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Liver Stiffness Thresholds to Predict Disease Progression and Clinical Outcomes in Bridging Fibrosis and Cirrhosis

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Abstract

Objective: In *retrospective* studies, liver stiffness (LS) by vibration-controlled transient elastography (VCTE) is associated with the risk of liver decompensation in patients with non-alcoholic steatohepatitis (NASH), but *prospective* data in biopsy-confirmed cohorts with advanced fibrosis are limited. We aimed to establish thresholds for LS by VCTE that predict progression to cirrhosis among patients with bridging fibrosis and hepatic decompensation among patients with cirrhosis due to NASH.

Design: We utilized data from four randomized placebo-controlled trials of selonsertib and simtuzumab in participants with advanced fibrosis (F3-F4). The trials were discontinued due to lack of efficacy. Liver fibrosis was staged centrally at baseline and week 48 (selonsertib study) or week 96 (sintuzumab study). Associations between LS by VCTE with disease progression were determined using Cox-proportional hazards regression analysis.

Results: Progression to cirrhosis occurred in 16% (103/664) of participants with bridging fibrosis and adjudicated liver-related events occurred in 4% (27/734) of participants with baseline cirrhosis. The optimal baseline LS thresholds were 16.6 kPa for predicting progression to cirrhosis, and 30.7 kPa for predicting liver-related events. Baseline LS 16.6 kPa (adjusted hazard ratio [HR] 3.99; 95% CI 2.66-5.98, $p < .0001$) and a 5kPa (and 20%) increase (adjusted HR 1.98; 95% CI 1.20, 3.26, $p = 0.008$) were independent predictors of progression to cirrhosis in participants with bridging fibrosis, while baseline LS 30.7 kPa (adjusted HR 10.13, 95% CI 4.38-23.41, $p < .0001$) predicted liver-related events in participants with cirrhosis.

Conclusion: The LS thresholds identified in this study may be useful for risk stratification of NASH patients with advanced fibrosis.

Keywords

NASH; cirrhosis; fibrosis; liver stiffness

INTRODUCTION

Nearly a third of the world's adult population has non-alcoholic fatty liver disease (NAFLD)^{1,2}. NAFLD encompasses both non-alcoholic fatty liver and nonalcoholic steatohepatitis (NASH), the inflammatory form of NAFLD that can progress to fibrosis, cirrhosis and subsequent decompensation³⁻⁷. The incidence of NASH cirrhosis and NAFLD-related

hepatocellular carcinoma (HCC) are projected to increase rapidly in the next decade^{8–12}. The risk of liver-related mortality and decompensation in NASH increases in parallel with fibrosis stage^{13–16}. Although histologic staging of fibrosis is the reference standard, liver biopsy is limited by invasiveness, potential complications and sampling variability^{17,18}. Noninvasive tests (NITs) of fibrosis, including serum markers such as NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) test, and liver stiffness (LS) by vibration-controlled transient elastography (VCTE) are not prone to these limitations, and accurately predict histologic fibrosis stage in patients with NASH^{19–27}. Retrospective studies report that increasing baseline LS by VCTE^{19,28,29} is associated with the risk of disease progression in patients with NAFLD, but prospective data in well-characterized NASH cohorts with biopsy-confirmed advanced fibrosis are limited. The optimal LS thresholds for prognostication of fibrosis progression and decompensation are unknown, however, a recent consensus report from the Baveno group has proposed incrementally increasing LS thresholds³⁰.

With these considerations in mind, we analyzed data from two recent phase 3 placebo-controlled trials of selonsertib, a selective inhibitor of apoptosis signal-regulating kinase 1 (ASK1) and two phase 2b placebo-controlled trials of simtuzumab, a humanized monoclonal antibody directed against lysyl oxidase-like 2^{31,32}. While the studies were discontinued prematurely due to lack of efficacy, the prospectively collected data in these well characterized participants with serial liver biopsies provides a unique opportunity to study the association between baseline LS by VCTE and disease progression. The primary aim of this study was to establish thresholds of LS that prognosticate risk of clinical outcomes in participants with bridging fibrosis and cirrhosis due to NASH. The secondary aims were to examine the association between a change in LS and clinical outcomes, and to compare the prognostic ability of baseline LS versus baseline LS plus a combination of routine clinical parameters (age, sex, AST, ALT, platelets and diabetes status), included within the Agile 3+ and Agile 4 scores, to define risk for fibrosis progression and decompensation^{33,34}.

METHODS

Study population

This analysis utilized data from four large, randomized placebo-controlled trials of selonsertib and simtuzumab in participants with advanced (F3-F4) fibrosis due to NASH^{31,32}. Pre-planned analysis of the selonsertib studies at 48 weeks and the simtuzumab studies at 96 weeks concluded that these therapies were ineffective, and therefore, the trials were discontinued. At baseline, there were no differences between treatment groups; thus, treatment groups were combined for the present analysis. The primary findings of these studies, as well as the detailed methods, have been reported elsewhere^{31,32}.

Briefly, the selonsertib STELLAR studies comprised of two 2 randomized, double-blind, placebo-controlled, phase III trials conducted in Europe, North America, South America, Asia, and the Pacific region. Eligible participants were 18 to 70 years of age with a histologic diagnosis of NASH, available data for baseline LS by VCTE and advanced fibrosis (F3-F4). Patients with liver disease of other etiologies, a history of solid organ transplantation, hepatic decompensation, or HCC were excluded. Participants with

bridging (F3) fibrosis (n=808; [NCT03053050](#)) and compensated cirrhosis (F4) (n=883; [NCT03053063](#)) were randomized 2:2:1 to receive selonsertib 18 mg, selonsertib 6 mg, or placebo once daily for 48 weeks. The primary efficacy endpoint was the proportion of participants with 1-stage improvement in fibrosis without worsening of NASH at week 48.

