The relationship between platelet count and fibrosis progression was not linear in the complementary log-log model; instead, our data showed that the rate of histological outcomes remained constant as the platelet count decreased from the normal range to 150 K/mm³ but increased sharply as the platelet count fell below this value (Table 7). We cannot discount the possibility, however, that the rapidity of fibrosis progression observed in patients starting with a low platelet count was an artifact, confounded by the presence of cirrhosis which was not detected on the baseline liver biopsy. Exclusion of these patients from the analysis resulted in a minimal change in the point estimates of the model to predict a two-point increase in fibrosis.

The advantages of the model we derived for predicting clinical progression are its derivation in a prospective, rather than retrospective, trial and its reliance on standard laboratory tests. If our model can be confirmed in other populations, a simple web-based calculator could be made available, as is the case for calculating MELD scores, which should allow clinicians to make a rapid assessment of the risk for hepatic decompensation, enhancing their ability to counsel patients about prognosis and to plan an appropriate monitoring schedule.

Our study has several limitations. Because half of our patients received low-dose peginterferon alfa-2a for 3.5 years, potentially, therapy could have confounded our analyses; however, because maintenance therapy was shown to have no effect on clinical or histological outcomes in the trial,¹¹ and treatment was shown in a post hoc exploratory analysis not to have any significant effect on the identified baseline variables including serum ALT, total bilirubin, albumin and platelet count,¹¹ we felt justified in combining patients receiving maintenance peginterferon and untreated control patients in the analysis. We also performed several analyses to control for any potential effect of treatment on outcomes. Breakthrough/relapsers were the subgroup who could have benefited from longer treatment. However, controlling for or excluding breakthrough/relapser had minor effects on both the clinical and histological models. Also, potentially influencing the timing of complications was the variability of intervals

between the baseline laboratory values and the baseline biopsy and between baseline laboratory values and the time of randomization. A small percentage of patients withdrew prior to completion of the study. Because we do not know the outcome of these patients, we cannot assess how this may have influenced the final model. Finally, whether these models might be applied to patients with milder degrees of liver disease remains to be established.

In conclusion, we have developed models based on standard laboratory tests and histological assessment to predict clinical or histological progression in patients with chronic hepatitis C and advanced liver disease. The clinical model in particular can be used to estimate the risk of future hepatic decompensation, allowing more intense monitoring and early detection of hepatic complications in those at highest risk for these outcomes. Our models should be validated in other cohorts and, if confirmed, may aid in assessing prognosis in patients with chronic hepatitis C and advanced hepatic fibrosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HALT-C	hepatitis C antiviral long-term treatment against cirrhosis
AST	aspartate aminotransferase
ALT	alanine aminotransferase
CTP	Child-Turcotte-Pugh
MELD	model for end-stage liver disease
HCC	hepatocellular carcinoma
TPI	two-point increase
HCV RNA	hepatitis C virus ribonucleic acid
AFP	alfa fetoprotein
BMI	body mass index
INR	International Normalized Ratio
WBC	white blood cell
HAI	histological activity index

References

1. Williams R. Global challenges in liver disease. *Hepatology* 2006;44:521–6. [PubMed: 16941687]
2. Wise M, Bialek S, Finelli L, Bell BP, Sorvillo F. Changing trends in hepatitis C-related mortality in the United States, 1995–2004. *Hepatology* 2008;47:1128–35. [PubMed: 18318441]
3. Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* 2000;31:777–82. [PubMed: 10706572]
4. Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002;36:S35–46. [PubMed: 12407575]
5. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–9. [PubMed: 4541913]
6. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864–71. [PubMed: 10733541]

