Predicting Clinical Outcomes Using Baseline and Follow-Up Laboratory Data from the Hepatitis C Long-Term Treatment Against Cirrhosis Trial

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Predicting clinical outcomes in patients with chronic hepatitis C is challenging. We used the hepatitis C long-term treatment against cirrhosis (HALT-C) trial database to develop two models, using baseline values of routinely available laboratory tests together with changes in these values during follow-up to predict clinical decompensation and liver-related death/liver transplant in patients with advanced hepatitis C. Patients randomized to no treatment and who had ≥2-year follow-up without a clinical outcome were included in the analysis. Four variables (platelet count, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ratio, total bilirubin, and albumin) with three categories of change (stable, mild, or severe) over 2 years were analyzed. Cumulative incidence of clinical outcome was determined by Kaplan-Meier analysis and Cox regression was used to evaluate predictors of clinical outcome. In all, 470 patients with 60 events were used to develop models to predict clinical decompensation. Baseline values of all four variables were predictive of decompensation. There was a general trend of increasing outcomes with more marked worsening of laboratory values over 2 years, particularly for patients with abnormal baseline values. A model that included baseline platelet count, AST/ALT ratio, bilirubin, and severe worsening of platelet count, bilirubin, and albumin was the best predictor of clinical decompensation. A total of 483 patients with 79 events were used to evaluate predictors of liver-related death or liver transplant. A model that included baseline platelet count and albumin as well as severe worsening of AST/ALT ratio and albumin was the best predictor of liver-related outcomes. *Conclusion:* Both the baseline value and the rapidity in change of the value of routine laboratory variables were shown to be important in predicting clinical outcomes in patients with advanced chronic hepatitis C. (HEPATOLOGY 2011;54:1527-1537)

Predicting clinical outcomes in patients with chronic hepatitis C has been a challenge. Most models to predict clinical and histological outcomes have used baseline clinical or laboratory data.[1-7] However, as the severity of liver disease changes over time, so do the surrogate laboratory tests that reflect the state of liver function. Therefore, a prognostic model should take the time factor into account and a laboratory parameter measured serially over time may be more accurate in predicting outcome compared to a single measurement obtained at baseline. In clinical practice, physicians use serial clinical data and patterns of laboratory values during follow-up to counsel patients on their risks of adverse outcomes. Thus, a patient with more rapidly deteriorating laboratory values is expected to have a higher risk of an adverse outcome than a patient with stable laboratory values even though the baseline laboratory values of the two

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; HALT-C, hepatitis C long-term treatment against cirrhosis; HCC, hepatocellular carcinoma; HR, hazards ratio; INR, international normalized ratio; MELD, Model for Endstage Liver Disease; MRI, magnetic resonance imaging.

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patients may be similar. This approach of using serial laboratory data to compute time-dependent Model for Endstage Liver Disease (MELD) scores has been shown to be more accurate in predicting wait list mortality than listing MELD in patients waiting for liver transplantation.[8-10]

The HALT-C (hepatitis C long-term treatment against cirrhosis) trial enrolled 1,050 patients with advanced hepatitis C followed prospectively to 8.7 years for clinical outcomes.[11] All the patients had laboratory tests at each study visit. The aim of this analysis was to develop models comprising baseline values of routinely available laboratory tests together with changes in these values during follow-up to predict outcomes in patients with advanced hepatitis C.

Patients and Methods

The design of the HALT-C trial has been described.[12] Briefly, patients with chronic hepatitis C had to meet the following criteria for enrollment: failure to achieve sustained virologic response after previous interferon treatment with or without ribavirin, the presence of advanced fibrosis on liver biopsy (Ishak fibrosis score $\geq$3), no history of hepatic decompensation or hepatocellular carcinoma (HCC), and the absence of defined exclusion criteria.

All patients were to receive the combination of full-dose peginterferon and ribavirin during the lead-in phase of the trial. Patients who remained viremic during the lead-in phase of treatment (lead-in patients), those who experienced virological breakthrough or relapse after initial response (breakthrough/relapser patients), and those who were nonresponders to peginterferon and ribavirin outside of the HALT-C trial (express patients) were randomized to maintenance therapy (peginterferon alpha-2a 90 μg weekly) or to remain as untreated controls for the next 3.5 years. Following completion of the 3.5 years of the randomized trial, all patients were invited to continue follow-up without treatment until October 20, 2009.

At entry, all patients were required to have an ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) demonstrating no evidence of hepatic mass lesions suspicious for HCC and to have an alpha fetoprotein (AFP) <200 ng/mL. All patients had a liver biopsy performed prior to enrollment. The Ishak scoring system was used to grade inflammation (0-18) and to stage fibrosis (0-6).[13] The patients were seen every 3 months during the randomized phase of the trial and every 6 months thereafter. At each visit, patients were assessed clinically for outcomes and blood was drawn for complete blood count, hepatic panel (albumin, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase), creatinine, prothrombin time / international normalized ratio (INR), and AFP. Upper gastrointestinal endoscopy was performed at randomization to assess for esophageal varices. Ultrasound was performed at randomization, 6 months after randomization, and then every 12 months during the randomized trial and every 6 months during the extended follow-up period. Patients with an elevated or rising AFP and those with new lesions on ultrasound were evaluated further with a CT or MRI. Diagnostic liver biopsy and HCC treatment were conducted at the discretion of investigators at each site.

