Quantitative Liver Function Tests Improve the Prediction of Clinical Outcomes in Chronic Hepatitis C: Results From the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis Trial

Gregory T. Everson,1 Mitchell L. Shiffman,2 John C. Hoefs,3 Timothy R. Morgan,3 Richard K. Sterling,4 David A. Wagner,5 Shannon Lauriski,1 Teresa M. Curto,6 Anne Stoddard,6 and Elizabeth C. Wright,7 the HALT-C Trial Group

Risk for future clinical outcomes is proportional to the severity of liver disease in patients with chronic hepatitis C virus (HCV). We measured disease severity by quantitative liver function tests (QLFTs) to determine cutoffs for QLFTs that identified patients who were at low and high risk for a clinical outcome. Two hundred and twenty-seven participants in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial underwent baseline QLFTs and were followed for a median of 5.5 years for clinical outcomes. QLFTs were repeated in 196 patients at month 24 and in 165 patients at month 48. Caffeine elimination rate constant ($k_{elim}$), antipyrine (AP) clearance (CI), MEGX concentration, methionine breath test (MBT), galactose elimination capacity (GEC), dual cholate (CA) clearances and shunt, perfused hepatic mass (PHM), and liver and spleen volumes (by single-photon emission computed tomography) were measured. Baseline QLFTs were significantly worse ($P < 0.0017$ to $P < 0.0001$) and spleen volumes were larger ($P < 0.0001$) in the 54 patients who subsequently experienced clinical outcomes. QLFT cutoffs that characterized patients as “low” and “high risk” for clinical outcome yielded hazard ratios ranging from 2.21 (95% confidence interval [CI]: 1.29-3.78) for GEC to 6.52 (95% CI: 3.63-11.71) for CA clearance after oral administration (Cloral). QLFTs independently predicted outcome in models with Ishak fibrosis score, platelet count, and standard laboratory tests. In serial studies, patients with high-risk results for CA Cloral or PHM had a nearly 15-fold increase in risk for clinical outcome. Less than 5% of patients with “low risk” QLFTs experienced a clinical outcome.

Conclusion: QLFTs independently predict risk for future clinical outcomes. By improving risk assessment, QLFTs could enhance the noninvasive monitoring, counseling, and management of patients with chronic HCV. (HEPATOLOGY 2012;55:1019-1029)

Chronic hepatitis C virus (HCV) is a major cause of liver disease, cirrhosis, and hepatocellular carcinoma (HCC) in the United States and worldwide.1-4 Early detection of patients with significant hepatic impairment, who are at risk for future decompensation, is a priority of clinical management. Progression of liver disease is defined histologically by accumulation of fibrosis and physiologically by...
impairment of hepatic function and blood flow. Increased Ishak fibrosis score\(^2,6\) or increased hepatic venous pressure gradient (HVPG)\(^7-9\) indicate greater severity of liver disease and identify patients at risk for future clinical complications. Quantifying fibrosis requires the performance of liver biopsy, and measuring HVPG is technically complex and requires catheterization of the jugular vein. Both liver biopsy and HVPG measurement are associated with potentially severe complications, prone to sampling error, and may not be embraced by patients. Accurate noninvasive methods for staging of disease are needed.

One noninvasive approach is to develop models based on clinical findings and standard blood tests. Child-Turcotte-Pugh (CTP) classification\(^10\) and model for end-stage liver disease (MELD) score\(^11,12\) are, perhaps, the best known and most commonly applied. Both were developed to predict surgical mortality or mortality after transjugular intrahepatic portal-systemic shunt (TIPS) in patients with advanced cirrhosis. Neither are applicable to the patient with earlier-stage or clinically compensated disease.\(^13\)

Other models target patients with compensated disease. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial investigators developed a model based upon bilirubin, albumin, aspartate aminotransferase/alanine aminotransferase (AST/ALT), and platelet count.\(^14\) This model identified high-risk patients, 59% of whom developed clinical outcomes in 3.5 years of follow-up. But, the high-risk cutoff was insensitive; only 46% of the patients who eventually developed outcomes were identified.

