For use in the U.S.

Literature Compendium

The Enhanced Liver Fibrosis (ELF) Test as a Prognostic Tool

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Introduction

NAFLD/NASH: a growing epidemic

NAFLD refers to a spectrum of diseases, from simple fatty liver to more-aggressive nonalcoholic steatohepatitis (NASH). In the U.S. alone, an estimated 80–90 million individuals currently have diagnosed or undiagnosed NAFLD. Among these individuals, up to 20 million people could have NASH, with as many as 4–6 million people projected to have advanced fibrosis.[1] While patients with NASH are more likely to develop progressive disease, which can result in cirrhosis, liver failure, or hepatocarcinoma (HCC), patients without histological evidence of NASH are also at risk.[2] Progressive CLD typically lacks signs and symptoms, with many patients remaining undiagnosed until uncompensated disease presents. Liver fibrosis versus the inflammatory process is recognized as the key driver of pathogenicity in NAFLD/ NASH.[3,4] Early recognition of progressive fibrosis and intervention is key for improved outcomes. While weight loss and lifestyle modifications can help reverse disease, compliance can be a challenge.

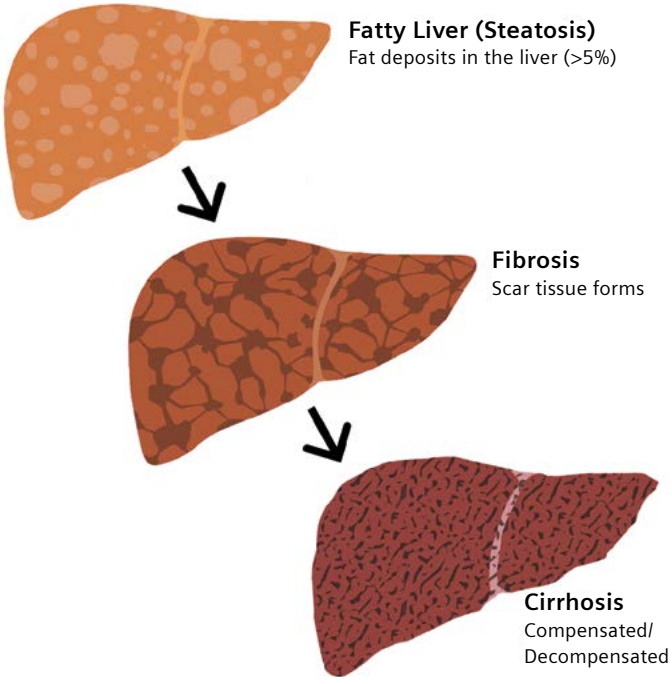


Figure 1: ELF score ≥9.8 indicates high risk of advanced fibrosis

Blood-based tests for advanced liver fibrosis due to NASH

Several therapies in late-stage development may offer a pharmacologic option if approved, but this will require identification of patients at highest risk (i.e., patients with advanced fibrosis). While tissue biopsy has been the historical standard, it is invasive, carries risk, has suboptimal accuracy, and is not amenable as a screening or routinely repeated test. Noninvasive tests (NITs)—both blood-based and imaging for liver elasticity—have emerged as alternatives. Blood-based tests can readily support high-volume testing, do not require patient access to specialized imaging equipment or highly trained operators, and generally have lower incidence rates of failure and unreliable results reported for imaging modalities.[3,4]

Blood-based tests for liver fibrosis include indirect and direct markers.[5] Indirect markers may reflect elements of inflammation or damage, while direct markers measure analytes directly involved in fibrosis and turnover of the extracellular matrix (ECM). Since fibrosis is the key indicator of damage and CLD progression, direct assessment of fibrosis has proven valuable for identifying at-risk patients. The widely studied ELF™ Test is a fully automated immunoassay requiring only a single serum sample that can assess active, dynamic fibrosis rather than the damage it has caused.