The simtuzumab studies consisted of two phase 2b trials in North America and Europe. Eligible participants were 18–65 years of age with a body mass index (BMI) of at least 18 kg/m² with NASH and bridging fibrosis, NASH cirrhosis or cirrhosis with at least 1 clinical feature suggestive of NASH (such as diabetes, obesity or dyslipidemia). Participants with liver disease of other etiologies, a history of solid organ transplantation, a history of malignancy other than non-melanomatous skin cancer and hepatic decompensation were excluded. Participants with bridging (F3) fibrosis (n=219; [NCT01672866](#)) were randomly assigned (1:1:1) to groups given weekly subcutaneous injections of simtuzumab (75 or 125 mg) or placebo for a planned duration of 240 weeks. The primary outcome was a decrease in hepatic collagen content by morphometry. Participants with compensated cirrhosis (F4) (n=258; [NCT01672879](#)) were randomly assigned (1:1:1) to receive intravenous infusions of simtuzumab (200 mg or 700 mg) or placebo every other week. The primary outcome was the change in hepatic venous pressure gradient.

Study assessments

Histology: Liver fibrosis was staged centrally at baseline (all patients), week 48 (all patients), and week 96 (simtuzumab studies only). All biopsies were read by a single central reader (Z.G.) who was blinded to treatment assignment but not biopsy sequence. Histological assessments included the adequacy of the biopsy specimen, confirmation of the diagnosis, fibrosis staged according to the NASH Clinical Research Network (CRN) and modified Ishak fibrosis classifications, and grading of steatosis, lobular inflammation, and hepatocellular ballooning according to the NAFLD activity score (NAS).

Liver stiffness measurements: LS was measured by VCTE (FibroScan®, Echosens, Paris, France) at baseline by trained operators, with participants in a fasting state and following standard reliability criteria, as previously described²⁷. Data on type of VCTE probe (M vs. XL) were available in the STELLAR studies only.

Serum markers: Fasting blood samples were obtained at baseline for clinical laboratory tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets, glucose and ELF score (Siemens Healthcare GmbH, Erlangen Germany).

The Agile 3+ and Agile 4 scores are novel non-invasive scores including LSM by VCTE and routine clinical parameters that were developed to identify advanced fibrosis (Agile 3+) and cirrhosis (Agile 4) among patients with NAFLD, and demonstrated better performance compared with FIB-4 and LS by VCTE^{33,34}. The Agile 3+ and Agile 4 scores were calculated as follows: Agile 3+ = $\frac{e^x}{1 + e^x}$, where $x = -3.92 + 2.30 \ln(\text{LS by VCTE}) - 0.01(\text{platelets}) - 0.99(1/(\text{AST/ALT})) + 1.09(\text{diabetes status}) - 0.39(\text{gender}) + 0.03(\text{age});$

Agile 4 = $\frac{e^y}{1 + e^y}$, where $y = 7.50 - 15.42(1/(\text{LS by VCTE})) - 0.01(\text{platelets}) - 1.41(1/(\text{AST/ALT})) - 0.53(\text{gender}) + 0.42(\text{diabetes status})$ ^{33,34}.

Objectives and outcome measures

The **primary objective** of this study was to determine the optimal thresholds of baseline LS by VCTE to predict progression to cirrhosis (F4) in participants with bridging (F3) fibrosis and liver-related clinical events in participants with cirrhosis. The **secondary objectives** were to determine if a ≥ 5 kPa (and $\geq 20\%$)²⁹ increase in LS predicts progression to cirrhosis (F4) in participants with bridging (F3) fibrosis and liver-related clinical events in participants with cirrhosis (F4). In addition, the performance of the Agile 3+ and Agile 4 scores as predictors for progression to cirrhosis and liver-related events were compared with baseline LS by VCTE.

At baseline, cirrhosis (F4) was defined by histology. Progression to cirrhosis from bridging (F3) fibrosis at baseline was defined by cirrhosis (F4) on a post-baseline biopsy, or the development of liver-related events. Liver-related events were adjudicated by a central committee of experts and defined as clinically apparent ascites requiring treatment, Grade 2 hepatic encephalopathy according to the West Haven criteria requiring treatment, and portal hypertension-related gastrointestinal bleeding, liver transplantation, qualification for transplantation (Model for End-Stage Liver Disease [MELD] ≥ 15), or mortality.

Statistical analysis

Baseline demographic and clinical characteristics are presented separately according to the presence of bridging fibrosis (F3) or cirrhosis (F4) at baseline. Associations between LS by VCTE and the Agile scores at baseline, and a ≥ 5 kPa (and $\geq 20\%$) increase of LS with disease progression through the end of follow-up were determined using Kaplan-Meier and Cox proportional hazards regression analysis. Discrimination of these measures for disease progression were described by c-statistics which are analogous to the area under a receiver operating characteristic curve estimated for logistic models ³⁵. The optimal baseline LS and Agile score thresholds were determined based on the maximal sum of sensitivity and specificity according to the logistic model, and the operating characteristics (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) for disease progression at these thresholds were calculated. Statistical significance was defined as a two-tailed P-value of ≤ 0.05 . All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Characteristics of the study population

A total of 664 participants with bridging (F3) fibrosis and 734 participants with cirrhosis (F4) were included in this study (Table 1). Among participants with bridging (F3) fibrosis, 56% were female, 72% were White, 70% had diabetes, and the median (IQR) age and BMI were 58 years (51-64) and 32.7 kg/m² (29.0-37.0), respectively. At baseline, the median (IQR) LS by VCTE was 12.7 kPa (9.7-17.3). Out of 664 participants with bridging (F3)

fibrosis had available data for LS prior to progression to cirrhosis, 14% had a 5 kPa (and 20%) increase in LS.

Among 734 participants with cirrhosis, 63% were female, 78% were White, and 76% had diabetes; the median (IQR) age and BMI were 59 years (53-65) and 33.1 kg/m² (28.7-38.0), respectively (Table 1). The median (IQR) platelet count was 160 x10³/μL (124-206) and MELD score was 7 (6-8). At baseline, the median (IQR) LS by VCTE was 21.1 kPa (14.2, 29.3) and 63% (434/694) of participants were scanned with the XL probe. Out of 734 participants with cirrhosis (F4) had available data for LS prior to hepatic decompensation, 22% had a 5 kPa (and 20%) increase in LS.

Progression to cirrhosis among participants with baseline bridging (F3) fibrosis

During a median follow-up of 16.6 months (IQR 15.0-19.4), 16% (103/664) of participants with bridging fibrosis progressed to cirrhosis. In total, 93.2% (n=96) of participants had cirrhosis diagnosed based on post-baseline histology, while 6.8% (n=7) developed liver-related events consistent with cirrhosis.