In this analysis, only patients randomized to no treatment were included because interferon even in low doses can have an effect on laboratory values. To assess changes in laboratory values during follow-up, only patients who had been followed up to month 24 from enrollment (18 months after randomization to no treatment) with no outcomes up to that timepoint were included. Two clinical outcomes were analyzed: Outcome 1, Clinical decompensation, was defined as

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any of the following: variceal bleeding, ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy; and Outcome 2, Liver-related deaths and liver transplantation. Diagnostic criteria were established for each clinical outcome and an Outcomes Review Panel adjudicated each outcome report. Only the first clinical outcome for each patient was included in this analysis.

Statistical Analyses. Statistical analyses were performed at the Data Coordinating Center with SAS (v. 9.2).

Four laboratory parameters were chosen for evaluation based on a prior multivariate analysis demonstrating their utility in predicting clinical and histological outcome in the HALT-C trial,[1] and whether they were widely available. These included platelet count, serum albumin, total bilirubin, and AST/ALT ratio. We selected baseline cutoffs for the current analysis based on a clinically meaningful value close to the median to dichotomize the cohort into high- and low-risk groups. These values were 150 k/mm^3 for baseline platelets, 3.9 mg/dL for baseline albumin, 0.7 mg/dL for baseline total bilirubin, and a ratio of 0.8 for baseline AST/ALT ratio. Changes in laboratory values were assessed by comparing values at the month 24 visit (18 months after randomization to no treatment) and baseline visit and categorized as stable (unchanged or less than 5% worsening), mild worsening (5%-15% change from baseline), and severe worsening (>15% worsening from baseline). The selected values of percent change from baseline used to define mild and severe worsening in laboratory values were arbitrary because there was no literature to reference regarding the chosen categories. The specific ranges we chose were to enable sufficient numbers of patients in each of the three categories (stable, mild, and severe) to allow for meaningful statistical analysis. The percent changes from baseline was computed based on the following formula, % change = (follow-up value-baseline value)/Baseline value*100. Patients with an outcome or censoring prior to the month 24 visit were excluded from the analyses.

Cumulative incidence of clinical outcome was determined by Kaplan-Meier analysis and Cox regression was used to evaluate predictors of clinical outcome. Patients with both baseline and month 24 values in platelet count, AST/ALT ratio, total bilirubin, and albumin were used to develop the predictive models of outcomes and patients with any missing values in any of the four laboratory variables selected were excluded to ensure the same sample size for each outcome (N = 470 for clinical decompensation and N = 483 for liver-related death/liver transplant) was used in each model. The model fit statistics (−2 log likelihood ratio, AIC and SBC) were used to compare models for each outcome, with a lower value indicating a more desirable model. The patients were stratified into low, intermediate, and high risks for clinical decompensation based on risk scores of <75th percentile, 75th-90th percentile, and >90th percentile, respectively.

Results

Of the 533 patients randomized to the control group, 63 were excluded from the analyses of clinical decompensation for the following reasons: 18 had an outcome or censoring prior to month 24 and 45 had missing month 24 laboratory values. The baseline characteristics of the 470 patients included in this analysis are listed in Table 1. The mean age of the patients was 49.8 years, 71.3% were men, 70.2% were white, 18.1% blacks, and 8.9% Hispanics. One hundred ninety (40%) patients had cirrhosis (Ishak fibrosis score 5 or 6) and 25.5% had esophageal varices at the time of randomization (month 6). During a median follow-up of 6.3 years (range 1.4 to 8.7 years), 60 patients had clinical decompensation (variceal hemorrhage 1.5% [7/470], ascites 8.1% [38/470] and hepatic encephalopathy 3.2% [15/470]) and 79 patients experienced liver-related death or liver transplantation (30 liver-related deaths, 44 liver transplantations, and five deaths after liver transplantation). The indication for liver transplantation was hepatic decompensation in 26 and HCC with or without decompensation in 23 patients. The mean MELD score at the last study visit obtained a mean of 6 months prior to transplantation was 13 (range 6-23; 16 for those transplanted for decompensation and nine for those transplanted for HCC). Patients who developed clinical decompensation were less likely to be white, had a higher body mass index (BMI), lower albumin and platelet count, and higher AST/ALT ratio, alkaline phosphatase, total bilirubin, and INR at baseline compared to those without clinical decompensation.

Clinical Decompensation

Platelet Count. Forty-five (21.5%) of 209 patients with baseline platelet count ≤150 k/mm^3 experienced clinical decompensation compared to 15 (5.8%) of 261 with baseline platelet count >150 k/mm^3 (Table 2). Within each stratum of baseline platelet count, patients who had severe worsening (>15% decrease between month 24 and baseline) had a higher rate of clinical decompensation than those with moderate (5% to 15% decrease) or no to mild (<5% decrease) worsening. The cumulative incidence of clinical decompensation at