The ELF Test is the first routine, standardized, direct-biomarker panel for prognostic risk assessment in advanced fibrosis due to NASH. The ELF score combines three serum biomarkers:

- Hyaluronic acid (HA)
- Procollagen III N-terminal peptide (PIIINP)
- Tissue inhibitors of metalloproteinase 1 (TIMP-1)

The three direct markers of the ELF test are complementary and, when combined into an ELF score, provide information that is prognostic for progression to cirrhosis and liver-related events.

ELF Test: a simple blood test for a complex process

Liver fibrosis is biochemically complex but is orchestrated primarily by activated hepatic stellate cells (HSCs). Activated HSCs produce components of the ECM that include proteins such as fibronectin, laminin, collagens, hyaluronic acid (HA), proteoglycans, and collagen types I, III, IV, and V that form scar tissue in the liver.[6] Deposited ECM progressively accumulates and replaces normal liver tissue with scarring that damages hepatic architecture and drives dysfunction.

Fibrosis of the liver is a largely bidirectional process.[7,8] Fibrosis and repair mechanisms have been linked to ECM-related pathways. HA and PIIINP are components of damage associated with progressive scarring. Regression and repair are associated with upregulation of matrix metalloproteinases (MMPs), which can degrade ECM deposition and therefore are central to healing. Levels of MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPs), which bind MMPs. TIMP-1 overexpression hinders degradation and clearance of the fibrotic matrix, leading to increased levels of interstitial ECM and progressive fibrosis.[9,10] Additionally, low levels of TIMP-1 may promote hepatic stellate cell apoptosis.[8] By testing for direct markers associated with both ECM deposition (PIIINP, HA) and inhibition of repair (TIMP-1), the ELF Test provides a direct quantitative measure for the assessment of disease progression in patients with advanced fibrosis due to NASH.

Conclusion

The three direct markers of the ELF Test are complementary and, when combined into an ELF score, provide information that is prognostic for progression to cirrhosis and liver-related events. The performance of the ELF Test has been well-established in the scientific literature, and ease of testing and interpretation support routine clinical use. This compendium highlights a small subset of the extensive number of ELF publications and focusses on patients with advanced fibrosis due to NASH.

The products/features mentioned here are not commercially available in all countries. Their future availability cannot be guaranteed.

Derivation and Performance of Standardized Enhanced Liver Fibrosis (ELF) Test Thresholds for the Detection and Prognosis of Liver Fibrosis

Day J, et al. J Appl Lab Med. 2019 Mar;3:815-26.

Objective

Identify standardized thresholds for the ELF test for the detection of fibrosis severity and prognosis using data from a large prospective study.

Methods

- Leveraging a Delphi approach, expert hepatologists were interviewed and asked to define clinically acceptable levels of test performance for the assessment of fibrosis in patients with CLD. Specifically, they were asked what proportion of patients with severe fibrosis or cirrhosis they would be willing to accept as misassigned for moderate or mild fibrosis. Additionally, the hepatologists also requested a highly specific value for the identification of cirrhosis.
- Clinician consensus for acceptable test sensitivity in low-risk patients was 80–85%, with the view that these patients could undergo repeat testing to aid assessment of progression. An 80% sensitivity was opted for in the detection of cirrhosis. An additional threshold that would identify cirrhosis with greater specificity and minimize inappropriate referral of patients with mild or moderate fibrosis was requested by the clinicians and identified as ≤5% (i.e., high specificity to minimize referral of patients without advanced disease).
- Data from the original ELF test patient cohort (EUROGOLF) was analyzed for thresholds that would conform to the requested performance parameters.
- Corresponding cutpoints identified for assessment were then investigated relative to outcomes in 501 patients. Thresholds identified for histological correlation were recalculated for prognosis with clinical outcome history at 5, 6, and 7 years.
- The prognostic performance of the ELF test at these cutpoints was assessed in the prediction of all-cause mortality or any liver-related event (LRE) post recruitment.