Optimal baseline LS threshold for predicting progression to cirrhosis

The risk of progression to cirrhosis was greater with higher LS by VCTE at baseline (hazard ratio [HR] per 3-kPa: 1.16; 95% confidence interval [CI] 1.12, 1.20). The optimal LS threshold at baseline was 16.6 kPa, with a c-statistic of 0.72 (95% CI 0.66-0.77) (Figure 1). The sensitivity, specificity, PPV, and NPV of this threshold for progression to cirrhosis were 58%, 76%, 31%, and 91%, respectively (Table 2). Progression to cirrhosis occurred in 31.1% (60/193) of participants with baseline LS ≥ 16.6 kPa compared with 9.1% (43/471) with LS <16.6 kPa (p<0.001; Figures 1 and 2). Baseline LS by VCTE ≥ 16.6 kPa was associated with a nearly 4-fold risk (HR 3.86, 95% CI 2.61, 5.72) of progression to cirrhosis in participants with bridging (F3) fibrosis. After adjustment for age, gender, ethnicity, and BMI, baseline LS ≥ 16.6 kPa remained a strong and independent predictor for progression to cirrhosis (adjusted HR 3.99; 95% CI 2.66, 5.98; p<.0001) (Supplemental Table 1).

5kPA (and 20%) increase in LS as a predictor of progression to cirrhosis

Progression to cirrhosis occurred in 22% (20/91) of participants with a 5kPa (and 20%) increase in LS compared with 14% (83/573) with <5kPa (and 20%) increase in LS (p=0.051; Supplemental Figures 1 and 2). A 5kPa (and 20%) increase in LS was associated with a nearly 1.6-fold risk (HR 1.59, 95% CI 0.97, 2.59) of progression to cirrhosis in participants with bridging (F3) fibrosis. After adjustment for baseline LS, age, gender, ethnicity, and BMI, a 5kPa (and 20%) increase in LS remained a strong and independent predictor for progression to cirrhosis (adjusted HR 1.98; 95% CI 1.20, 3.26; p=0.008) (Supplemental Table 2).

Optimal Agile 3+ threshold for predicting progression to cirrhosis

A subgroup of 629 participants with bridging (F3) fibrosis (95%) had complete data for calculation of the Agile 3+ score (Supplemental Table 3). At baseline, the median (IQR) Agile 3+ score was 0.76 (0.53-0.89). In this subgroup, 15% (95/629) progressed to cirrhosis (89 on histology and 6 with clinical events) during a median follow-up of 16.6 months (IQR

15.0-19.4). The risk of disease progression was greater with higher baseline Agile 3+ score (HR per 0.1-units: 1.34; 95% CI 1.19, 1.52; $p < 0.001$). The median (IQR) baseline Agile 3+ score in participants with versus without progression to cirrhosis was 0.94 (0.82, 0.98) vs 0.88 (0.68, 0.97), respectively ($p = 0.001$). The optimal threshold for baseline Agile 3+ score to predict progression to cirrhosis was 0.90 (Supplemental Figure 3). After adjustment for age, gender, ethnicity and BMI, baseline Agile 3+ 0.90 was an independent predictor for progression to cirrhosis (adjusted HR 4.75, 95% CI 3.07, 7.34; $p < .0001$) (Supplemental Table 4)

Comparison of LS versus Agile 3+ score for predicting progression to cirrhosis

Among participants with sufficient data ($n = 629$) for calculation of the Agile 3+ score, the performance of LS by VCTE and Agile 3+ for predicting progression to cirrhosis were similar (c-statistic 0.71 [0.65-0.76] vs 0.70 [0.64, 0.76], $p = 0.88$) (Supplemental Table 5).

Liver-related events among participants with baseline cirrhosis (F4)

During a median follow-up of 16.2 months (IQR 13.9-18.7), 4% (27/734) of participants with cirrhosis at baseline had liver-related events: ascites ($n = 15$), hepatic encephalopathy ($n = 5$), portal hypertension-related upper gastrointestinal bleeding ($n = 3$), qualification for liver transplantation ($n = 2$), liver transplantation ($n = 1$), and death ($n = 1$).

Optimal baseline LS threshold for predicting liver-related events among participants with cirrhosis

The risk of liver-related events was greater with higher LS by VCTE at baseline (HR per 5-kPa: 1.29; 95% CI 1.18, 1.41). The optimal LS threshold at baseline was 30.7 kPa, which had a c-statistic of 0.77 (95% CI 0.67-0.87) (Figure 3). The sensitivity, specificity, PPV, and NPV of this threshold for liver-related events were 70%, 79%, 11%, and 99%, respectively (Table 2). Liver-related events occurred in 11.1% (19/171) of cirrhotic participants with baseline LS 30.7 kPa compared with 1.4% (8/563) of participants with baseline LS <30.7 kPa ($p < 0.001$; Figures 3 and 4). Baseline LS by VCTE 30.7 kPa was associated with an 8-fold risk (HR 8.24; 95% CI 3.61, 18.82) of clinical events in participants with cirrhosis (F4). LS by VCTE 30.7 kPa remained a strong and independent predictor of liver-related events after adjustment for age, gender, ethnicity and BMI (adjusted HR 10.13; 95% CI 4.38, 23.41; $p < .0001$) (Supplemental Table 6), with a similar finding in another model incorporating weight changes (Supplemental Table 7). A sensitivity analysis for classic clinical events related to portal hypertension (development of ascites, hepatic encephalopathy and portal hypertension-related bleeding) determined similar findings (Supplemental Table 8).

5kPa (and 20%) increase in LS as a predictor of liver-related events among participants with cirrhosis

Liver-related events occurred in 3% (4/160) of participants with a 5kPa (and 20%) increase in LS compared with 4% (23/574) with <5kPa (and 20%) increase in LS ($p = 0.36$; Supplemental Figures 4 and 5). Among participants with cirrhosis, a 5kPa (and 20%) increase in LS was not associated with liver-related events in univariable (HR 0.61, 95%

CI 0.21, 1.76; $p=0.36$) and multivariable analysis (adjusted HR 0.75; 95% CI 0.26, 2.18; $p=0.60$) (Supplemental Table 9).