Table 1. Characteristics of the Patients

	Patients with Clinical Decompensation (N = 60)		Patients Without Clinical Decompensation (N = 410)		Total Patients (N = 470)		*P*-value
	N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	
Demographics							
Age, years	49.7	6.90	49.8	7.09	49.8	7.06	0.87
Gender, male	42	70	293	71.5	335	71.3	0.82
Race							
White	37	61.7	293	71.5	330	70.2	0.02
Black	12	20.0	73	17.8	85	18.1	
Hispanic	11	18.3	31	7.6	42	8.94	
Others	0	0.0	13	3.2	13	2.77	
Metabolic factors							
Diabetes	18	30	88	21.5	106	22.6	0.14
BMI, kg/m^2	31.7	6.11	29.6	5.35	29.9	5.49	0.01
Lab values: baseline							
Albumin (g/dL)	3.67	0.42	3.91	0.38	3.88	0.39	<0.0001
AST (U/L)	98.4	66.8	86.1	59.2	87.7	60.3	0.14
ALT (U/L)	104.3	69.5	112.5	84.8	111.4	83.0	0.48
AST/ALT ratio	1.02	0.31	0.84	0.28	0.86	0.29	<0.0001
Alk Phos (U/L)	120.1	53.5	95.3	46.5	98.5	48.1	0.0002
T Bilirubin (mg/dL)	1.00	0.52	0.74	0.35	0.77	0.39	<0.0001
INR	1.09	0.13	1.03	0.10	1.04	0.11	0.0002
Platelet (1,000/mm^3)	128.9	57.9	172.6	66.7	167.0	67.2	<0.0001
Lab values: month 24							
Albumin (g/dL)	3.36	0.53	3.83	0.42	3.77	0.46	<0.0001
AST (U/L)	100.7	51.5	82.7	57.1	85.0	56.7	0.02
ALT (U/L)	93.8	42.3	99.9	73.9	99.1	70.6	0.54
AST/ALT ratio	1.12	0.36	0.89	0.30	0.92	0.32	<0.0001
Alk Phos (U/L)	131.5	59.9	97.7	44.7	102.0	48.2	<0.0001
T Bilirubin (mg/dL)	1.38	0.87	0.90	0.49	0.96	0.57	<0.0001
INR	1.15	0.13	1.08	0.26	1.09	0.25	0.03
Platelet (1,000/mm^3)	109.6	53.4	167.0	69.2	159.6	70.0	<0.0001
Change in lab value**: (Month 24-baseline)							
Albumin (g/dL)	−0.31	0.41	−0.07	0.34	−0.10	0.36	<0.0001
AST (U/L)	2.23	67.1	−3.47	57.6	−2.74	58.8	0.48
ALT (U/L)	−10.5	55.9	−12.6	79.6	−12.3	77.0	0.84
AST/ALT ratio	0.10	0.25	0.06	0.20	0.06	0.21	0.12
Alk Phos (U/L)	11.5	39.2	2.37	28.1	3.53	29.8	0.03
T Bilirubin (mg/dL)	0.38	0.69	0.16	0.41	0.19	0.46	0.001
INR	0.07	0.12	0.05	0.25	0.05	0.24	0.59
Platelet (1,000/mm^3)	−19.4	32.1	−5.58	32.2	−7.33	32.5	0.002
Liver histology: Baseline							
Ishak Fibrosis score	4.65	1.10	4.01	1.26	4.09	1.26	0.002
HAI	7.08	2.04	7.54	2.04	7.48	2.04	0.10
Steatosis score	1.38	0.78	1.31	0.88	1.32	0.87	0.53
Endoscopy: month 24							
Esophageal varices	30	50	88	21.8	118	25.5	<0.0001

3, 5, and 7 years was 6.4%, 18.9%, and 26.8%, respectively, for patients with baseline platelet $\leq$150 k/mm^3 and 0.0%, 2.6%, and 7.4%, respectively, for those with baseline platelet >150 k/mm^3 ($P < 0.0001$) (Fig. 1A; Supporting Table 2C). A sharp linear rise in decompensation events was noted in those with baseline platelet counts $\leq$150 k/mm^3 after 24 months (18 months after randomization to no treatment) of observation.

Among the patients with baseline platelet $\leq$150 k/mm^3, the cumulative incidence of clinical decompensation at 3, 5, and 7 years was 5.2%, 13.3%, and 13.3%, respectively, for patients with stable platelet count; 2.3%, 4.8%, and 18.5%, respectively, for those with mild worsening of platelet count; and 11.0%, 36.3%, and 50.5%, respectively, for those with severe worsening of platelet count (Fig. 1B; Supporting Table 2C). For patients with baseline platelet >150 k/mm^3, the cumulative incidence of clinical decompensation at 3, 5, and 7 years was 0.0%, 1.7%, and 8.9%, respectively, for patients with stable platelet count; 0.0%, 0.0%, and 0.0%, respectively, for those with mild worsening of platelet count; and 0.0%, 7.0%, and 12.6%, respectively, for those with severe worsening of platelet count (Fig. 1C; Supporting Table 2C).

Table 2A. Prediction of Clinical Decompensation Based on Change in Laboratory Value from Baseline to Month 24

	No. of Patients		No. of Patients		No. of Patients		No. of Patients	
Month 24-Baseline (Change)	Platelet × 1,000/mm^3	No. (%) with Outcome	AST/ALT Ratio	No. (%) with Outcome	T Bilirubin (mg/dL)	No. (%) with Outcome	Albumin (G/Dl)	No. (%) with Outcome
	Baseline ≤150		Baseline >0.8		Baseline >0.7		Baseline ≤3.9	
Stable <5%	99	12 (12.1)	129	23 (17.8)	124	14 (11.3)	161	15 (9.3)
Worse, 5-15%	43	5 (11.6)	44	6 (13.6)	35	6 (17.1)	81	19 (23.5)
Worse, >15%	67	28 (41.8)	59	15 (25.4)	104	28 (26.9)	19	9 (47.4)
Total	209	45 (21.5)	232	44 (19)	263	48 (18.3)	261	43 (16.5)
	Baseline >150		Baseline ≤0.8		Baseline ≤.7		Baseline >3.9	
Stable <5%	131	7 (5.3)	94	4 (4.3)	53	0	115	8 (7)
Worse, 5-15%	66	1 (1.5)	41	6 (14.6)	0	0	85	5 (5.9)
Worse, >15%	64	7 (10.9)	103	6 (5.8)	154	12 (7.8)	9	4 (44.4)
Total	261	15 (5.8)	238	16 (6.7)	207	12 (5.8)	209	17 (8.1)