Hepatic elastography and serum fibrosis markers correlate with stage of fibrosis, as well as risk for cirrhosis or varices.\(^15-18\) In one study, hyaluronic acid, YKL-40, and tissue inhibitor of matrix metalloprotease-1 (TIMP-1), combined with standard laboratory tests, were significantly associated with disease progression.\(^18\) Further studies of elastography and serum fibrosis markers in predicting future risk for clinical outcomes are needed to validate their prognostic value.

We have previously demonstrated that a battery of quantitative liver function tests (QLFTs) correlated with stage of fibrosis, risk for cirrhosis and varices, size of varices, and other indicators of disease severity in patients enrolled in the HALT-C Trial.\(^19,20\) In the current study, we evaluated the independent ability of these QLFTs to prospectively define the risk for development of future clinical outcomes (i.e., hepatic decompensation or liver-related death).

**Patients and Methods**

The designs and methods of the HALT-C Trial and the QLFT ancillary study have been previously described.\(^19,21\) All patients had advanced fibrosis or cirrhosis and had previously failed to achieve sustained virologic response (SVR) with a previous course of interferon (INF) or pegylated interferon (Peg-IFN) with or without ribavirin (RBV). Most important, no patient had a previous history of any clinical complication of liver disease and all had baseline CTP scores of 5 or 6. Three clinical centers enrolled patients: University of Colorado Denver (Denver, CO), Virginia Commonwealth University (Richmond, VA), and University of California, Irvine (Irvine, CA).

Baseline QLFTs were performed in 285 patients. “Lead-in” patients (n = 232) underwent baseline QLFTs before retreatment with Peg-IFN and RBV, ribavirin in the lead-in phase of HALT-C. “Express” patients (n = 53) were treated with Peg-IFN plus RBV before enrollment in HALT-C and underwent
baseline QLFTs just before randomization. Thirty-two lead-in patients who achieved SVR, 9 relapers, and 7 nonresponders did not participate in the randomized phase, and 10 dropped out from the study before week 20. The remaining 227 patients (174 lead-in and 53 express) formed the cohort for the current study and were randomized to untreated control (n = 120) or maintenance with low-dose Peg-IFN monotherapy (n = 107). Patients were followed for clinical outcomes for a median of 5.5 years (mean, of 4.9 ± 2.2; range, 0-8.3). QLFTs were repeated at month 24 in 196 patients and at month 48 in 165 patients.

Assessment of Clinical Outcomes. Patients were evaluated every 3 months during the period of follow-up. Clinical outcomes included CTP progression (CTP score ≥7 on two consecutive evaluations), variceal bleeding, ascites, hepatic encephalopathy, and liver-related death. Listing for liver transplantation, liver transplantation, HCC, presumed HCC, and death resulting from nonhepatic causes were not outcomes in this analysis. Ten patients underwent liver transplantation: 4 for presumed HCC and 6 for hepatic decompensation. In these 6 patients, liver transplantation occurred subsequent to a different initial clinical outcome (CTP progression in 4 and encephalopathy in 2). The 4 patients with liver transplantation before clinical outcome were included in our analyses, but censored at the time of transplantation. An outcomes review panel, comprised of investigators from three clinical centers of the HALT-C Trial, verified all outcomes.21

Statistical Analyses. Results are expressed as means, standard deviations (SDs), and ranges. Baseline differences in demographic, clinical, histologic, and endoscopic characteristics, and results of QLFTs between patients with and without clinical outcomes, were evaluated by Cox proportional hazards analysis.

QLFT results were divided into tertiles of equal numbers of patients, stratifying results into low, intermediate, or high ranges, and the risks for clinical outcomes across QLFT tertiles were analyzed by Kaplan-Meier log-rank tests. QLFT cutoffs were defined using the boundary for the high-risk tertile, and these cutoffs were further verified by ROC (receiver operator curve) analyses. The independence of QLFTs in predicting clinical outcomes was analyzed by multivariable models that included histologic stage (e.g., Ishak fibrosis scores of 2, 3, and 4 versus 5 and 6) and platelet count or the HALT-C laboratory model.14 The performance of these same QLFT cutoffs in predicting initial clinical outcome was also evaluated in the serial QLFT studies by pooled relative risk analyses (i.e., the Mantel-Haenzel method). In the latter analyses, patients were censored once they had experienced a clinical outcome.

