Enhanced Liver Fibrosis Score Can Be Used to Predict Liver-Related Events in Patients With Nonalcoholic Steatohepatitis and Compensated Cirrhosis

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Background

There is a growing need for a non-invasive tool to identify patients at higher risk of hepatic decompensation among individuals with compensated non-alcoholic steatohepatitis (NASH) cirrhosis\(^1\). HVPG has value in risk stratification\(^2\) and prediction of mortality among cirrhotics\(^3\) but has limitations of being invasive, costly, and requirement for expertise\(^4\).

Enhanced Liver Fibrosis (ELF) score is based on circulating markers of hepatic matrix turnover and consists of hyaluronic acid, tissue inhibitor of metalloproteinases-1 (TIMP-1) and propeptide of type III collagen (PIIINP). It identifies NAFLD patients with advanced fibrosis quite reliably\(^5\),\(^6\). However, its utility as a prognostic biomarker among individuals with compensated cirrhosis due to NASH is unclear. This study evaluated the prognostic significance of ELF score for predicting short-term liver-related outcomes among patients with compensated NASH cirrhosis.

Methods

This study was based on a 52-week phase 2 randomized controlled trial (NCT02462967), which evaluated belapectin (galectin receptor antagonist) for treating NASH cirrhosis\(^7\). It consisted of 162 patients with biopsy-proven NASH compensated cirrhosis and portal hypertension. ELF (Advia Centaur Immunoassay), FIB-4 index, APRI, NAFLD fibrosis score, Child-Turcotte-Pugh (CTP) and MELD scores were determined at baseline. The development of liver-related events was defined as at least one of the following: development or progression of gastroesophageal varices, new-onset ascites, variceal hemorrhage, and hepatic encephalopathy, an increase of Child-Turcotte-Pugh (CTP) score ≥ 2 points from baseline or an increase in MELD score to >15. One subject dropped out of the study, and 161 were available for analysis. Using baseline ELF score, subjects were stratified as ELF ≥ 9.8 and ≥ 11.3 to assess risk (Kaplan-Meier curves) and clinical concordance (sensitivity, specificity, PPV, NPV, LR+, and LR-) of subsequent events. ELF cutoff values for stratification were based on existing literature\(^8\).

Cox proportional hazard regressions were adjusted for age, sex, body mass index and type 2 diabetes. C-statistics were used for discriminative capability of diagnostic tools.
Results

Supplemental Tables 1 and 2 describe the baseline characteristics according to presence of liver-related events and baseline ELF of 11.3 respectively. At 52 weeks, 33 (20%) patients developed liver-related events as follows: development or progression of varices, 17 (11%); decompensations, 13 (8%) or CTP≥2 or MELD>15, 3 (2%). Fourteen (9%) patients developed medium-large size varices and/or presence of red signs. As shown in Table 1 and Supplemental Figure 1A, there was a stepwise increase in the frequency of developing liver-related events among patients with ELF <9.8 (10.5%), 9.8 to 11.2 (16.9%), and ≥ 11.3 (32.7%). Compared to ELF <9.8, patients with ELF of ≥ 11.3 had a significantly higher frequency of liver-related events (HR: 4.81, 95% CI: 1.54-15.05, P <0.01). Patients with ELF between 9.8 and 11.2 did not have a higher frequency of liver-related events compared to ELF <9.8 (HR 1.46, 95% CI: 0.45-4.65, P=0.08). We found a strong correlation between ELF and HVPG measurements at baseline (r=0.469, P<0.001) and end of study (r=0.657, P<0.001).

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ELF > 9.8 for predicting liver-related outcomes by 52 weeks was 87.9%, 26.6%, 23.6%, and 89.5% respectively. The sensitivity, specificity, PPV, and NPV for ELF ≥ 11.3 for predicting liver-related outcomes by 52 weeks was 51.5%, 72.7%, 32.7%, and 85.3%, respectively.

Supplemental figure 1B shows ELF’s capability to discriminate patients with 1-year liver-related outcomes in comparison to NAFLD fibrosis score, FIB4, APRI, CTP and MELD scores. The area under the ROC curve was 0.67 (95% CI: 0.57-0.77) for baseline ELF and 0.68 (95% CI: 0.57-0.77) if a change in ELF over time was added to its baseline values (Supplemental figure 1C).

Discussion

This study demonstrates that ELF score strongly correlates with short-term risk of liver-related events, and a threshold of ≥11.3 is associated with a 5-fold higher risk of developing a liver-related outcome. Importantly, an ELF threshold <9.8 will be particularly accurate in ruling out the occurrence of liver-related outcomes in the short term (NPV 90%). ELF was superior to Fib4, MELD and CTP for predicting one-year risk of liver-related events. Correlation of ELF score with
HVPG could explain its precise performance. Our study provides external validation for the ELF cut off scores used by Sanyal et al. for predicting liver-related complications among NASH patients with advanced fibrosis.

Our data is limited to small sample size with a short period of follow-up. Furthermore, our results might only apply to cirrhotic populations. If validated in large-scale studies with long-term follow-up, ELF could be used to provide prognostic information and evaluate new treatment strategies among individuals with compensated NASH cirrhosis.
Table 1: Risk of Liver Related Event Based on ELF Score

<table>
<thead>
<tr>
<th>Risk Group Based on ELF Score</th>
<th>N</th>
<th>Liver Related Event</th>
<th>Absolute Risk (95% CI)</th>
<th>LR (95% CI)</th>
<th>Cox Proportional Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 9.8</td>
<td>36</td>
<td>4</td>
<td>34</td>
<td>10.5%</td>
<td>0.46 (0.17, 1.20)</td>
</tr>
<tr>
<td>9.8 to &lt; 11.3</td>
<td>70</td>
<td>12</td>
<td>59</td>
<td>16.9%</td>
<td>0.79 (0.48, 1.29)</td>
</tr>
<tr>
<td>≥ 11.3</td>
<td>55</td>
<td>17</td>
<td>35</td>
<td>32.7%</td>
<td>1.88 (1.22, 2.91)</td>
</tr>
<tr>
<td>All</td>
<td>161</td>
<td>33</td>
<td>128</td>
<td>20.5%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ELF, Enhanced Liver Fibrosis; LR, likelihood ratio; CI, confidence interval.
REFERENCES