P-value to compare % categories among the group with PLT ≤ 150: $P < 0.0001$.
P-value to compare % categories among the group with PLT > 150: $P = 0.0749$.
P-value to compare % categories among the group with AST/ALT ≤ 0.8: $P = 0.0766$.
P-value to compare % categories among the group with AST/ALT > 0.8: $P = 0.2833$.
P-value to compare % categories among the group with Bili ≤ 0.7: $P = 0.0392$.
P-value to compare % categories among the group with Bili > 0.7: $P = 0.0096$.
P-value to compare % categories among the group with Albumin ≤ 3.9: $P < 0.0001$.
P-value to compare % categories among the group with Albumin > 3.9: $P = 0.0002$.
Fisher's Exact Test.

AST/ALT Ratio. Forty-four (19%) of 232 patients with baseline AST/ALT ratio >0.8 experienced clinical decompensation compared to 16 (6.7%) of 238 with baseline AST/ALT ratio ≤0.8 (Table 2). Within each stratum of baseline AST/ALT ratio, patients who had severe worsening (>15% increase between month 24 and baseline) had a higher rate of clinical decompensation. The cumulative incidence of clinical decompensation at 3, 5, and 7 years is shown in Supporting Table 2C.

Total Bilirubin. Forty-eight (18.3%) of 263 patients with baseline total bilirubin >0.7 mg/dL experienced clinical decompensation compared to 12 (5.8%) of 207 with baseline total bilirubin ≤0.7 mg/dL (Table 2). Within each stratum of baseline total bilirubin, patients who had severe worsening (>15% increase between month 24 and baseline) had a higher rate of clinical decompensation. The cumulative incidence of clinical decompensation at 3, 5, and 7 years is shown in Supporting Table 2C.

Albumin. Forty-three (16.5%) of 261 patients with baseline albumin ≤3.9 mg/dL experienced clinical decompensation compared to 17 (8.1%) of 209 with baseline albumin >3.9 mg/dL (Table 2). Within each stratum of baseline albumin, patients who had severe worsening (>15% decrease between month 24 and baseline) had a higher rate of clinical decompensation. The cumulative incidence of clinical decompensation at 3, 5, and 7 years is shown in Supporting Table 2C.

Multivariate Models to Predict Clinical Decompensation. A multivariate model including baseline platelet count, AST/ALT ratio, bilirubin, and albumin (Model IA) showed that each of these four baseline laboratory values independently predicted the

Table 2B. Prediction of Clinical Decompensation Based on Change in Laboratory Value from Baseline to Month 48

	No. of Patients		No. of Patients		No. of Patients		No. of Patients	
Month 48-Baseline (change)	Platelet x 1,000/mm^3	No. (%) with Outcome	AST/ALT Ratio	No. (%) with Outcome	T Bilirubin (mg/dL)	No. (%) with Outcome	Albumin (g/dL)	No. (%) with Outcome
	Baseline ≤150		Baseline >0.8		Baseline >0.7		Baseline ≤3.9	
Stable <5%	84	4 (4.8%)	98	7 (7.1%)	102	7 (6.9%)	151	6 (4.0%)
Worse, 5-15%	22	1 (4.5%)	27	1 (3.7%)	25	3 (12.0%)	45	5 (11.1%)
Worse, >15%	66	16 (24.2%)	69	14 (20.3%)	95	14 (14.7%)	27	10 (37.0%)
Total	172	21 (12.2%)	194	22 (11.3%)	222	24 (10.8%)	223	21 (9.4%)
	Baseline >150		Baseline ≤0.8		Baseline ≤.7		Baseline >3.9	
Stable <5%	121	2 (1.6%)	64	0 (0.0%)	47	0 (0.0%)	107	4 (3.7%)
Worse, 5-15%	41	2 (4.9%)	43	3 (7.0%)	0	0 (0.0%)	65	5 (7.7%)
Worse, >15%	79	10 (12.7%)	112	10 (8.9%)	144	11 (7.6%)	18	5 (27.8%)
Total	241	14 (5.8%)	219	13 (5.9%)	191	11 (5.8%)	190	14 (7.4%)