Statistical analyses were performed at the Data Coordinating Center for HALT-C (New England Research Institutes, Watertown, MA), using SAS release 9.2 (SAS Institute, Cary, NC).

Results

Clinical Outcomes. Fifty-four patients (24%) experienced at least 1 clinical outcome. These included progression in CTP score (N = 37), variceal bleeding (N = 4), ascites (N = 4), hepatic encephalopathy (N = 6), and liver-related death (N = 3). Nineteen patients, whose initial outcome was an increase in CTP score, subsequently experienced 28 additional clinical outcomes (ascites, n = 13; liver-related death, n = 10; encephalopathy, n = 4; and spontaneous bacterial peritonitis, n = 1). Clinical outcomes occurred in 12% of patients with Ishak fibrosis scores of 3 or 4 and in 40% of patients with Ishak fibrosis scores of 5 or 6.

Lack of Treatment Effect on QLFTs. In the main, HALT-C Trial Peg-IFN alpha-2a (90 µg/week) failed to improve clinical outcomes or halt histologic progression.22 In the current study, untreated patients and patients treated with maintenance Peg-IFN had similar baseline QLFTs, and treatment had no effect on changes in QLFTs from baseline to months 24 and 48 (Table 1). Given the lack of treatment effect, treatment and control groups were combined for the analyses of QLFTs in predicting clinical outcomes.

Baseline Demographic and Clinical Variables Associated with Clinical Outcomes. Baseline patient characteristics and standard laboratory results of patients with and without subsequent clinical outcomes are listed in Table 2. Patients who developed outcomes had higher bilirubin and international normalized ratio (INR) as well as lower albumin. Although these differences were statistically significant, means for these tests were within normal range, even in patients who developed outcomes. Only 6% of patients who developed outcomes had INR >1.2, 22% had bilirubin >1.2 mg/dL, and 52% had albumin <3.5 g/dL. In contrast, mean platelet count of patients who developed outcomes was below the lower limit of normal range, and 70% had a platelet count <140,000/µL.

Patients with subsequent outcomes had higher fibrosis scores and were more likely to have cirrhosis on liver histology and varices at endoscopy.

Baseline QLFTs Associated With Clinical Outcomes. QLFTs were worse at baseline in patients who subsequently experienced clinical outcomes (Table 2). Although differences varied by test, patients who in follow-up had subsequent clinical outcomes had
greater hepatic impairment, including microsomal (i.e., antipyrine [AP], caffeine, and lidocaine- monoethylglycine xylidide; MEGX), mitochondrial (methionine), and cytosolic (galactose) functions, and flow-dependent clearances (galactose, cholates [CAs], and perfused hepatic mass; PHM).

QLFTs are more sensitive than standard liver blood tests in identifying patients with hepatic impairment.