7. Yoo HY, Edwin D, Thuluvath PJ. Relationship of the model for end-stage liver disease (MELD) scale to hepatic encephalopathy, as defined by electroencephalography and neuropsychometric testing, and ascites. *Am J Gastroenterol* 2003;98:1395–9. [PubMed: 12818287]
8. Huo TI, Lin HC, Wu JC, Hou MC, Lee FY, Lee PC, Chang FY, Lee SD. Limitation of the model for end-stage liver disease for outcome prediction in patients with cirrhosis-related complications. *Clin Transplant* 2006;20:188–94. [PubMed: 16640525]
9. Lee WM, Dienstag JL, Lindsay KL, Lok AS, Bonkovsky HL, Shiffman ML, Everson GT, Di Bisceglie AM, Morgan TR, Ghany MG, Morishima C, Wright EC, Everhart JE. Evolution of the HALT-C Trial: pegylated interferon as maintenance therapy for chronic hepatitis C in previous interferon nonresponders. *Control Clin Trials* 2004;25:472–92. [PubMed: 15465617]
10. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;22:696–9. [PubMed: 7560864]
11. Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, Lee WM, Lok AS, Bonkovsky HL, Morgan TR, Ghany MG, Morishima C, Snow KK, Dienstag JL. Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon. *N Engl J Med* 2008;359:2429–2441. [PubMed: 19052125]
12. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999;131:174–81. [PubMed: 10428733]
13. Okanoue T, Itoh Y, Minami M, Sakamoto S, Yasui K, Sakamoto M, Nishioji K, Murakami Y, Kashima K. Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group. *J Hepatol* 1999;30:653–9. [PubMed: 10207807]
14. Lok AS, Seeff LB, Morgan TR, Di Bisceglie AM, Sterling RK, Curto TM, Everson GT, Lindsay KL, Lee WM, Bonkovsky HL, Dienstag JL, Ghany MG, Morishima C, Goodman ZD. Incidence of Hepatocellular Carcinoma and Associated Risk Factors in Hepatitis C-Related Advanced Liver Disease. *Gastroenterology*. 2008
15. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW, Realdi G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463–72. [PubMed: 9024300]
16. Serfaty L, Aumaitre H, Chazouilleres O, Bonnard AM, Rosmorduc O, Poupon RE, Poupon R. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998;27:1435–40. [PubMed: 9581703]
17. Hu KQ, Tong MJ. The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. *Hepatology* 1999;29:1311–6. [PubMed: 10094980]
18. Benvegnu L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004;53:744–9. [PubMed: 15082595]
19. Khan MH, Farrell GC, Byth K, Lin R, Weltman M, George J, Samarasinghe D, Kench J, Kaba S, Crewe E, Liddle C. Which patients with hepatitis C develop liver complications? *Hepatology* 2000;31:513–20. [PubMed: 10655279]
20. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, Del Ninno E, Morabito A, Colombo M. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. *Hepatology* 2006;43:1303–10. [PubMed: 16729298]
21. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 1998;93:44–8. [PubMed: 9448172]

22. Bonacini M, Hadi G, Govindarajan S, Lindsay KL. Utility of a discriminant score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 1997;92:1302–4. [PubMed: 9260794]
23. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997;349:825–32. [PubMed: 9121257]
24. Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Croce LS, Mazzoran L, Masutti F, Cristianini G, Tiribelli C. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. *Gut* 1999;44:874–80. [PubMed: 10323892]
25. Ghany MG, Kleiner DE, Alter H, Doo E, Khokar F, Promrat K, Herion D, Park Y, Liang TJ, Hoofnagle JH. Progression of fibrosis in chronic hepatitis C. *Gastroenterology* 2003;124:97–104. [PubMed: 12512034]
26. Ryder SD, Irving WL, Jones DA, Neal KR, Underwood JC. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. *Gut* 2004;53:451–5. [PubMed: 14960533]
27. Jonsson JR, Barrie HD, O'Rourke P, Clouston AD, Powell EE. Obesity and steatosis influence serum and hepatic inflammatory markers in chronic hepatitis C. *Hepatology* 2008;48:80–7. [PubMed: 18571785]
28. Moucari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, Sobesky R, Martinot-Peignoux M, Maylin S, Nicolas-Chanoine MH, Paradis V, Vidaud M, Valla D, Bedossa P, Marcellin P. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008;134:416–23. [PubMed: 18164296]
29. Fartoux L, Poujol-Robert A, Guechot J, Wendum D, Poupon R, Serfaty L. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 2005;54:1003–8. [PubMed: 15951550]
30. Conjeevaram HS, Kleiner DE, Everhart JE, Hoofnagle JH, Zacks S, Afdhal NH, Wahed AS. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. *Hepatology* 2007;45:80–7. [PubMed: 17187406]
31. Leandro G, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, Colloredo G, Adinolfi LE, Asselah T, Jonsson JR, Smedile A, Terrault N, Pazienza V, Giordani MT, Giostra E, Sonzogni A, Ruggiero G, Marcellin P, Powell EE, George J, Negro F. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology* 2006;130:1636–42. [PubMed: 16697727]
32. Fartoux L, Chazouilleres O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. *Hepatology* 2005;41:82–7. [PubMed: 15690484]
33. Everhart JE, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT, Bonkovsky HL, Ghany MG. Weight-Related Effects on Disease Progression in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial. *Gastroenterology*. 2009
34. Hu KQ, Kyulo NL, Esrailian E, Thompson K, Chase R, Hillebrand DJ, Runyon BA. Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. *J Hepatol* 2004;40:147–54. [PubMed: 14672626]
35. Friedenbergs F, Pungpapong S, Zaeri N, Braitman LE. The impact of diabetes and obesity on liver histology in patients with hepatitis C. *Diabetes Obes Metab* 2003;5:150–5. [PubMed: 12681021]
36. Younossi ZM, McCullough AJ, Ong JP, Barnes DS, Post A, Tavill A, Bringman D, Martin LM, Assmann J, Gramlich T, Mullen KD, O'Shea R, Carey WD, Ferguson R. Obesity and non-alcoholic fatty liver disease in chronic hepatitis C. *J Clin Gastroenterol* 2004;38:705–9. [PubMed: 15319656]
37. Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol* 2002;97:2408–14. [PubMed: 12358265]
38. Lo Iacono O, Venezia G, Petta S, Mineo C, De Lisi S, Di Marco V, Rodolico V, Amato M, Ferraro D, Giordano C, Almasio PL, Craxi A. The impact of insulin resistance, serum adipocytokines and visceral obesity on steatosis and fibrosis in patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2007;25:1181–91. [PubMed: 17451564]

