NASH Fibrosis Assessment

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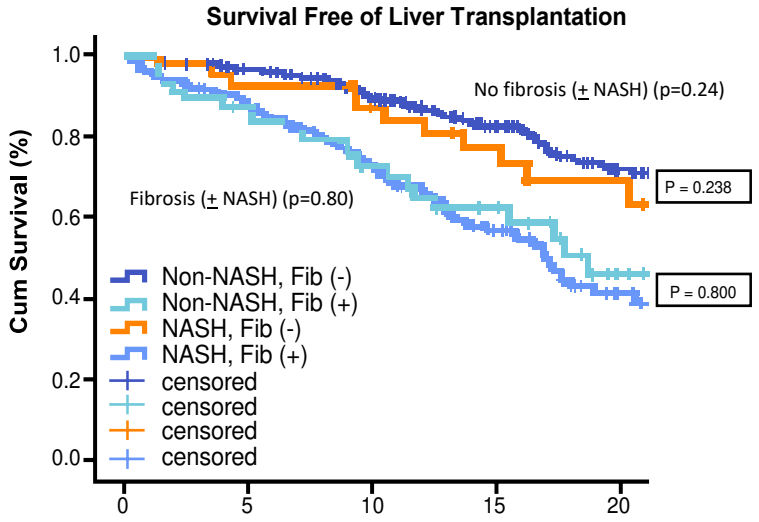
Harm Reduction ECHO: Hepatitis and Liver Health

The Purposes determining Fibrosis Stage

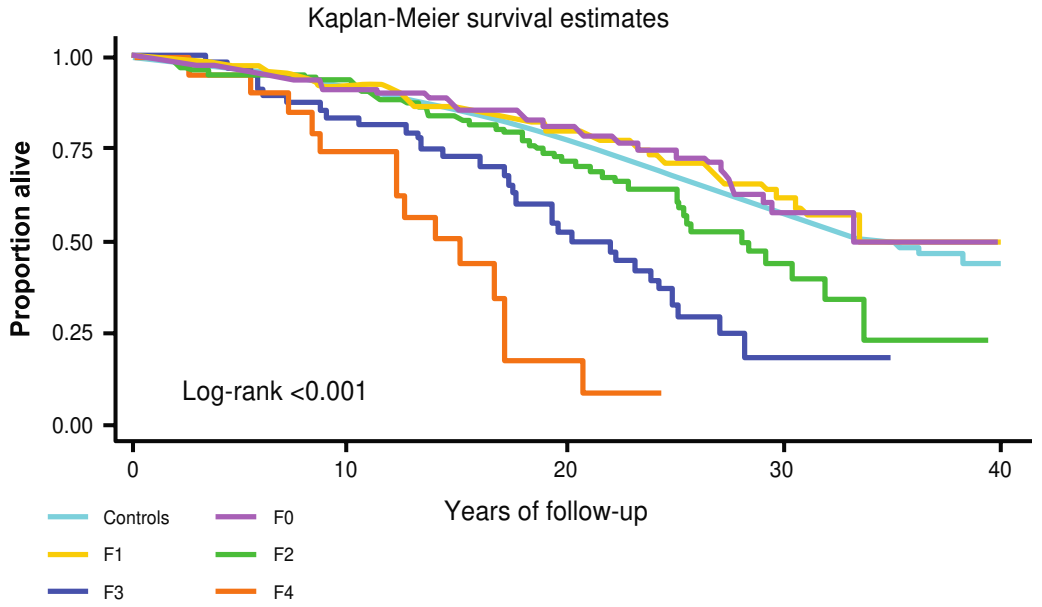
- To reduce the need for liver biopsy. (F0-1,F4).
- To identify patients who needs intensive interventions and monitoring.
- To assess longitudinal progression/regression of liver injury and fibrosis.

Liver Fibrosis, but No Other Histologic Features, Associates With Long-term Outcomes of Patients With NAFLD

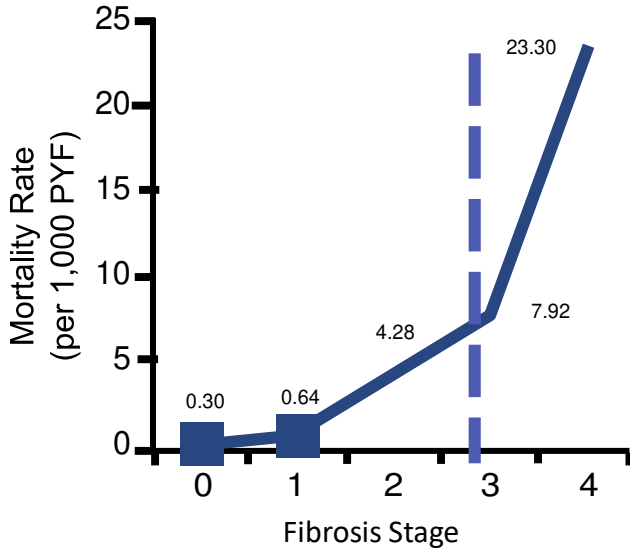


- *Fibrosis stage, but no other histologic features of steatohepatitis, were independently associated with overall lmortality, liver transplantation, and liver-related events*

Angulo P, et al. *Gastroenterology.* 2015; 149(2): 389–397.



Hagstrom H, et al. *J Hepatology.* 2017;67:1265-1273.



Systematic search of 5 studies of adult NAFLD cohort (N=1495) studies with mortality data and biopsy stage (0–4)

Dulai PS, et al. *Hepatology.* 2017;65(5):1557-1565.