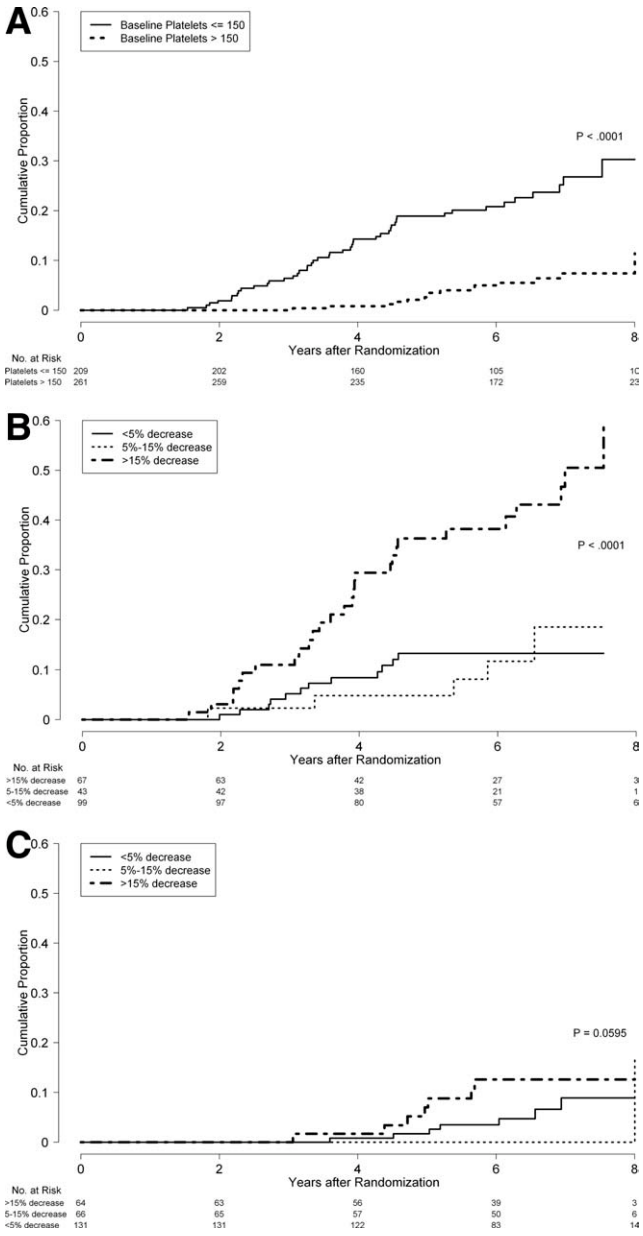

Fig. 1.

occurrence of clinical decompensation (Table 3A). A model including changes in values of these four laboratory tests between month 24 and baseline (Model IIA) found that severe worsening (>15% change) but not mild worsening (5%-15% change) of platelet count, bilirubin, as well as albumin were independent predictors of clinical decompensation, whereas changes in AST/ALT ratio were not. Inclusion of both baseline laboratory values and changes in laboratory values (Model IIIA) showed that baseline platelet, AST/ALT ratio, and bilirubin; and severe worsening of platelet count, bilirubin, and albumin were independent predictors of clinical decompensation. Model IIIA has the lowest AIC (621), indicating that it has a better fit than Model IA (AIC: 651) and Model IIA (AIC: 655). Addition of age, gender, and race did not improve the fit of any of these models. The duration of follow-up was similar among the three categories of change for each variable irrespective of whether the variable was normal or abnormal at baseline and did not impact the accuracy of the model.

To address the issue whether a longer observation period would have any effect on the accuracy of the model, we used change in laboratory values from baseline to month 48 (Table 2B), and compared the results with those obtained using change in laboratory values from baseline to month 24. For patients whose baseline laboratory values were abnormal, extending the observation period from 24 to 48 months resulted in lower outcome rate, i.e., slower worsening of laboratory values was associated with a lower rate of adverse outcome. During the period between month 24 and 48, 25/60 (42%) patients with abnormal baseline laboratory values experienced a decompensation outcome. In contrast, for patients whose baseline labs were normal the outcome rate for each category of change from baseline to M48 was similar to same category of change from baseline to M24.

The cumulative incidence of clinical decompensation in the low-, intermediate-, and high-risk groups based on Model IA and Model IIIA are shown in Fig. 2. Table 4 illustrates the application of these models to four examples of patients. Patients A and B (baseline platelet count >150 k/mm^3, AST/ALT ratio <0.8, total bilirubin <0.7 mg/dL, and albumin >3.9 mg/dL) fell into the low-risk category based on both Models IA and IIIA, whereas patient C (baseline platelet count <150 k/mm^3, AST/ALT ratio >0.8, total bilirubin >0.7 mg/dL, and albumin <3.9 mg/dL) with stable/mild change in laboratory values was classified as intermediate risk by Model IA and low risk by Model IIIA and patient D (baseline platelet count <150 k/mm^3, AST/ALT ratio >0.8, total bilirubin >0.7 mg/dL, and albumin <3.9 mg/dL) with mild/severe change in laboratory values was classified as intermediate risk by Model IA and high risk by Model IIIA.

Liver-Related Death or Liver Transplant

Bivariate Cox regression analyses of baseline laboratory values found that all four baseline laboratory values predicted liver-related death or liver transplant: platelet ≤150 k/mm^3 (hazards ratio [HR] 5.48, 95% confidence interval [CI] 3.17-9.5), AST/ALT ratio <0.8 (HR 0.36, 95% CI 0.22-0.58), bilirubin <0.7 mg/dL (HR 0.51, 95% CI 0.31-0.82), and albumin <3.9 g/dL (HR 3.4, 95% CI 2.0-5.81). When