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¹=study concept and design

²=acquisition of data

³=analysis and interpretation of data

⁴=drafting of manuscript

⁵=critical revision of manuscript

⁶=statistical analyses

⁷=obtained funding

Section B

In addition, many of the HALT-C Trial investigators have other associations with industry relating to the area of hepatitis C, and, to achieve the highest level of disclosure, we list these for you as well.

A. S. F. Lok: Schering-Plough Corporation – Consultant and receives research support. Vertex Pharmaceuticals – consultant. Idenix Pharmaceuticals – receives research support. Eisai Pharmaceuticals – receives research support.

G. T. Everson receives research support from Schering-Plough, Pharmasset, GlobeImmune, Source, Novartis/Human Genome Sciences, and GlaxoSmithKline; and is a consultant and receives research support from Vertex Pharmaceuticals.

W. M. Lee receives research support from Aegerion, GlobeImmune, Orasure, Schering-Plough, Siemens Diagnostics, and Vertex Pharmaceuticals.

A.M. Stoddard: Equity interest in Johnson & Johnson, Procter & Gamble, Bristol-Myers Squibb, and Elan.

R. K. Sterling is a consultant and on the speaker's bureau for Schering-Plough; is on an advisory board for Vertex Pharmaceuticals; and is a consultant and receives research support from Wako Chemicals USA.

A. M. Di Bisceglie is a consultant, on the speaker's bureau and receives research support from Idenix Pharmaceuticals; is a consultant for Schering-Plough, Novartis, Bristol-Myers-Squibb and Abbott; is a consultant and receives research support from Vertex Pharmaceuticals, Anadys, GlobeImmune, Pharmasset, Sci-Clone, Gilead Sciences and Novartis.

H. L. Bonkovsky: Glaxo Smith Kline—serves on a data monitoring and safety committee. Boehringer-Ingelheim and Infacare Pharmaceuticals—served as a paid consultant. Merck—receives research support. Novartis Pharmaceuticals – consultant and receives research support. Ovation, Inc—consultant and on speakers' bureau. Schering-Plough Corporation – receives research support. Vertex Pharmaceuticals – receives research support.

T. R. Morgan is on the speaker's bureau and receives research support from Schering-Plough; and is a consultant and receives research support from Vertex Pharmaceuticals.

J. L. Dienstag: Vertex Pharmaceuticals – Receives research support. Serves on a Data Monitoring Committee for Schering-Plough Research Institute and Human Genome Sciences. Boehringer-Ingelheim – ad hoc hepatitis advisory board.

Time to Outcome

* Derived from Model a, Table 3

Figure 1.