Results

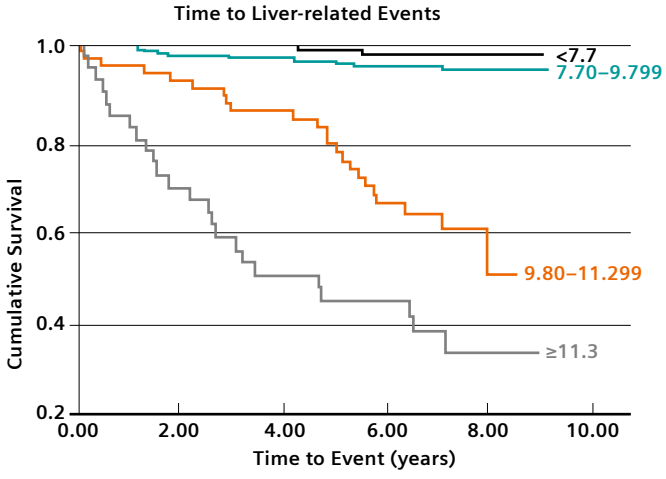
- Evaluation of the prognostic performance relative to the initial ELF score was assessed up to 7 years for LRE in patients grouped by low to high ELF score threshold values (<7.7; 7.7–9.8; 9.8–11.3; ≥11.3).
- LREs and relative risk of death were significantly elevated in patients with ELF scores >9.8.
- Hazard ratios for patients with ELF scores ≥11.3 for LREs more than doubled compared to ELF scores falling between 9.80 and 11.29.

Significance

- Three ELF score thresholds corresponding to values for fibrosis assessment were prognostic. Use of the ELF score identified four categories of risk for liver-related outcomes, supporting clinical management and decision making.
- This study's cutoffs have been subsequently validated in several randomized controlled studies.

Conclusion

"Using data derived from a large prospective study and the opinions of expert hepatologists, we have identified standard thresholds for the Enhanced Liver Fibrosis test. These thresholds can be used to determine the prognosis of chronic liver disease."



The data from this study was used to derive the ELF cutoffs. Although these cutoffs were originally based on correlation to histology in a mixed etiology population, the 9.8 and 11.3 cutoffs were subsequently applied prognostically to more defined patient populations.
In the U.S., the ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events. In the U.S., the ELF Test is not for use in the diagnosis of NASH or for the staging of fibrosis.

The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data from the Simtuzumab Trials

Sanyal AJ, et al. Hepatology. 2019 Dec;70(6):1913-27.

Objective

Analyze the control and trial arms of patients enrolled in a clinical trial for simtuzumab using serum markers of fibrosis and other testing parameters of NASH progression; assess changes and clinical outcomes.

Methods

- Patients with NASH and bridging fibrosis (F3) or compensated cirrhosis (F4) were enrolled.
- The treatment and trial arms were combined after 96 weeks due to lack of treatment efficacy to assess tests and outcomes.
- Outcomes analyzed included progression to cirrhosis in the F3 group and liver-related events in the F4 group.
- Tests included biopsy (with Ishak staging), ELF Test, FibroSure/FibroTest, FIB-4, APRI, NAFLD Activity Score (NAS), and hepatic collagen content and alpha-smooth muscle actin (by morphometry). Core biopsies were obtained at baseline and weeks 48 and 96 and staged using modified Ishak. Serum markers (including the ELF Test) were measured at baseline and every three months.
- Outcomes were assessed relative to baseline values of the ELF Test and other tests.

Results

- The primary determinant of disease progression in both patient subgroups was fibrosis as determined histologically or based on the ELF Test or other serum markers.
- During a mean follow-up of 29 months, patients with bridging fibrosis were evaluated for progression to cirrhosis (based on histologic findings, signs, or symptoms). Higher ELF scores at baseline were significantly associated with disease progression.
- The optimal cutoff for baseline ELF score to predict disease progression (balancing sensitivity and specificity) was 9.76.
- 21% of patients with bridging fibrosis achieved ≥1 stage improvement over the 2-year follow-up. Lower ELF scores at baseline, but not FibroSure/FibroTest, NAS, or severity of steatosis and lobular inflammation, were associated with improvement/regression.*
- During a mean follow-up of 30.9 months, 19% patients with compensated cirrhosis experienced a liver-related event. A higher ELF score at baseline was associated with an increased risk of events.
- The optimal cutoff for baseline ELF score to predict clinical events (balancing sensitivity and specificity) was 11.27. Baseline ELF score outperformed biopsy for the prediction of liver-related events.*
- Cirrhosis regression was achieved in 8.6% of patients through the end of the study and associated with lower baseline ELF score.