Optimal Agile 4 threshold for predicting liver-related events among participants with baseline cirrhosis (F4)

A subgroup of 701 participants (96%) had data sufficient for calculation of the Agile 4 score (Supplemental Table 1). The median (IQR) Agile 4 score at baseline was 0.63 (0.34-0.80). In this subgroup, 3% (23/701) had liver-related events during a median follow-up of 16.3 months (IQR 13.9-18.7). The risk of disease progression was greater with higher baseline Agile 4 score (HR per 0.1-units: 1.91; 95% CI 1.40, 2.61; $p<0.001$). The median baseline Agile 4 scores in participants with versus without liver-related events were 0.53 (IQR 0.23, 0.75) versus 0.37 (IQR 0.13, 0.69), respectively ($p=0.002$). The optimal Agile 4 threshold for predicting liver-related events was 0.72 (Supplemental Figure 6). After adjustment for age, gender, ethnicity and BMI, baseline Agile 4 0.72 was an independent predictor for liver-related events (adjusted HR 11.84; 95% CI 3.51, 39.99; $p<.0001$) (Supplemental Table 10).

Comparison of LS versus Agile 4 score and other NITs for predicting liver-related events

Among participants with sufficient data for analysis of the baseline Agile 4 score ($n=701$), the performance of LS by VCTE and Agile 4 for predicting liver-related events were similar (c-statistic 0.81 [0.72-0.90] versus 0.82 [0.74-0.90], $p=0.97$) (Supplemental Table 5). Baseline LS by VCTE had a similar performance compared to baseline NFS, ELF and FIB-4 for predicting liver-related events among those with baseline cirrhosis (F4) (Supplemental Table 11)

Optimal baseline LS threshold for predicting liver-related events among participants with advanced (F3-F4) fibrosis

Among 664 participants with baseline advanced fibrosis (F3-F4), there were 34 incident liver-related events (7 from participants with baseline F3 and 27 from participants with baseline F4). The optimal LS threshold at baseline for predicting liver-related events remained 30.7 kPa, which had a c-statistic of 0.77 (95% CI 0.68-0.86). The sensitivity, specificity, PPV, and NPV of this threshold for liver-related events were 62%, 87%, 10%, and 99%, respectively. Baseline LS by VCTE 30.7 kPa was associated with an 11-fold risk (adjusted HR 10.52; 95% CI 5.15, 21.48; $p<.0001$) of liver-related events in participants with advanced fibrosis (F3-F4) after adjustment for age, gender, ethnicity, treatment arm and BMI (Supplemental Table 12).

DISCUSSION

Main findings

In this analysis of four large, randomized, placebo-controlled trials of selonsertib and simtuzumab in participants with NASH and biopsy-confirmed advanced fibrosis (F3-F4), baseline LS by VCTE was a strong and independent predictor of disease progression (Graphical summary enclosed as Figure 5). Among participants with bridging fibrosis (F3), the optimal LS threshold at baseline LS to predict progression to cirrhosis was 16.6 kPa,

which had a c-statistic of 0.72, consistent with good prognostic performance. Overall, 31% of participants with bridging fibrosis (F3) and LS ≥ 16.6 kPa at baseline progressed to cirrhosis, compared with only 9% with LS < 16.6 kPa. After adjustment for age, gender, ethnicity and BMI, baseline LS ≥ 16.6 kPa was associated with a four-fold higher risk of progression to cirrhosis during follow-up. A ≥ 5 kPa (and $\geq 20\%$) increase in LS by VCTE was associated with an increased risk of progression to cirrhosis among participants with baseline bridging (F3) fibrosis.

Similar findings were observed among participants with cirrhosis (F4) at baseline, although a higher threshold for identifying patients at risk of liver-related complications was observed, as expected. Specifically, the optimal threshold of LS at baseline to predict liver-related events was ≥ 30.7 kPa, which had a c-statistic of 0.77. A total of 11% of participants with cirrhosis and baseline LS ≥ 30.7 kPa developed liver-related events versus only 1% of those with baseline LS < 30.7 kPa. After adjustment for demographic factors and BMI, baseline LS by VCTE ≥ 30.7 kPa was associated with a ten-fold higher risk of liver-related events. In a sensitivity analysis of the F3 and F4 patient populations, the prognostic performance of VCTE did not differ based on the type of VCTE probe (M versus XL) used to measure LS (data not shown). In addition, we determined that the optimal LS threshold by VCTE (≥ 30.7 kPa) to predict development of liver-related events among participants with advanced fibrosis (F3-F4) was the same as the threshold for participants with cirrhosis (F4).

The Agile 3+ and Agile 4 scores — which include LS by VCTE plus other clinical and demographic factors — and were designed to identify patients with bridging fibrosis and cirrhosis, respectively, were also significant predictors of disease progression in this cohort. However, their diagnostic performance was similar to LS measurement alone, suggesting that these additional parameters do not improve upon the prognostic utility of LS by VCTE. Further studies are required to define the relationship between serum-based NITs and LS by transient elastography for the prediction of future clinical outcomes.

In context with current literature

Multiple studies have demonstrated a correlation between LS by VCTE with liver-related complications and mortality among patients with liver disease of various etiologies, but prospective data in patients with NASH and advanced fibrosis are limited^{36,37}. A retrospective analysis of 1,039 participants (53% with biopsy) with NAFLD and advanced fibrosis (F3 or F4) or with LS by VCTE > 10 kPa, demonstrated that baseline LS was associated with liver-related events and mortality²⁹. However, this study did not provide data for progression from bridging fibrosis to cirrhosis. Another study of 2,251 patients with NAFLD demonstrated that baseline LS by VCTE was an independent predictor of survival, and liver-related and cardiovascular events, however, this study did not evaluate the utility of baseline LS for patients with F3 or F4 fibrosis due to the relatively small numbers with advanced fibrosis (13% had baseline LS > 12 kPa)²⁸. The current prospective study of patients with biopsy-confirmed, advanced fibrosis (F3 or F4) provides clinical validation that baseline LS by VCTE can be used as a prognostic tool for progression to cirrhosis and development of liver-related events. In addition, the LS thresholds identified

in this study may be useful for risk stratification of patients with NASH in clinical trials and in clinical practice to identify patients at increased risk of disease progression³⁸. For example, high-risk patients could be offered increased clinical surveillance or targeted for enrollment in clinical trials of novel therapies. Finally, LS by VCTE, along with platelet count, may be useful to predict the development of clinically significant portal hypertension in patients with NASH and compensated advanced chronic liver disease, as suggested in a recent Baveno consensus report^{30,39}. In this regard, the LS thresholds recommended by this group (e.g., 15 and 30 kPa) are close to those of the optimal thresholds identified in our dataset (16.7 and 30.7 kPa) and have similar prognostic utility (Supplemental Table 13).