Risk Category and Time to Clinical Outcome. Figure derived from data in Table 3, Model a. The lowest risk group (lowest 50% of patients) was associated with a risk of decompensation of 2%, while the highest risk group (top 10% of patients) was associated with a risk of hepatic decompensation of 65% over 3.5 years

Table 1Distribution of First Clinical Outcome[/]

First outcome	Frequency	Percent (%)
Death	3	2
CTP _≥ 7	89	66
Variceal hemorrhage	9	7
Ascites	21	16
Bacterial peritonitis	1	<1
Encephalopathy	12	9
Total	135	100

[/]Death not liver-related and HCC excluded.

Table 2

Baseline Characteristics of Patients by Clinical Outcome (n=1050)

Variable (mean)	Outcome		Hazard Rate Ratio	p value
	No	Yes		
	N=915	N=135		
Mean or %	Mean or %			
DEMOGRAPHICS				
Age (Years)	50.1	50.2	1.0	0.88
% Female	28.2	34.8	1.32	0.12
Race/ethnicity				0.11
% Black or black Hispanic	18	19.3	1.12	
% White non-Hispanic	72.2	67.4	ref	
% Hispanic	7.3	12.6	1.76	
% Others	2.4	0.7	0.33	
Duration of Infection ^I (Years)	28.2	27.6	0.99	0.38
Treatment Stratification (Lead-in, BT/R or Express)				0.01
Treatment Assignment Interferon Group	48.9	51.9	1.10	0.57
% Lead-in	62.3	68.2	ref	
% Breakthrough/relapsers	15.6	5.9	0.36	
% Express	22.1	25.9	1.11	
Smoking status (Packs/day)				0.04
Never	24.1	24.4	1.57	
Not now	45.8	45.2	1.59	
Now <1	13.7	21.5	2.54	
Now 1+	16.4	8.9	ref	
Esophageal varices ²	22	50	3.25	<.0001
METABOLIC FACTORS				
Body Mass Index	29.7	31	1.04	0.01
% with Diabetes	23.4	29.6	1.40	0.08
VIRAL FACTORS				
% Genotype 1	93.6	91.9	.77	0.41
Log HCV RNA (log ₁₀ IU/mL)	6.5	6.2	.44	<0.0001
LABS				
AST (U/L)	83	116	1.01	<0.0001
ALT (U/L)	107	109	1.00	0.85
AST/ALT ratio	0.84	1.13	7.82	<0.0001
Alk Phosphatase (U/L)	96	125	1.01	<0.0001
Total Bilirubin (mg/dL)	0.74	1.1	3.21	<0.0001
Albumin (g/dL)	3.9	3.5	0.06	<0.0001
INR	1.03	1.11	47.24	<0.0001

Variable (mean)	Outcome		Hazard Rate Ratio	p value
	No	Yes		
	N=915 Mean or %	N=135 Mean or %		
Platelet count (1000/mm ³)	173	114	0.98	<0.0001
AFP (ng/ml)	14.8	35.3	1.01	<0.0001
Creatinine (mg/dl)	.85	.80	0.18	0.002
WBC (1000/mm ³)	5.9	4.9	0.72	<0.0001
Iron saturation (%)	.36	.42	7.36	<0.0001
Serum ferritin (ng/ml ³)	351	510	1.00	0.0001
HISTOLOGY (HAI)				
Periportal Inflammation	2.7	3.2	1.81	<.0001
Portal Inflammation	2.2	2.2	1.05	0.67
Praenchymal Injury	2.6	2.7	1.19	0.08
Confluent Necrosis	.01	0	0	0.98
Histology Activity Index	7.5	8.1	1.16	0.0004
Hepatic steatosis	1.4	1.3	0.94	0.52
Hepatocellular Iron grade ⁴	0.48	0.56	1.17	0.20
Fibrosis (Ishak)	4	5	1.88	<0.0001

¹ n=984 due to missing data

² n=1016 due to missing data

³ n = 1049 due to missing data

⁴ n = 1047 due to missing data

Table 3

Cox proportional hazards survival analysis of factors associated with time to first clinical outcome (n=1050): Hazard rate ratio, 95% confidence interval and p-value.