### Table 1. Change of QLFTs From Baseline Comparing Treated Patients to Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>M24 (Base)</th>
<th>M48 (Base)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Control</td>
</tr>
<tr>
<td>Metabolic tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP kelim (h⁻¹)</td>
<td>60</td>
<td>0 (0.013)</td>
</tr>
<tr>
<td>AP Cl (mL min⁻¹)</td>
<td>59</td>
<td>−0.97 (11.7)</td>
</tr>
<tr>
<td>Caffeine kelim (h⁻¹)</td>
<td>78</td>
<td>−0.01 (0.046)</td>
</tr>
<tr>
<td>GEC (mg kg⁻¹ min⁻¹)</td>
<td>93</td>
<td>0.265 (0.908)</td>
</tr>
<tr>
<td>MEGX₁₅min (ng mL⁻¹)</td>
<td>83</td>
<td>−1.98 (15.34)</td>
</tr>
<tr>
<td>CA clearances and shunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA kelim (min⁻¹)</td>
<td>95</td>
<td>−0.003 (0.03)</td>
</tr>
<tr>
<td>CA Cliv (mL min⁻¹)</td>
<td>95</td>
<td>−15.7 (134.8)</td>
</tr>
<tr>
<td>CA Cloral (mL kg⁻¹ min⁻¹)</td>
<td>94</td>
<td>−18.5 (488.9)</td>
</tr>
<tr>
<td>CA shunt (%)</td>
<td>94</td>
<td>2 (16)</td>
</tr>
<tr>
<td>SPECT liver-spleen scan</td>
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<td></td>
</tr>
<tr>
<td>PHM</td>
<td>89</td>
<td>0.49 (7.72)</td>
</tr>
<tr>
<td>Liver volume (mL kg⁻¹)</td>
<td>89</td>
<td>−0.55 (2.78)</td>
</tr>
<tr>
<td>Spleen volume (mL kg⁻¹)</td>
<td>88</td>
<td>0.39 (1.82)</td>
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### Table 2. Baseline Assessment of Patients With and Without Clinical Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Without Outcomes</th>
<th>Patients With Outcomes</th>
<th>Cox Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>N</td>
<td>Mean/%</td>
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<tr>
<td>Metabolic tests</td>
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<tr>
<td>AP kelim (h⁻¹)</td>
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<tr>
<td>AP Cl (mL kg⁻¹ min⁻¹)</td>
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<td>111</td>
<td>0.399</td>
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<tr>
<td>Caffeine kelim (h⁻¹)</td>
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<td>157</td>
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<tr>
<td>GEC (mg kg⁻¹ min⁻¹)</td>
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<td>170</td>
<td>4.95</td>
</tr>
<tr>
<td>MEGX₁₅min (ng mL⁻¹)</td>
<td></td>
<td>169</td>
<td>19.5</td>
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<tr>
<td>MBT</td>
<td></td>
<td>145</td>
<td>71.8</td>
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<tr>
<td>CA clearances and shunt</td>
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</tr>
<tr>
<td>CA kelim (min⁻¹)</td>
<td></td>
<td>171</td>
<td>0.098</td>
</tr>
<tr>
<td>CA Cliv (mL kg⁻¹ min⁻¹)</td>
<td></td>
<td>170</td>
<td>4.65</td>
</tr>
<tr>
<td>CA Cloral (mL kg⁻¹ min⁻¹)</td>
<td></td>
<td>170</td>
<td>14.19</td>
</tr>
<tr>
<td>CA shunt (%)</td>
<td></td>
<td>171</td>
<td>36.3</td>
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<tr>
<td>SPECT liver-spleen scan</td>
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</tr>
<tr>
<td>PHM</td>
<td></td>
<td>170</td>
<td>99.5</td>
</tr>
<tr>
<td>Liver volume (mL kg⁻¹)</td>
<td></td>
<td>169</td>
<td>18.52</td>
</tr>
<tr>
<td>Spleen volume (mL kg⁻¹)</td>
<td></td>
<td>167</td>
<td>4.33</td>
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**Abbreviations:** Vₚ, volume of distribution; CA kelim, rate constant of the rapid first phase of elimination of intravenously administered [24-¹³C]cholate; CA shunt, equivalent to CA Cliv/CA Cloral; CA Cliv, clearance of intravenously administered [24-¹³C]cholate calculated from dose/AUC; CA Cloral, clearance of orally administered [2,2,4,4-D]cholate calculated from dose/AUC; CA shunt, calculated from CA Cliv/CA Cloral.

*P value for caffeine kelim was <0.0001 after adjustment for current smoking.
In contrast to standard laboratory tests, baseline QLFTs were beyond normal range in nearly all patients who developed outcomes. Sixty-four percent had a caffeine elimination rate ($k_{elim}$) $<0.05 \text{ h}^{-1}$, 89% had AP $k_{elim}$ $<0.04 \text{ h}^{-1}$, 80% had AP clearance (Cl) $<0.4 \text{ mL min}^{-1} \text{ kg}^{-1}$, 81% had monoethylglycylxylidide concentration at 15 minutes postlidocaine ($\text{MEGX}_{15\text{min}}$) $<20 \text{ ng/mL}$, 73% had a methionine breath test.

Fig. 1. Metabolic tests. Results were divided into tertiles of equal numbers of patients, stratifying results into low (solid line), intermediate (dashed line), or high ranges (dotted and dashed line). Risks for clinical outcomes across tertiles were analyzed by Kaplan-Meier log-rank tests. Cutoffs were defined using the boundary for the high-risk tertile. For these metabolic tests, the high-risk tertile had the lowest test results. Survival probability is freedom from clinical outcome.
(MBT) <50, 74% had galactose elimination capacity (GEC) <5 mg min⁻¹ kg⁻¹, 93% had CA Cl after oral administration (Cloral) <15 mL min⁻¹ kg⁻¹, 89% had CA shunt >30%, and 79% had PHM <100.