Significance

- This study independently derived the ELF Test cutoffs of 9.8 and 11.3 demonstrating high inter-study consistency.
- The data supports the notion that reductions in fibrosis may offer the greatest clinical benefit in a high-risk population.
- As a quantitative measure of direct markers of fibrosis, the baseline ELF score or changes over time could be used for risk assessment or evaluation for improvement or disease progression. As a blood-based NIT, an ELF score can be readily obtained using a routine serum sample.
- This study revealed a relatively more-rapid rate of disease progression over a 2-year period, suggesting the natural history of NASH may be faster than previously described.

Use of quantitative markers of fibrosis such as the ELF score might aid more expedient identification of patients at higher risk for disease progression and trigger intervention.

Conclusion

"Unlike baseline Ishak fibrosis stage, which had no prognostic value in either cohort, the ELF score at baseline and its change over time was associated with disease progression in patients with bridging fibrosis and cirrhosis."*

**The ELF Test provides prognostic information supplemental to biopsy to assess the likelihood of progression to cirrhosis and liver-related clinical events. Test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including information obtained by alternative methods, and clinical evaluation as appropriate.*

Enhanced Liver Fibrosis Score Can be Used to Predict Liver-related Events in Patients with Nonalcoholic Steatohepatitis and Compensated Cirrhosis

Are VS, Vuppalanchi R, Vilar-Gomez E, Chalasani N. Clin Gastroenterol Hepatol. 2021;19(6):1292-1293.e3

Objective

Investigate the prognostic performance of the ELF score to predict short-term liver-related outcomes among patients with compensated NASH cirrhosis.

Methods

- Study evaluated the response of 162 patients to belapectin (galectin receptor antagonist) who had biopsy-proven NASH with compensated cirrhosis and portal hypertension as part of a phase II randomized controlled trial (NCT02462967).
- At 52 weeks, patients were evaluated for development of LREs in the short term.
- 161 patients had baseline and 52-week ELF Scores measured. Using the baseline scores, patients were risk stratified by ≥9.8 and >11.3.

Results

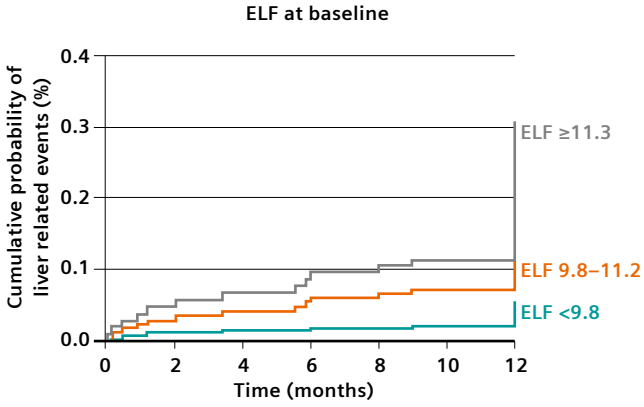
- One-fifth of patients had developed LREs at the end of 52 weeks.
- Patients with ELF scores ≥9.8 had a significantly higher risk of a liver-related outcome than patients with ELF scores <9.8.
- The ELF Test was a better predictor of LREs at 1 year than FIB-4, MELD score, and CTP score.*

Significance

- Study supports that the ELF Score correlates with short-term risk of LREs, and patients with an ELF Score of ≥11.3 are 5 times more likely to have a liver-related outcome.
- Study supports that in the short term an ELF Score <9.8 can rule out liver-related outcomes.**

Conclusion

"Our study provides external validation for the ELF cutoff scores used by Sanyal et al. for predicting liver-related complications among NASH patients with advanced fibrosis."