Variable	Model a			* Model a'			Model b			* Model b'		
	HR	95% CI	p value	HR	p value		HR	95% CI	p value	HR	p value	
Log(AST/ALT) ratio	3.34	1.84, 6.06	<.0001	2.63	0.002		3.06	1.69, 5.55	0.0002	2.52	0.0036	
Total Bilirubin mg/dL	1.82	1.37, 2.42	<.0001	2.61	<.00001		1.92	1.44, 2.55	<.0001	2.47	<.00001	
Albumin g/dL	0.20	0.13, 0.32	<.0001	0.14	<.00001		0.21	0.13, 0.33	<.0001	0.15	<.00001	
Platelet count/50K/mm ³	0.59	0.49, 0.72	<.0001	0.63	<.00001		0.66	0.53, 0.81	<.0001	0.67	0.0002	
Fibrosis Ishak							1.31	1.12, 1.53	0.001	1.18	0.06	
Score Overall model			<.00001						<.00001			

$R_a = 1.21^{*} \log_{10} (\text{AST/ALT}) + 0.60^{*} \text{total bilirubin (mg/dL)} - 1.60^{*} \text{albumin (g/dL)} - 0.52^{*} \text{platelets/50}$.

$R_b = 1.12^{*} \log_{10} (\text{AST/ALT}) + 0.65^{*} \text{total bilirubin (mg/dL)} - 1.58^{*} \text{albumin (g/dL)} - 0.42^{*} \text{platelets/50} + 0.27^{*} \text{Ishak fibrosis score}$.

* Models a' and b' exclude breakthrough/relapsers from the analysis.

Table 4

Risk Stratification by Platelets, Albumin, AST/ALT, total bilirubin and Cox Regression Hazards Models to Predict Clinical Outcome.

	Total Patients	N with Outcome	Outcome % ^I
Platelets (K/mm³)			
39–99	188	70	41
100–149	279	38	15
150–199	284	18	7
200–426	299	9	3
Albumin (g/dL)			
2.7–3.5	207	82	44
3.6–3.8	262	29	12
3.9–4.0	226	10	5
4.1–4.9	355	14	4
AST/ALT (IU/L)			
0.29 – 0.7	302	4	2
0.7 – <0.9	351	33	11
0.9 – <1.2	255	48	20
1.2 – 2.47	142	50	38
Total Bilirubin (mg/dL)			
0.1 – 0.5	309	13	5
0.6 – 0.7	273	27	11
0.8 – 1.9	448	86	21
2.0 – 3.8	20	9	49
Percentiles of Risk (Model a)			
< 50 th percentile ($R_a < -7.82$)	525	10	2
50 th – <75 th percentile ($-7.82 \leq R_a < -6.91$)	262	21	9
75 th – <90 th percentile ($-6.91 \leq R_a < -5.81$)	158	42	29
$\geq 90^{\text{th}}$ percentile ($R_a \geq -5.81$)	105	62	65
Percentiles of Risk (Model b)			
< 50 th percentile ($R_b < -6.21$)	525	8	2
50 th – <75 th percentile ($-6.21 \leq R_b < -5.12$)	263	26	11
75 th – <90 th percentile ($-5.12 \leq R_b < -4.14$)	157	38	26
$\geq 90^{\text{th}}$ percentile ($R_b \geq -4.14$)	105	63	66
Total	1050	135	13

^I Cumulative probability of a clinical outcome at 1400 days (3.8 years) derived from Lifetable.

As an example: Consider a patient with the following values:

$$\text{AST/ALT} = 1.13$$

$$\text{Log}(\text{AST/ALT}) = 0.053$$

$$\text{bilirubin} = 1.1 \text{ mg/dL}$$

$$\text{albumin} = 3.5 \text{ g/dL}$$

$$\text{platelets} = 114,000/\text{mm}^3$$

$$\text{platelets}/50,000 = 2.28$$

Compute R for that patient using $R = 1.21 * \log(\text{AST/ALT}) + 0.60 * \text{total bilirubin} - 1.60 * \text{albumin} - 0.52 * \text{platelets}/50$.

$$R = -6.06$$

Go to Table 4, Model a, the patient's risk category is 50th to <75th percentile which estimates the risk of developing an outcome in 3.8 years to be 29%.