Table 3A. Multivariate Cox Models to Predict Clinical Decompensation

	Model IA		Model IIA		Model IIIA	
	HR	95% CI	HR	95% CI	HR	95% CI
Baseline lab values						
Platelet (x1,000/mm^3) $\leq$ 150 vs. $>$ 150	2.893	1.568-5.338			2.766	1.472-5.199
AST/ALT ratio $\leq$ 0.8 vs. $>$ 0.8	0.416	0.233-0.743			0.500	0.270-0.925
T Bilirubin (mg/dL) $\leq$ 0.7 vs. $>$ 0.7	0.404	0.211-0.775			0.375	0.185-0.759
Albumin (g/dL) $\leq$ 3.9 vs. $>$3.9	1.801	1.014-3.200			1.508	0.822-2.767
Change in lab values, month 24 - baseline						
Platelet count						
5-15% worse vs. stable			0.631	0.249-1.598	0.560	0.219-1.436
$>$15% worse vs. stable			2.717	1.502-4.914	2.292	1.268-4.145
AST/ALT ratio						
5-15% worse vs. stable			1.268	0.625-2.572	1.503	0.726-3.113
$>$15% worse vs. stable			0.892	0.498-1.597	1.278	0.690-2.367
T Bilirubin						
5-15% worse vs. stable			2.135	0.786-5.797	1.963	0.732-5.268
$>$15% worse vs. stable			2.083	1.116-3.888	2.626	1.376-5.009
Albumin						
5-15% worse vs. stable			1.585	0.877-2.865	1.361	0.740-2.506
$>$15% worse vs. stable			6.466	3.120-13.40	3.854	1.816-8.180
Model fit statistics						
-2 LOG L		642.789		639.433		596.792
AIC		650.789		655.433		620.792
SBC		659.166		672.188		645.924

No. of patients = 470, no. of events = 60.

Model IA compared to Model IIIA $P < 0.0001$ by Likelihood ratio test.

Model IIA compared to Model IIIA $P < 0.0001$ by Likelihood ratio test.

Formulae are provided as Supporting material to Table 3A and on the HALT-C website at http://www.haltctrial.org.

Table 3B. Multivariate Cox Models to Predict Liver-Related Deaths or Liver Transplants

	Model IB		Model IIB		Model IIIB	
	HR	95% CI	HR	95% CI	HR	95% CI
Baseline lab values						
Platelet count $\leq$ 150 vs. $>$ 150	4.110	2.307-7.321			4.143	2.296-7.476
AST/ALT ratio $\leq$ 0.8 vs. $>$ 0.8	0.558	0.342-0.910			0.657	0.396-1.091
T Bilirubin $\leq$ 0.7 vs. $>$ 0.7	0.890	0.543-1.459			0.940	0.544-1.625
Albumin $\leq$3.9 vs. $>$3.9	2.357	1.363-4.076			2.329	1.334-4.064
Change in lab values, month 24 -baseline						
Platelet count						
5-15% worse vs. stable			0.922	0.474-1.793	0.940	0.479-1.844
$>$15% worse vs. stable			1.812	1.077-3.046	1.662	0.986-2.803
AST/ALT ratio						
5-15% worse vs. stable			1.707	0.950-3.070	2.146	1.162-3.964
$>$15% worse vs. stable			0.964	0.573-1.621	1.300	0.757-2.232
T Bilirubin						
5-15% worse vs. stable			1.107	0.428-2.865	1.065	0.415-2.732
$>$15% worse vs. stable			1.695	1.014-2.833	1.570	0.916-2.691
Albumin						
5-15% worse vs. stable			1.470	0.879-2.458	1.318	0.778-2.234
$>$15% worse vs. stable			5.724	3.021-10.85	3.569	1.825-6.979
Model fit statistics						
-2 LOG L		845.113		863.141		809.034
AIC		853.113		879.141		833.034
SBC		862.591		898.097		861.467

No. of patients = 483, no. of events = 79.

Model IB compared to Model IIIB $P < 0.0001$ by Likelihood ratio test.

Model IIB compared to Model IIIB $P < 0.0001$ by Likelihood ratio test.

Formulae are provided as Supporting material to Table 3B and on the HALT-C website at http://www.haltctrial.org.

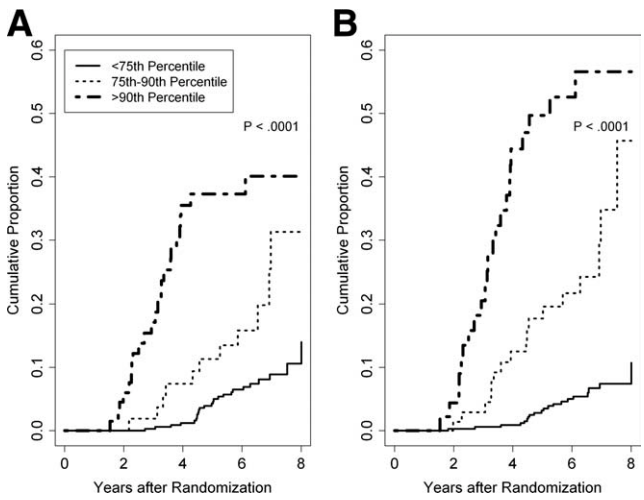

Fig. 2.

changes in laboratory values between month 24 and baseline were analyzed, severe worsening (>15% change) of all laboratory values was predictive of liver-related death or liver transplant.

A multivariate model including baseline platelet count, AST/ALT ratio, bilirubin, and albumin (Model IB) showed that baseline platelet, AST/ALT ratio, and albumin were predictive of liver-related death or liver transplant (Table 3B). A model including changes in values of these four laboratory tests (Model IIB) between month 24 and baseline found that severe worsening of platelet count, total bilirubin, and albumin were predictive of liver-related death or liver transplant. Inclusion of both baseline laboratory values and changes in laboratory values (Model IIIB) showed that baseline platelet count and albumin as well as moderate worsening of AST/ALT ratio and severe worsening of albumin were predictive of liver-related death or liver transplant. Model IIIB had the lowest AIC (833), indicating that it has a better fit than Model IB (AIC: 853) and Model IIB (AIC: 879).