Strengths and limitations

The novelty of this study includes its prospective design, well-phenotyped participants with serial, centrally-read liver biopsies, adjudication of liver-related events by a committee of experts, and the establishment of thresholds for baseline LS by VCTE that predict disease progression in NAFLD with F3-F4 fibrosis. However, this study is not without limitations. Firstly, all included participants were selected for clinical trials and it is unclear whether these data are generalizable to the broader population of NASH patients with advanced fibrosis. Therefore, these data require validation in clinical practice. Secondly, the histologic definition of progression to cirrhosis in patients classified as having bridging fibrosis (F3) at baseline is susceptible to misclassification due to sampling variability of liver biopsy¹⁷. Third, the median follow-up duration was relatively short (~16-17 months) given the slow rate of disease progression in NASH, potentially contributing to a relatively low rate of clinical liver-related events; therefore, prospective studies with longer follow-up duration are required⁵. All liver biopsies were evaluated by a single pathologist, which may introduce an element of interpretation bias. Finally, although VCTEs were performed by trained operators, there was no quality control of the VCTE measurements, and further data are required to examine the variability of VCTE in NASH and advanced fibrosis. Nevertheless, our data demonstrate that LS by VCTE provides highly discriminant prognostic information even when performed under standards of usual clinical practice and lend further justification for the use of non-invasive surrogates in prognosticating clinically meaningful outcomes beyond ordinal histologic staging of fibrosis alone.

Conclusion

In this analysis of four large, randomized placebo-controlled trials of participants with NASH and biopsy-proven advanced fibrosis (F3-F4), clinical disease progression was associated with higher LS by VCTE at baseline. The optimal LS thresholds for predicting progression to cirrhosis among patients with bridging fibrosis (F3) and development of liver-related events among patients with cirrhosis were 16.6 kPa and 30.7 kPa, respectively. A 5kPa (and 20%) increase in LS by VCTE was associated with an increased risk of progression to cirrhosis among participants with baseline bridging (F3) fibrosis. The LS thresholds identified in this study may be useful for risk stratification of patients with NASH in clinical trials and in clinical practice and lend further support to the use of non-invasive surrogates rather than liver histology to predict the risk of clinically meaningful outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest disclosure:

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Abbreviations:

NAFLD non-alcoholic fatty liver disease

LS	liver stiffness
VCTE	vibration controlled transient elastography
BMI	body mass index

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What is already known on this topic

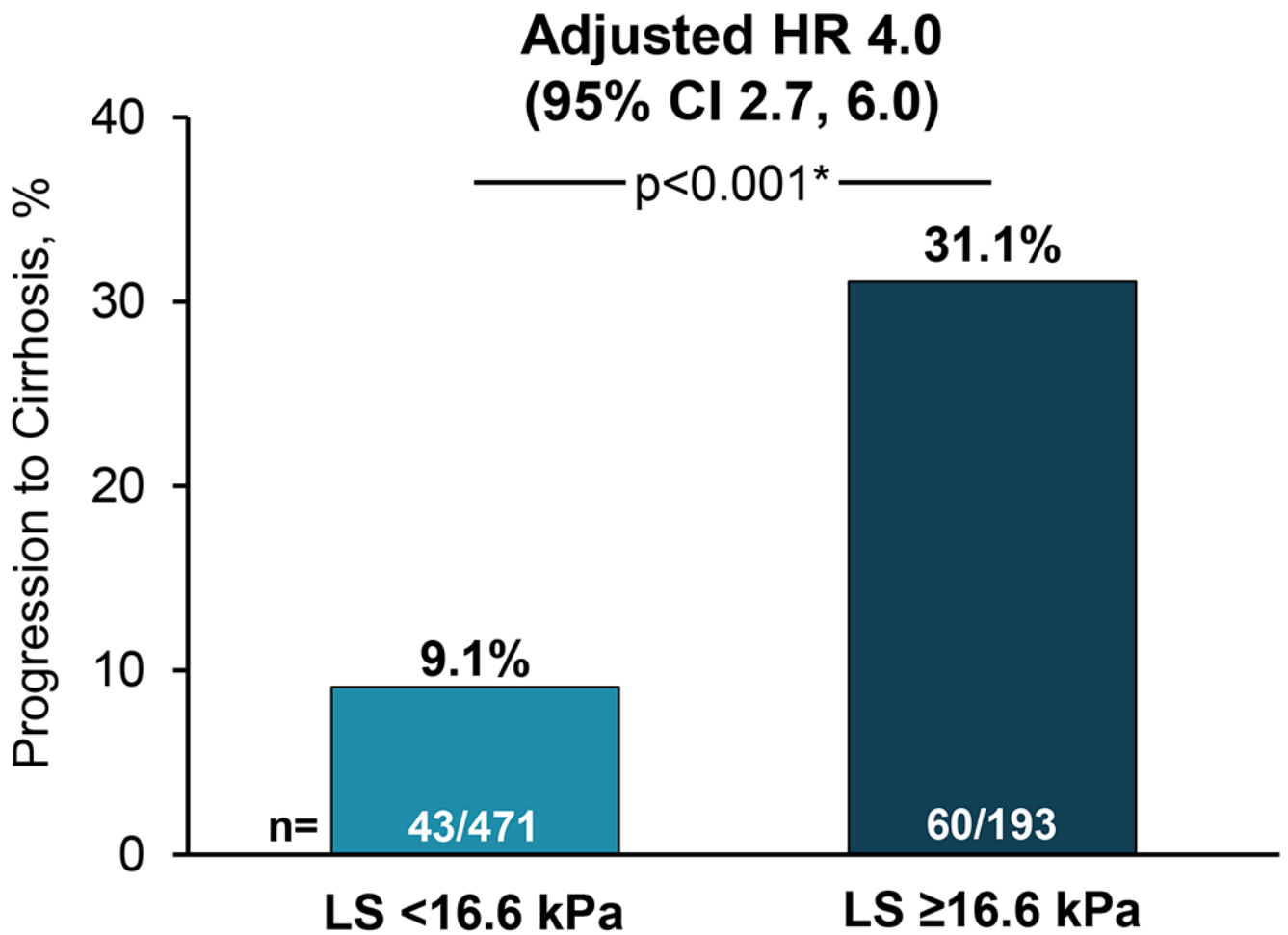
Retrospective studies report that increasing liver stiffness as assessed by vibration-controlled transient elastography is associated with the increased risk of liver disease progression in patients with non-alcoholic fatty liver disease (NAFLD). However, there are limited *prospective* data in well-characterized patients with biopsy-confirmed non-alcoholic steatohepatitis (NASH) with bridging fibrosis and cirrhosis regarding the optimal cut-points associated with higher risk of progression to cirrhosis, and hepatic decompensation among patients with cirrhosis.