Table 5

Univariate Analysis of Baseline Characteristics with time to Two-Point Increase (TPI) in Ishak Fibrosis Score, Controlling for Treatment Assignment (n=547)

Variable (Mean)	TPI		Coefficient	p value
	No	Yes		
	n=395	n=152		
	Mean or %	Mean or %		
DEMOGRAPHICS				
Age (Years)	50.5	49.5	−0.014	0.21
% Female	29.1	30.3	0.061	0.73
Race/ethnicity				0.34
% Black or black Hispanic	21.8	16.4	−0.14	
% White non-Hispanic	70.9	75.0	Ref	
% Hispanic	4.1	6.6	0.43	
% Others	3.3	2.0	−0.41	
Duration of Infection ^I (Years)	27.8	27.5	−0.00301	0.78
Treatment Stratification (Lead-in, BT/ R or Express)				0.24
% Lead-in	62.5	59.9		
% Breakthrough/relapsers	18.2	15.1		
% Express	19.2	25.0		
Treatment Assignment –Interferon Group	51.1	46.7	0.1227	N/A
Smoking status (Packs/day)				0.49
Never	27.1	25.0	−0.047	
Not now	44.6	48.7	0.091	
Now <1	12.4	13.2	0.10	
Now 1+	15.9	13.2	Ref	
Esophageal varices ²	13.1	21.6	0.60	0.003
METABOLIC FACTORS				
Body Mass Index	29.3	30.5	0.028	0.04
% Diabetes	19.7	25.7	0.035	0.06
VIRAL FACTORS				
% Genotype 1	95.2	92.1	−0.47	0.17
Log HCV RNA (log ₁₀ IU/mL)	6.54	6.49	−0.24	0.15
LABS				
AST (U/L)	70	93	0.0050	<0.0001
ALT (U/L)	94	120	0.0028	0.0001
AST/ALT ratio	0.81	0.87	0.72	0.009
Alk Phosphatase (U/L)	88	99	0.0040	0.007
Total Bilirubin (mg/dL)	0.69	0.81	0.90	<0.0001
Albumin (g/dL)	3.97	3.9	−0.65	0.008

Variable (Mean)	TPI		Coefficient	p value
	No	Yes		
	n=395 Mean or %	n=152 Mean or %		
INR	1.00	1.03	1.94	0.003
Platelet count (1000/mm ³)	196	166	-0.0091	<0.0001
AFP (ng/mL)	10.4	19.7	0.010	<0.0001
Creatinine (mg/dl)	0.86	0.84	-0.51	0.30
WBC (1000 mm ³)	6.0	5.6	-0.12	0.01
Iron saturation %	0.34	0.37	1.13	0.04
Serum ferritin (ng/ml ³)	341.5	431.1	0.00047	0.007
HISTOLOGY				
Periportal Inflammation	2.5	2.6	0.16	0.09
Portal Inflammation	2.2	2.0	-0.35	0.003
Parenchymal Injury	2.5	2.7	0.12	0.21
Confluent Necrosis	0.023	0.00	-10.69	0.97
Histology Activity Index	7.2	7.3	0.0038	0.92
Hepatic steatosis	1.2	1.6	0.36	<0.0001
Hepatocellular Iron grade	0.49	0.45	-0.075	0.57
Fibrosis score (Ishak)	3.1	3.2	0.16	0.20

¹ n = 507 due to missing data

² n = 536 due to missing data

³ n = 546 due to missing data

Table 6

Complementary Log-Log Regression Analysis Of Factors Associated With Time To Two-Point Increase in Ishak Fibrosis Score (Fibrosis Patients Only n=547)

Variable	Coefficient	Model C	
		95% CI	p-value
BMI	0.032	0.017, 0.063	0.04
Platelet count/50	-1.33	-1.59, -0.82	<.0001
Platelet count/50-Sq	0.12	0.08, 0.18	0.0003
Hepatic Steatosis	0.31	0.22, 0.49	0.0006
Overall model			<0.0001

$R_C = 0.032 * \text{BMI} - 1.33 * \text{platelets}/50 + 0.12 * (\text{platelets}/50)^2 + 0.31 * \text{steatosis score}$

Table 7
Risk Stratification by Platelet Count to Predict Two-point increase (TPI) in Ishak fibrosis score

	Total Patients	N with TPI	% with TPI	HR Grouped	95% CI
Platelet Count (K/mm ³)					
<100	35	20	57	5.19	2.41,11.2
100–149	112	50	45	2.73	1.49,4.99
150–199	175	40	23	1.04	0.57,1.91
200–249	143	25	17	0.77	0.4,1.47
250+	82	17	21	1.00	