**Predicting Clinical Outcomes by QLFTs.** Figure 1 shows the relationships of tertiles of baseline metabolic QLFTs to the subsequent development of clinical outcomes. MBT and AP Cl performed best. The boundaries and hazard ratios (HRs) for high-risk tertiles, which also defined QLFT cutoffs, were MBT ≤48 (HR, 5.92), AP Cl ≤0.28 mL kg⁻¹ min⁻¹ (HR, 3.62), caffeine kelim ≤0.04 h⁻¹ (HR, 2.67), MEGX15min ≤9.0 ng/mL (HR, 2.50), and GEC ≤4.32 mg kg⁻¹ min⁻¹ (HR, 2.21) (Table 3). By ROC analyses, the c-statistic for MBT was 0.79.

Figure 2 shows the relationships of tertiles of baseline CA Cls and shunt and single-photon emission computed tomography (SPECT) liver-spleen scan results to subsequent clinical outcomes. The boundaries and HRs for high-risk tertiles were CA Cloral ≤9.47 mL kg⁻¹ min⁻¹ (HR, 6.52), PHM ≤94.5 (HR, 4.97), spleen volume ≥5.93 mL kg⁻¹ (HR, 4.16), and CA shunt ≥46% (HR, 3.98) (Table 3). By ROC analyses, c statistics were 0.84 for CA Cloral, 0.79 for CA shunt, 0.79 for PHM, and 0.78 for spleen volume.

Baseline prevalence of cirrhosis (Ishak fibrosis stage 5 or 6) was higher and platelet count lower in the patients who subsequently experienced clinical outcomes (Table 2). Therefore, we tested the independence of QLFTs in predicting clinical outcomes by including these two factors as covariates. Interestingly, histologic stage dropped from significance in the prediction of clinical outcomes in models with AP Cl, CA Cloral, CA shunt, PHM, and spleen volume. Each QLFT, except spleen volume, retained significance in predicting clinical outcome in models of the QLFT with platelet count and histologic stage (Table 3).

We further tested the independence of QLFTs in models of each QLFT with the HALT-C laboratory score, which is derived from platelet count, bilirubin, albumin, and AST:ALT ratio. MBT, CA Cloral, PHM, and spleen volume remained significant, and CA shunt approached significance in these models (Table 3).

**Serial QLFTs and Clinical Outcomes.** Figure 3 displays the results for the serial QLFTs. The percentages of patients above and below QLFT cutoffs who experienced clinical outcomes during the 2-year intervals after QLFT studies at baseline, month 24, and month 48 are shown. AP Cl, caffeine kelim, CA Cloral, CA shunt, PHM, and spleen volume performed best. Eleven to thirty percent of patients characterized as high risk by QLFTs experienced their initial clinical outcomes in the 2-year intervals between testing periods. Pooled relative risks (RRs) for initial clinical outcomes, based on these QLFT cutoffs, were (RR [95% CI]) AP Cl 7.25 (2.98-17.63), caffeine kelim 5.63 (2.66-11.90), GEC 3.08 (1.73-5.49), MEGX15min 2.48 (1.33-4.61), MBT 5.43 (2.18-13.55), CA shunt 7.62 (3.77-15.42), CA Cloral 14.09 (6.03-32.95), PHM 14.47 (6.24-33.55), and spleen volume 6.07 (3.10-11.89). Sensitivities (pooled) of the serial QLFTs in identifying patients who developed outcomes were

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**Table 3. Performance Characteristics of QLFT Cutoffs in Prediction of Clinical Outcomes**