What this study adds

In this analysis of four large, prospective, international, multicenter, randomized placebo-controlled trials of participants with NASH and biopsy-proven advanced fibrosis (F3-F4), clinical disease progression was associated with higher liver stiffness by vibration-controlled transient elastography at baseline. We identified optimal liver stiffness thresholds for predicting progression to cirrhosis among patients with bridging fibrosis, and development of liver-related events among patients with compensated cirrhosis. In addition, we determined that a 5kPa (and 20%) increase in liver stiffness was associated with progression to cirrhosis, among participants with bridging fibrosis at baseline.

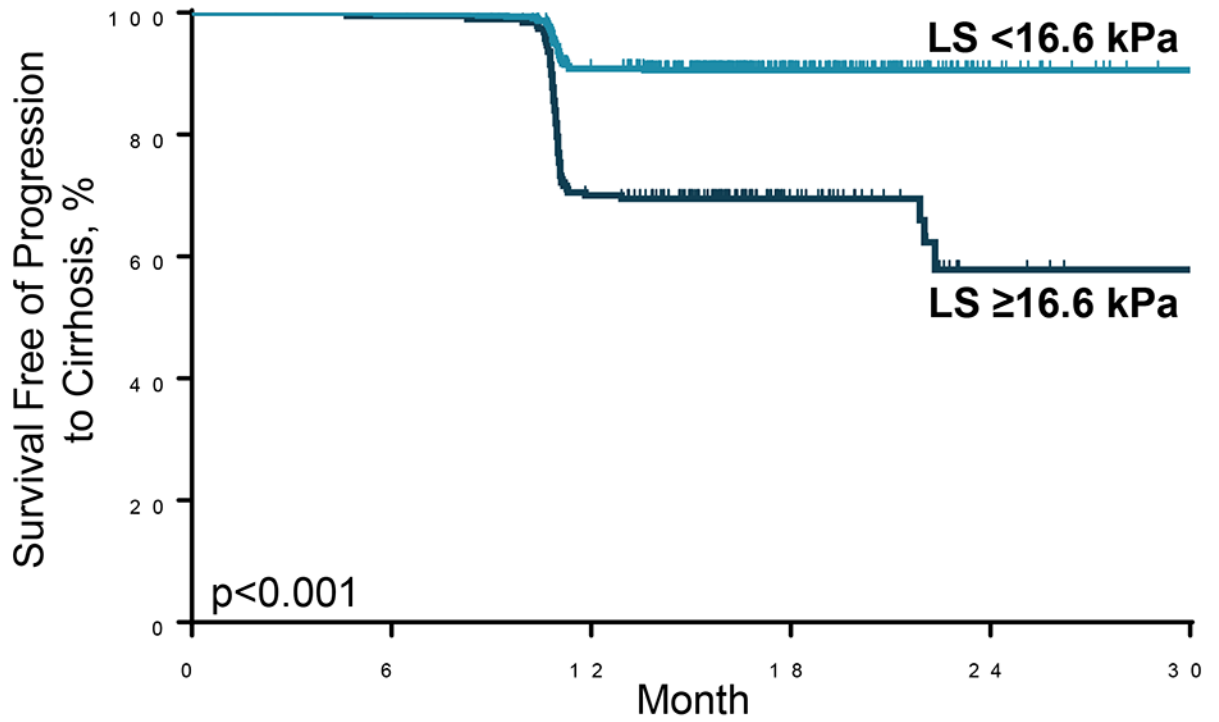
How this study might affect research, practice or policy

The liver stiffness thresholds identified in this study will be useful for risk stratification of patients with NASH in clinical trials and in clinical practice. High-risk patients identified using these thresholds could be offered increased clinical surveillance or targeted for enrolment in clinical trials for treatment of NASH related fibrosis and cirrhosis. These data further support the use of non-invasive biomarkers as a surrogate to predict the risk of clinically meaningful outcomes.