Validation of Models

We utilized all patients randomized to the low-dose peginterferon arm of the HALT-C trial as a validation cohort for the two models. We also assessed performance of the model in patients with cirrhosis using control and treated patients with cirrhosis. For both models (model for prediction of clinical decompensation and model for liver deaths or transplants) the analysis revealed no statistical difference in outcomes between control and treated patients in any of the three risk categories (low, intermediate, or high) (Supporting Fig. 1a-d). Comparison of the models between control and treated patients with cirrhosis yielded similar results (data not shown).

Discussion

The HALT-C trial enrolled more than 1,000 patients with advanced hepatitis C who were prospectively followed for up to 8.7 years for clinical outcomes. Half of the subjects served as control patients, which provided the opportunity to define the natural history of advanced chronic hepatitis C. We had previously identified four clinical variables, platelet count, AST/ALT ratio, total bilirubin, and albumin, to be predictive of clinical and histological progression in patients with chronic hepatitis C.[1] The current analysis focused on whether including the change (stable or worse) from baseline in each of these laboratory values over a 24-month period would be superior to the baseline value in predicting two clinically relevant outcomes in previously treated patients with chronic hepatitis C: clinical decompensation (including ascites, spontaneous bacterial peritonitis, variceal hemorrhage, and hepatic encephalopathy) and liver-related death and liver transplant. The analysis demonstrated that the outcome of advanced chronic hepatitis C was dependent not only on the value of the laboratory parameter at initial presentation, but also on the magnitude of the change in the particular parameter over time. The two models that incorporated both baseline and change in laboratory values over a 24-month period (Models IIIA and IIIB) were the most accurate in predicting clinical outcome in patients with advanced chronic hepatitis C.

Approximately 17%-22% of patients with baseline laboratory values below the cutoff developed a decompensation event compared to only 6%-8% of those above the cutoff. Categorizing the change from

Table 4. Application of Models 1A and IIIA to Predict Risks of Clinical Decompensation

Patient	Platelet Count		AST/ALT ratio		Total Bilirubin		Albumin		Risk Scores					
	Baseline	M24	Baseline	M24	Baseline	M24	Baseline	M24	Model IA		Model IIA		Model IIIA	
A	200	190	0.7	0.8	0.4	0.4	4.3	4.3	−1.78	low	−0.22	low	−1.85	low
B	200	160	0.7	0.8	0.4	0.4	4.3	4	−1.78	low	1.70	inter	−0.13	low
C	110	100	0.9	1	0.75	0.75	3.7	3.6	1.65	inter	−0.22	low	1.26	low
D	110	80	0.9	1.2	0.75	0.8	3.7	3.4	1.65	inter	2.10	high	3.49	High

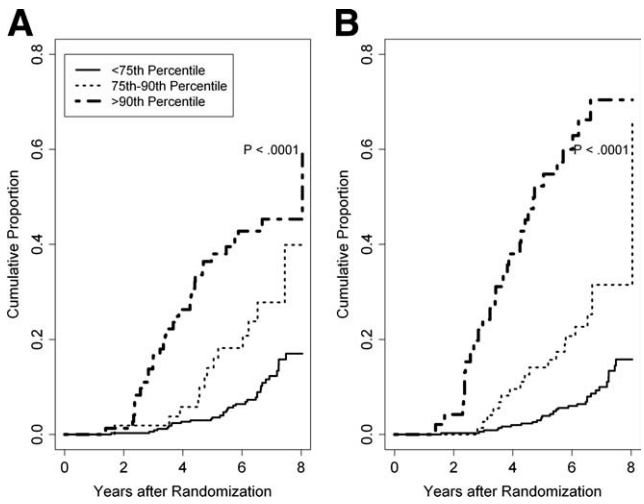

Fig. 3.

baseline in the laboratory parameter into three grades of worsening (stable to mild, moderate, and severe) over a 24-month period allowed a better risk stratification for development of a clinical outcome than the baseline value alone over an 8-year period. There was a linear increase in clinical decompensation with worsening laboratory values, with the exception of AST/ALT ratio, and the rate of events was significantly higher in those with a >15% worsening in laboratory values compared to those with a stable laboratory value. Thus, 12% of patients with a baseline platelet count $\leq$150 k/mm^3 who had a <5% change over 24 months developed a clinical outcome compared to 42% of those who had a >15% change over the same time period. The rate of clinical outcomes was also dependent on the baseline laboratory value. Only 6% of patients with a baseline platelet count >150 k/mm^3 and a >15% worsening in platelet count over 24 months developed a clinical outcome compared to 42% of those with a baseline platelet count of $\leq$150 k/mm^3 and similar degree of worsening over 24 months. Thus, monitoring the rate of change of laboratory values should allow physicians to better predict the risk of a patient developing a clinical outcome. Ideally, it would be preferable if models could be developed to accurately predict the risk of a clinical outcome at the time of initial evaluation or after a short period of observation. However, this will be difficult if not impossible because every patient is at a different point in the natural history at the time of presentation and has different rates of disease progression. In general, changes in laboratory values over time periods of less than a year reflect changes around the mean and are not consistently accurate enough to be used for prediction purposes unless a definite trend is observed. We calculated the slope of the rate of change of the laboratory parameters over 12, 24, and 48 months and found it difficult to interpret because of fluctuations in the laboratory values at each visit. However, we found that the rapidity of change in the laboratory value was important as a predictor of a clinical outcome.