<table>
<thead>
<tr>
<th>Category</th>
<th>QLFT</th>
<th>Patients (N)</th>
<th>High-Risk</th>
<th>Univariate (Histology, Platelet Count)</th>
<th>Multivariate (Histology, Platelet Count)</th>
<th>Multivariate (HALT-C Lab Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic tests</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>AP Cl</td>
<td>146</td>
<td>35</td>
<td>≤0.28 mL kg⁻¹ min⁻¹</td>
<td>3.62 (1.83-7.14)</td>
<td>3.0 (1.5-5.9)</td>
<td>1.8 (0.8-4.0)</td>
</tr>
<tr>
<td>Caffeine kelim</td>
<td>207</td>
<td>50</td>
<td>≤0.04 h⁻¹</td>
<td>2.67 (1.53-4.66)</td>
<td>1.9 (1.1-3.4)</td>
<td>1.2 (0.6-2.2)</td>
</tr>
<tr>
<td>GEC</td>
<td>223</td>
<td>53</td>
<td>≤4.32 mg kg⁻¹ min⁻¹</td>
<td>2.21 (1.29-3.78)</td>
<td>1.8 (1.0-3.1)</td>
<td>1.3 (0.7-2.3)</td>
</tr>
<tr>
<td>MEGX15min</td>
<td>217</td>
<td>48</td>
<td>≤9.0 ng mL⁻¹</td>
<td>2.50 (1.42-4.40)</td>
<td>2.2 (1.2-3.9)</td>
<td>0.9 (0.4-1.6)</td>
</tr>
<tr>
<td>MBT</td>
<td>185</td>
<td>40</td>
<td>≥48</td>
<td>5.92 (3.01-11.66)</td>
<td>4.4 (2.2-8.8)</td>
<td>2.9 (1.4-6.1)</td>
</tr>
<tr>
<td>CA clearance and shunt</td>
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<tr>
<td>CA Cliv</td>
<td>224</td>
<td>54</td>
<td>≤3.59 mL kg⁻¹ min⁻¹</td>
<td>2.87 (1.68-4.91)</td>
<td>2.2 (1.3-3.8)</td>
<td>1.2 (0.6-2.3)</td>
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<tr>
<td>CA Cloral</td>
<td>224</td>
<td>54</td>
<td>≤9.47 mL kg⁻¹ min⁻¹</td>
<td>6.52 (3.63-11.71)</td>
<td>4.0 (2.1-7.9)</td>
<td>2.8 (1.4-5.7)</td>
</tr>
<tr>
<td>CA shunt</td>
<td>225</td>
<td>54</td>
<td>≥46%</td>
<td>3.98 (2.28-6.92)</td>
<td>2.4 (1.3-4.3)</td>
<td>1.8 (1.0-3.5)</td>
</tr>
<tr>
<td>SPECT liver-spleen scan</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHM</td>
<td>223</td>
<td>53</td>
<td>≤94.5</td>
<td>4.97 (2.83-8.74)</td>
<td>2.3 (1.2-4.5)</td>
<td>2.2 (1.2-4.1)</td>
</tr>
<tr>
<td>Spleen volume</td>
<td>219</td>
<td>52</td>
<td>≥5.93 mL kg⁻¹</td>
<td>4.16 (2.38-7.26)</td>
<td>1.7 (0.9-3.2)</td>
<td>2.2 (1.2-4.0)</td>
</tr>
</tbody>
</table>

Abbreviations:
- LCI, lower confidence interval (95%);
- UCI, upper confidence interval (95%).
CA Cl\textsubscript{oral} 86%, PHM 83%, AP Cl 80%, CA shunt 79%, caffeine k\textsubscript{elim} 76%, MBT 75%, spleen volume 72%, GEC 57%, and MEGX\textsubscript{15min} 51%.

Perhaps even more important, characterization of a patient as low risk by QLFT cutoffs was associated with a very low risk for clinical outcome. The negative
predictive values (pooled) for clinical outcome of QLFT cutoffs defining low risk were CA Cl_total 98.4%, PHM 98.2%, AP CI 97.6%, CA shunt 97.6%, caffeine k_elim 97.1%, MBT 97.4%, spleen volume 97.0%, GEC 95.3%, and MEGX_{15min} 95.0%.

At each testing period, the mean values for QLFTs (except GEC) were significantly worse in the group of patients experiencing subsequent clinical outcomes. In addition, in the patients whose initial clinical outcome occurred after the month 48 QLFT study, mean values for nearly all QLFTs worsened from either baseline or month 24 to month 48 (data not shown).