ELF Test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including information obtained by alternative methods, and clinical evaluation as appropriate.

**An ELF score < 9.8 is associated with a lower prognostic risk, but disease progression is still possible for patients with ELF measurements below this threshold.*

The Association of Histologic and Noninvasive Tests with Adverse Clinical and Patient-reported Outcomes in Patients with Advanced Fibrosis Due to Nonalcoholic Steatohepatitis

Younossi ZM, Anstee QM, Wong VW, et al. Gastroenterology. 2021;160(5):1608-19.

Objective

Investigate the associations between histology and NITs for fibrosis with clinical outcomes in patients with advanced fibrosis due to NASH.

Methods

- Study evaluated the response of 2154 patients with advanced NASH enrolled in four global phase II and phase III randomized controlled trials (NCT01672866, NCT01672879, NCT03053050, NCT03053063) for simtuzumab and selonsertib.
- Study collected liver biopsy samples and NIT results

Results

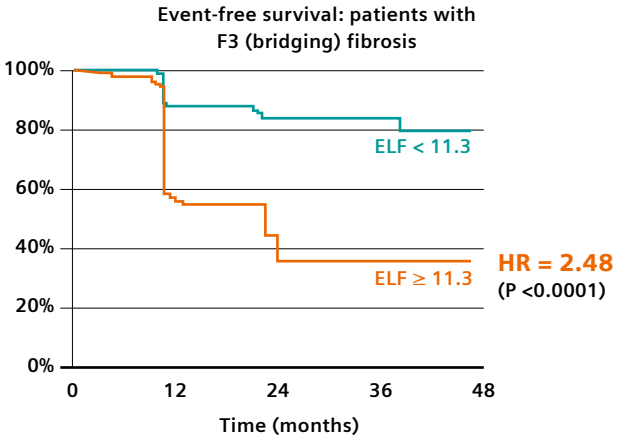
- Of the 2154 patients with advanced NASH (biopsy confirmed), 47.5% were F3 and 52.5% were F4, 72% had type 2 diabetes, 60% were female, and 40% were male. The mean follow-up was 16 months.
- NASH patients with ELF ≥11.3 have 2.5 to 2.8 times the risk of experiencing a liver-related event.
- The negative predictive value was also very high for both groups, indicating that those with ELF <11.3 were less likely to experience an unfavorable progression.

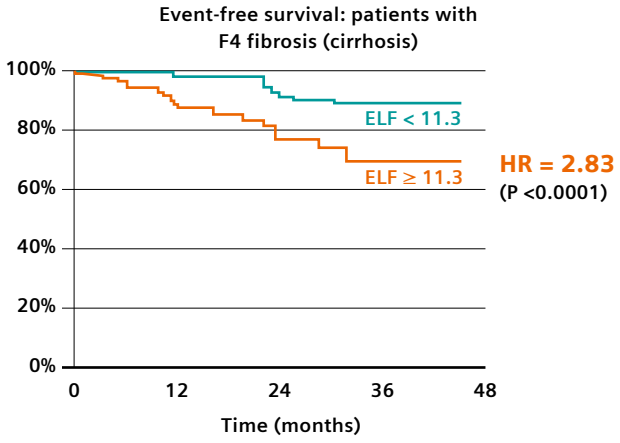
Significance

- The data derived from four phase II and III trials of combined use of simtuzumab and selonsertib that were conducted in a total of 27 countries, including the U.S.
- This study group included a high population of patients with diabetes and demonstrated that in patients with either F3 or F4 fibrosis, ELF ≥11.3 was associated with over 2 times the risk of fibrosis progression, a decompensation event, or development of HCC.
- Study demonstrates that the ELF Test is strongly associated with prognostic outcome.

Conclusion

This study suggests that NITs, especially ELF, are good predictors of adverse clinical outcomes. "[I]t seems plausible that ELF score is sensitive to both baseline disease stage and the disease dynamics in terms of clinical outcomes."





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