Extending the observation period from 48 months instead of 24 months from baseline was associated with an almost 50% lower rate of outcomes in each of the risk categories among those with abnormal baseline laboratory values. This is because a substantial proportion of patients with more rapid progression of disease (42%) developed an outcome between month 24 and 48. In contrast, among patients with normal baseline laboratory values there was no significant difference in the rate of outcomes for the same category of change in laboratory values after a 24- or 48-month interval. This may be related to the low rate of outcome in patients with normal baseline laboratory values In addition, laboratory values may remain within the normal range in some of these patients despite a change from baseline. For patients with normal baseline laboratory values, additional studies are needed to develop models based on longer periods of observation.

We confirmed the accuracy of our two models using the patients randomized to treatment as a validation cohort. Both models (model for prediction of clinical decompensation and model for liver deaths or transplants) performed well and there was no statistical difference in outcomes between control and treated patients in any of the three risk categories (low, intermediate, or high). The models also performed equally well in the subset of patients with cirrhosis. Thus, we believe these models can be helpful, allowing more accurate risk stratification than reliance on baseline laboratory values only in determining frequency of monitoring and screening procedures.

The multivariate Cox model using a time-dependent covariate identified change from baseline in platelet count, total bilirubin, and albumin but not AST/ALT ratio as independent predictors of a clinical decompensation event. This probably relates to the fact that clinical decompensation is related to the severity of portal hypertension and synthetic dysfunction. Individual ALT and AST values correlate better with underlying necroinflammation and have been shown to be predictive of fibrosis progression.[7,14] The AST/ALT ratio has been shown to be a predictor of cirrhosis[15] but not of hepatic synthetic dysfunction.[11] It is possible that if changes in AST and ALT occur in the same direction, it would have a minimal effect on the AST/ALT ratio. Thus, monitoring the AST/ALT ratio was not found to be helpful in predicting a clinical decompensation outcome.

A model including baseline platelet count and albumin together with worsening serum albumin and AST/ALT ratio (Model IIIB) was the best predictor of liver-related death or liver transplant. Interestingly, neither baseline serum bilirubin nor change in bilirubin level over 24 months was predictive of liver-related death or liver transplant. This may be related to the fact that a substantial number of deaths and liver transplants in this analysis were due to HCC and not decompensation. Removal of HCC as an outcome resulted in bilirubin being a significant predictor of liver-related outcomes.

Many models have been developed to predict severity of fibrosis and cirrhosis in patients with chronic hepatitis C. Only a few have looked at clinical outcomes but these models have used laboratory tests that are not widely available or the sample size has been small with limited follow-up.[16] The strength of this study was the large number of patients who were prospectively monitored for over 8 years for liver outcomes and each outcome was adjudicated by a review panel. The combined model using baseline laboratory values in combination with a change in the laboratory value over a 24-month period was the most accurate at predicting risk of a clinical outcome.

We chose not to consider the most recent laboratory values when determining whether a change in laboratory values was important. This analytic approach would necessitate selecting an arbitrary timepoint as "current." Moreover, the approach we selected more closely resembles that used in clinical practice, beginning with a baseline laboratory value and monitoring the change prospectively. We selected a 24-month period for calculating change in laboratory values from baseline. This was a compromise over an earlier timepoint which would not allow sufficient time for the laboratory values to change (or only detect patients with rapid changes) and a later time period such as 48 months, which meant patients with early outcomes, would be excluded. We believe using changes in laboratory values over a shorter time period (<24 months) in our model would underestimate the risk of a clinical outcome. We showed that calculating the risk score using changes in laboratory values over a longer period (48 months) would overestimate the risk because the latter patient would in reality have a slower rate of worsening in laboratory values than our model would suggest. Our models were derived from patients followed for a median of 6.3 and maximum of 8.7 years; these models may not apply to longer-term predictions. We did not assess whether the model could be utilized for repeat measurements over time, always maintaining a 2-year interval between laboratory assessments.

A reasonable criticism of our approach is that one has to wait a minimum of 24 months before the model could be used. In the HALT-C cohort, only 3.8% of patients had a clinical outcome during this period. Moreover, even in patients with cirrhosis, 80% are alive at 10 years, which would allow sufficient time to intervene if the model suggested a higher rate of outcomes.[17] Finally, the model could be used on retrospective data on any patient in whom 2 years of follow-up is available. Thus, our models can be applied to patients who have historical laboratory values up to 2 years prior to presentation. For patients with no historical laboratory values, the models that include baseline laboratory values only can be used to predict outcomes at the time of presentation and the prediction refined after the patient had been followed for 2 years. All of the patients used in this analysis had previously failed therapy and it is unclear how the model would perform on an untreated cohort. Therefore, it would be important to validate the model in other populations with advanced chronic hepatitis C.

In conclusion, we developed two straightforward models using widely available laboratory tests to accurately predict the outcome of advanced chronic hepatitis C. We demonstrated that the change in an individual laboratory variable over time complements the baseline value of that variable as a predictor of a clinical decompensation in patients with advanced chronic hepatitis C. Furthermore, the rapidity of the change is associated with the development of outcomes. Such information may be useful to the physician for designing a monitoring schedule and timely referral for liver transplantation, to patients in planning for the future, and to third-party payers for allocation of resources for screening and monitoring.

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