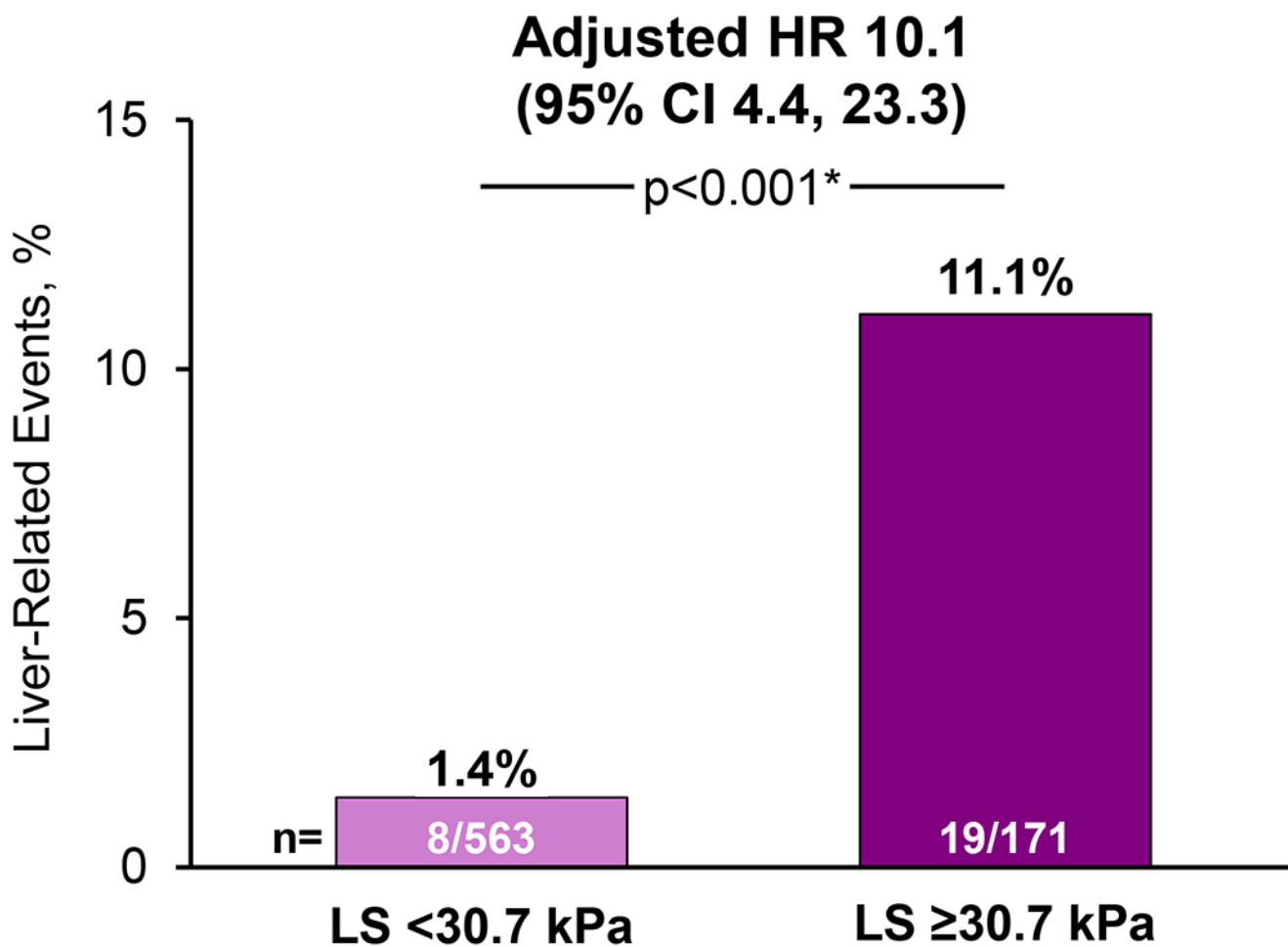
*Fisher exact test.

Figure 1. Liver stiffness (LS) by vibration-controlled transient elastography (VCTE) 16.6 kPa is associated with increased risk of progression to cirrhosis among patients with baseline bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis



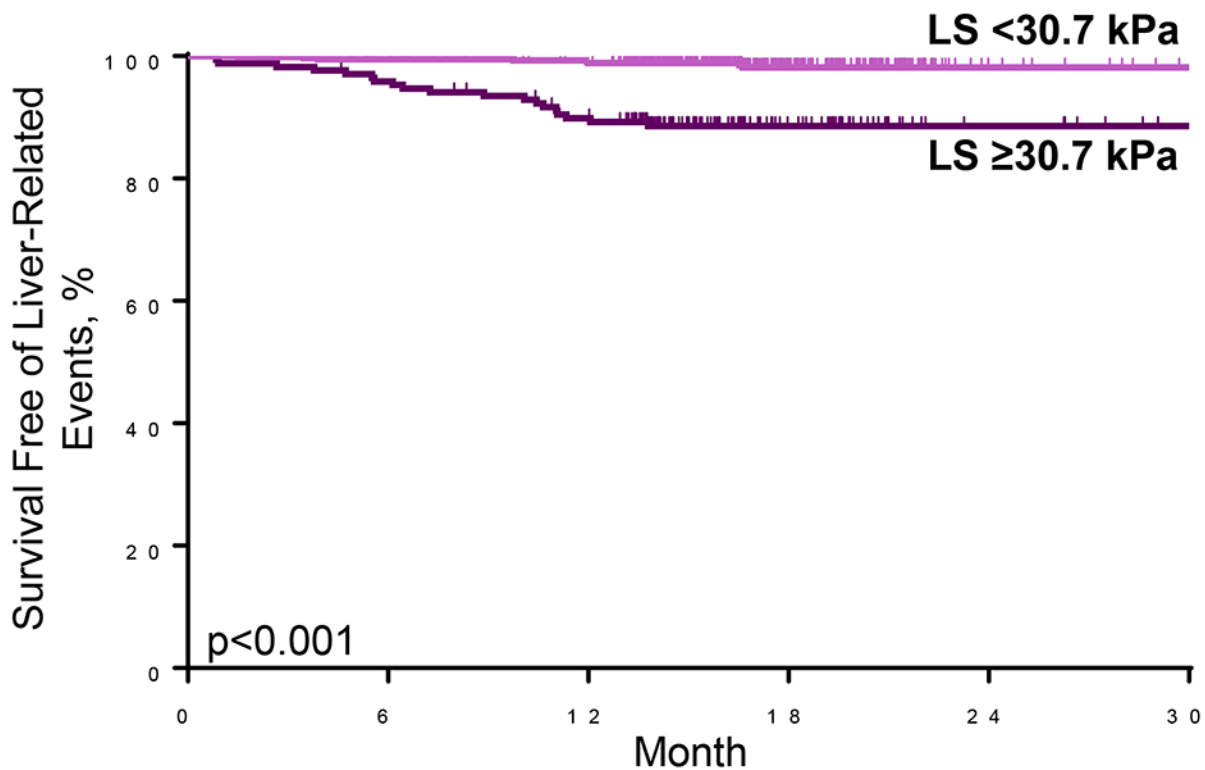
n at risk (events)		0	6	12	18	24	30
<16.6 kPa	471 (0)	460 (1)	410 (42)	166 (43)	28 (43)	13 (43)	
≥16.6 kPa	193 (0)	188 (1)	129 (56)	39 (57)	6 (60)	3 (60)	

Figure 2. Progression to cirrhosis in patients with bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis, stratified by liver stiffness (LS) by vibration-controlled transient elastography (VCTE) 16.6 kPa versus <16.6 kPa



*Fisher exact test.