Discussion

One aim of our study was to define the impact of Peg-IFN maintenance therapy on hepatic function in patients with advanced, but compensated, chronic HCV. In three large clinical trials, maintenance therapy failed to slow disease progression or reduce clinical outcomes.22-24 In the HALT-C Trial, serum HCV RNA and ALT and hepatic inflammation were reduced by maintenance therapy. The latter effects could potentially reflect a reduction in hepatic injury, which might improve hepatic function or blood flow. However, in the current study, Peg-IFN maintenance therapy failed to improve any of the serially performed QLFTs—a group of tests that evaluated a broad range of hepatic functions and blood flow. The lack of improvement in QLFTs in the current study provides additional evidence that maintenance therapy with low-dose Peg-IFN is ineffective.

Another major aim of our study was to evaluate the independent ability of QLFTs to predict future clinical outcomes. Our patient cohort was ideal for addressing this aim because all had advanced fibrosis, all were at risk for future clinical outcome, and none had experienced previous decompensation. In follow-up, 24% of our cohort experienced a clinical outcome similar to the rate of clinical outcome observed in the HALT-C Trial as a whole.22 Our results are likely representative of the whole HALT-C cohort, and the general population of compensated patients with advanced chronic HCV.

Because QLFTs monitor changes in hepatic metabolism and blood flow, changes common to all liver diseases, they could potentially be useful in monitoring patients with any liver disease. Despite a 48.5% prevalence of hepatic steatosis in our cohort, the relationships of CA Cls, shunt, and PHM to stages of hepatic fibrosis and cirrhosis are preserved and not altered by body mass index (BMI), hepatic steatosis, homeostasis model assessment (HOMA) score, hepatic inflammation, alcohol use, and smoking.19 In addition, SPECT
liver-spleen scan has correlated with the severity of a variety of liver diseases.\(^\text{25-28}\)

Progression of chronic HCV is characterized pathologically by accumulation of fibrosis and physiologically by impairment of hepatic function and blood flow. In our study, we measured physiologic impairment using a battery of QLFTs. We previously demonstrated that these QLFTs predicted cirrhosis, stage of fibrosis, varices, and variceal size.\(^\text{19}\) Also, they identified the subgroup of patients with the most severe disease who failed to respond to antiviral therapy and tracked improvement in hepatic function after SVR.\(^\text{20}\) In the current study, QLFTs identified patients with the greatest hepatic impairment who developed clinical outcomes.

We defined cutoffs for QLFTs that predicted risk for future clinical decompensation over a median duration of follow-up of 5.5 years. In multivariable analyses, all QLFTs enhanced the prediction of clinical outcomes when these tests were combined with hepatic histology and platelet count. In models with AP Cl, CA Cl\(_{\text{oral}}\), CA shunt, PHM, and spleen volume, histologic cirrhosis dropped from significance. Cirrhosis did not improve the prediction of clinical outcomes by these QLFTs. In a previous analysis, CA Cl\(_{\text{oral}}\), CA shunt, and PHM were able to predict which patients had varices—a prediction that was also not improved by adding hepatic histology to the models.\(^\text{19}\) These results raise the possibility that the measurement of hepatic function by noninvasive QLFTs could be clinically relevant and useful and could potentially supplant the staging of hepatic fibrosis by liver biopsy as the “gold standard” for defining risk for future outcomes. Our results also suggest that QLFTs could complement histology and standard laboratory tests in the assessment of a patient’s risk for hepatic decompensation and liver-related death.

Serial testing identified high-risk patients from our initial cohort of stable patients with advanced fibrosis and compensated cirrhosis. The RR for clinical outcome was nearly 15-fold greater for patients with high-risk, compared to low-risk, results for CA Cl\(_{\text{oral}}\) and PHM. Serial QLFT testing identified up to 86% of all patients who developed outcomes. Perhaps more important, less than 5% of patients with low-risk QLFT results experienced a clinical outcome. These findings indicate that serial QLFTs performed every 2 years could be useful in detecting not only patients at highest risk for clinical outcome, but also patients with stable disease who would have a benign clinical course.

Stage of fibrosis, especially histologic cirrhosis, determined by liver biopsy is considered the gold standard for assessing disease severity and predicting clinical outcome. In the HALT-C cohort, with 6 years of follow-up, baseline Ishak fibrosis stage 6 (definite cirrhosis) or stages 5 (incomplete cirrhosis) plus 6 had 35% (83 of 238) and 66% (157 of 238) sensitivity for the prediction of future clinical outcome.\(^\text{7}\) In the current study, serial QLFT testing was up to 86% sensitive. In the same study of histology, 18% (155 of 853) of patients with Ishak fibrosis stage \(<6\) and 13% (81 of 622) of patients with Ishak fibrosis stage \(<5\) experienced clinical outcomes.\(^\text{7}\) As noted above, \(<5%\) of patients with low-risk QLFT results experienced a clinical outcome. These comparisons suggest that QLFTs may be superior to histologic staging by liver biopsy in identifying both high- and low-risk groups and may be more accurate than staging fibrosis\(^\text{6,7,25-40}\) in predicting clinical outcomes.

Prognostic models utilizing standard blood tests (e.g., AST:ALT ratio, bilirubin, albumin, and platelet count) and Ishak fibrosis score were previously developed in the HALT-C cohort.\(^\text{14}\) However, we observed that mean values for baseline bilirubin, INR, and albumin were within normal range in patients who subsequently developed clinical outcomes. In clinic populations with less severe disease, the ability of these standard tests to identify patients at higher risk for clinical outcomes would be limited. In addition, hepatic histology was a significant predictor of clinical outcome in these laboratory models, indicating that liver biopsy would still be required to optimize the prediction of risk for developing a clinical outcome. In contrast, nearly all of the patients who experienced clinical outcomes had values for QLFTs outside norm range, suggesting that QLFTs could provide greater discrimination between high- and low-risk patients in clinic populations enriched with patients who have milder disease. Indeed, in the current study, CA Cl\(_{\text{oral}}\), PHM, spleen volume, MBT, and, possibly, CA shunt enhanced the predictability of the HALT-C laboratory model.

Although normal ALT and minimal fibrosis on liver biopsy may imply minimal disease, a proportion of these patients have more advanced disease and are at risk for clinical outcomes.\(^\text{41-43}\) QLFTs could potentially be useful in this population by defining those with significant hepatic impairment who would be predicted to experience future clinical outcomes.

Historically, clinical assessment of patients with liver disease has relied on surrogates of hepatic function (i.e., fibrosis stage or liver blood tests), as opposed to a true measurement of function. In the evaluation of disease affecting other organs, functional assessment
defines prognosis and clinical management. Because fibrosis and standard blood tests have been the standards for assessing severity of liver disease, functional tests have been compared to these surrogates. Unfortunately, these comparisons cannot differentiate the advantages of functional testing over surrogates, or vice versa. Using a relevant, discriminating endpoint (i.e., clinical outcome), we compared QLFTs to hepatic histology and standard blood tests and demonstrated that QLFTs compared favorably to hepatic histology and enhanced standard blood tests in the prediction of clinical outcome.

Analyses of our battery of QLFTs suggest that CA Cl and PHM performed best in identifying patients at risk for clinical outcomes. When used serially, these tests had the highest pooled RR, sensitivity, and negative predictive value. In contrast to CA Cl and PHM, metabolic tests may be influenced by age, gender, medications, BMI, and hepatic steatosis.19,44-50

We conclude that QLFTs identify patients at risk for future clinical decompensation and, also, patients with adequate hepatic reserve who would have a benign clinical course. Despite these favorable characteristics, questions remain. Are QLFTs practical or ready for routine use in clinical practice, or, will any of the QLFTs gain approval by the U.S. Food and Drug Administration? It is our opinion that broader clinical application of QLFTs is not only possible, but also likely. Noninvasive quantification of hepatic function and reserve by QLFTs is safer than the determination of hepatic fibrosis by liver biopsy and QLFT methods have been simplified.35,52 Herein, we demonstrated that QLFTs, particularly CA Cl and PHM, more accurately predict risk for clinical outcome. Improved safety and accuracy are appealing to patients, care providers, regulatory bodies, and payors. Although elastography or serum fibrosis tests are safer than liver biopsy, they yield no additional characterization of liver disease beyond stage of fibrosis. In addition, elastography is expensive, operator dependent, and results may be influenced by body habitus, hepatic steatosis, and hepatic inflammation. We speculate that the time may come when quantifying liver function, in preference to measuring liver fibrosis, becomes the new standard for assessing disease severity in patients with chronic liver disease.


References

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