Figure 3. Liver stiffness (LS) by vibration-controlled transient elastography (VCTE) ≥ 30.7 kPa is associated with increased risk of liver-related events among patients with baseline cirrhosis (F4) secondary to non-alcoholic steatohepatitis



n at risk (events)	0	6	12	18	24	30
<30.7 kPa	563 (0)	549 (3)	533 (6)	170 (8)	22 (8)	12 (8)
≥30.7 kPa	171 (0)	162 (7)	148 (17)	52 (19)	11 (19)	5 (19)

Figure 4. Liver-related events in patients with cirrhosis (F4) secondary to non-alcoholic steatohepatitis, stratified by liver stiffness (LS) by vibration-controlled elastography (VCTE) 30.7 kPa versus <30.7 kPa

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Liver Stiffness Thresholds to Predict Disease Progression and Clinical Outcomes in Advanced Fibrosis

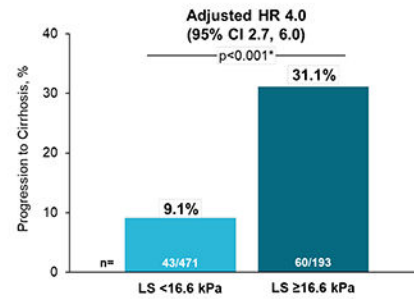
Aim:
To establish thresholds for Liver stiffness (LS) by vibration controlled transient elastography (VCTE) that predict progression to cirrhosis among patients with bridging fibrosis and hepatic decompensation among patients with cirrhosis due to NASH

Methods:
Prospective data from four randomized placebo-controlled trials of selonsertib (STELLAR-3; STELLAR-4) and simtuzumab (GS-US-321-0105; GS-US-321-0106) in participants with bridging fibrosis (n=664) and cirrhosis (n=734)

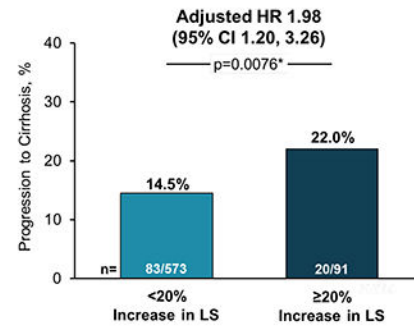
Conclusions:
The LS thresholds identified in this *prospective* study may be useful for risk stratification of patients with NASH in clinical trials and in clinical practice

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Baseline LS ≥ 16.6 kPa predicts progression to cirrhosis



5 kPa (and 20%) increase in LS predicts progression to cirrhosis



Baseline LS ≥ 30.7 kPa predicts development of liver-related events

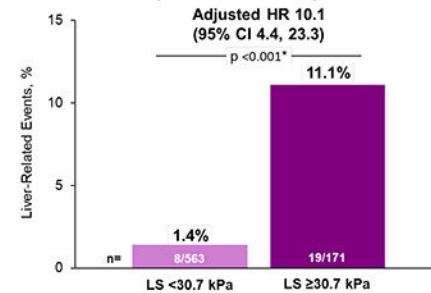


Figure 5.
Graphical summary

Table 1.

Baseline demographics and clinical characteristics of patients with bridging fibrosis and cirrhosis due to non-alcoholic steatohepatitis

		Bridging Fibrosis (F3): n=664	Cirrhosis (F4): n=734	
Demographics	Age, y	58 (51, 64)	59 (53, 65)	
	Women	371/664 (56)	461/734 (63)	
	USA	336/664 (51)	432/734 (59)	
	White	479/664 (72)	572/734 (78)	
	Hispanic/Latino	94/664 (14)	95/734 (13)	
	BMI, kg/m ²	32.7 (29.0, 37.0)	33.1 (28.7, 38.0)	
	Diabetes	466/664 (70)	556/734 (76)	
Liver biochemistry	ALT, U/L	53 (35, 80)	42 (31, 61)	
	GGT, U/L	58 (38, 99)	81 (47, 144)	
	Bilirubin, mg/dL	0.6 (0.4, 0.8)	0.6 (0.5, 0.9)	
	MELD	6 (6, 7)	7 (6, 8)	
	Platelets, x10 ³ /μL	206 (166, 257)	160 (124, 206)	
Liver histology	NAS 4	628/664 (95)	691/730 (95)	
	Steatosis 2	60/664 (9)	33/730 (5)	
	Lobular inflammation 3	332/664 (50)	396/730 (54)	
	Ballooning 2	514/664 (77)	594/730 (81)	
	Ishak fibrosis stage	F3	378/664 (57)	—
		F4	286/664 (43)	—
		F5	—	281/733 (38)
		F6	—	452/733 (62)
Collagen content, %	4.4 (2.7, 6.4)	10.6 (7.4, 14.7)		
αSMA expression, %	6.0 (3.0, 9.2)	13.4 (8.9, 19.7)		
Noninvasive tests	ELF	9.94 (9.34, 10.61)	10.60 (9.99, 11.26)	
	FIB-4	1.66 (1.23, 2.50)	2.50 (1.73, 3.51)	
	NAFLD fibrosis score	-0.227 (-1.053, 0.484)	0.615 (-0.215, 1.495)	
	LS by VCTE, kPa XL probe, %	12.7 (9.7, 17.3) 334/620 (54)	21.1 (14.2, 29.3) 434/694 (63)	

* Data are median (interquartile range) or n/n (%).

ALT, alanine aminotransferase; αSMA, α-smooth muscle actin; BMI, body mass index; ELF, Enhanced Liver Fibrosis score (Siemens Healthcare GmbH, Erlangen Germany); FIB-4 index, fibrosis-4 index; GGT, γ-glutamyltransferase; NAFLD Activity Score, NAS.

Table 2.

Performance of liver stiffness by vibration-controlled transient elastography for predicting progression to cirrhosis among patients with baseline bridging (F3) fibrosis and liver-related clinical events among patients with cirrhosis (F4)

	Progression to Cirrhosis (F4) in Patients with Bridging Fibrosis (F3) (n=664)	Liver-Related Clinical Events Among Patients with Cirrhosis (F4) (n=734)
c-statistic (95% CI)	0.72 (0.66, 0.77)	0.77 (0.67, 0.87)
Optimal threshold	16.6 kPa	30.7 kPa
Sensitivity (95% CI)	58% (48, 68) (60/103)	70% (50, 86) (19/27)
Specificity (95% CI)	76% (73, 80) (428/561)	79% (75, 81) (555/707)
PPV (95% CI)	31% (25, 38) (60/193)	11% (7, 17) (19/171)
NPV (95% CI)	91% (88, 93) (428/471)	99% (97, 99) (555/563)

NPV, negative predictive value; PPV, positive predictive value.

95% CI for sensitivity, specificity, PPV, and NPV are based on exact limits.