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Diagnosing NASH and Fibrosis: Biopsy

Biopsy advantages[1,2]

- NASH diagnosis
- Fibrosis staging and architectural distortion
- Scoring severity of NAFLD disease (SAF, NASH-CRN)
- Contribution of other comorbidities (alcohol, iron overload, viral hepatitis, etc..)

Biopsy disadvantages

- Invasive procedure with risk of complications[1]
- 0.35% serious bleeding and 0.14% death[3]
- Associated with poor patient experience[4]
- Mis-staging of fibrosis in 33–41% of cases[5,6]
- Sampling variability[1]
- Inter- and intra-observer variability[3]
- Reading by an experienced pathologist[1]
- Cost

NASH-CRN: NASH Clinical Research Network; SAF: steatosis, activity and fibrosis

1. Bedossa P. Liver Int 2018;38 Suppl 1:64–6; 2. Castera L. Liver Int 2018;38 Suppl 1:67–70; 3. Myers RP, et al. Liver Int 2008;28:705–12;
4. Castera L et al. Hepatology 1999;30:1529–30; 5. Ratziu V, et al. Gastroenterology 2005;128:1898–906; 6. Regev A, et al. Am J Gastroenterol 2002;97:2614–8

Who Is Not a Candidate for Liver Biopsy?

Defer Liver Biopsy[a]

- ≤ 2 features of metabolic syndrome
- No T2D
- Normal liver transaminases
- **VCTE < 6.5 kPa[b]**
- Low value with fibrosis scoring system **(NAFLD fibrosis score ≤ -1.455 = F0-F2[c])**
- Motivated to make lifestyle modifications

"We have people with NASH that have normal liver enzymes and people with elevated liver enzymes that do not have NASH."
-- Dr Steven Harrison

a. Gunn NT, et al. *Clin Liv Dis*. 2018;22:109-119;
b. Siddiqui MS, et al. *Clin Gastroenterol Hepatol*. 2018. [Epub ahead of print]
c. Cheah MCC, et al. *J Clin Trans Hepatol*. 2017;5:261-271.

Diagnostic Modalities for NAFLD, NASH and Fibrosis

Serum Biomarkers

- FIB-4 index
- NFS
- APRI
- ELF®
- Hepascore®
- FibroSure®
- FibroMeter®

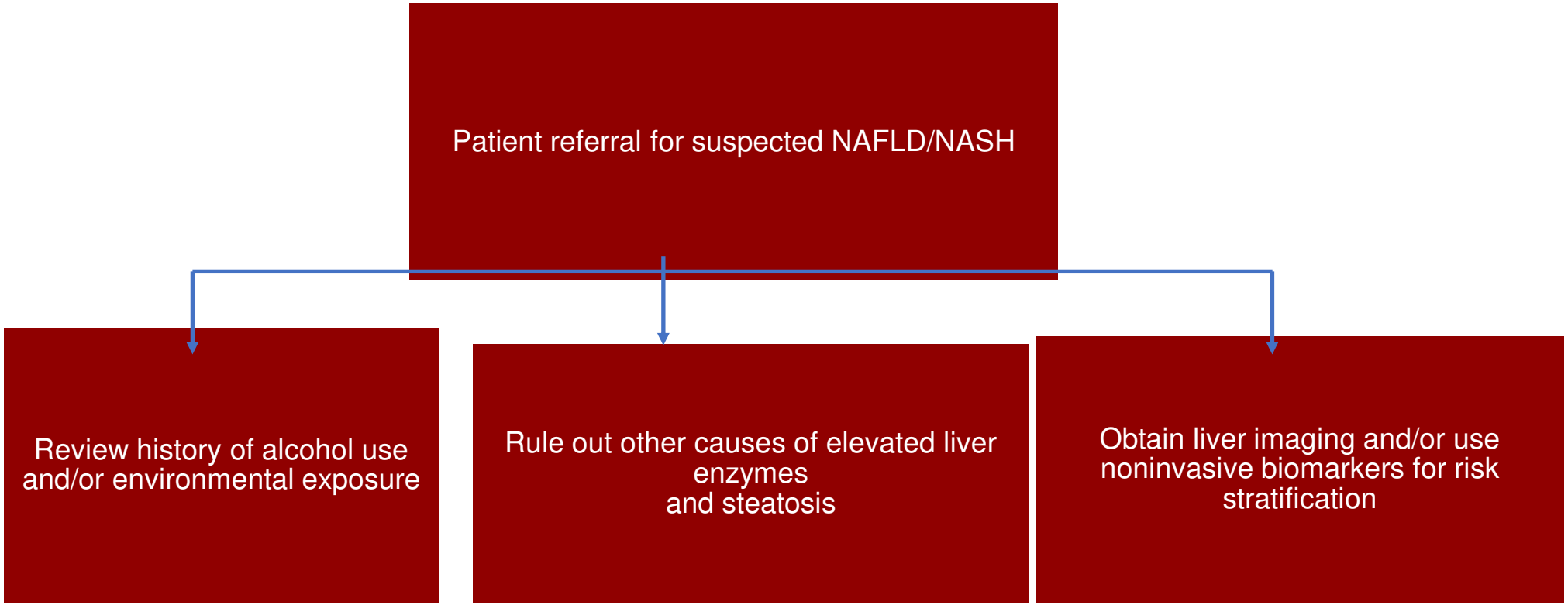
Imaging Biomarkers

- Transient elastography
- Shear wave elastography
- Magnetic resonance techniques
- FAST Score (FibroScan-AST)
- Acoustic radiation force impulse

FIB-4, Fibrosis-4 Index; NFS, NAFLD Fibrosis Score; ELF, Enhanced Liver Fibrosis.

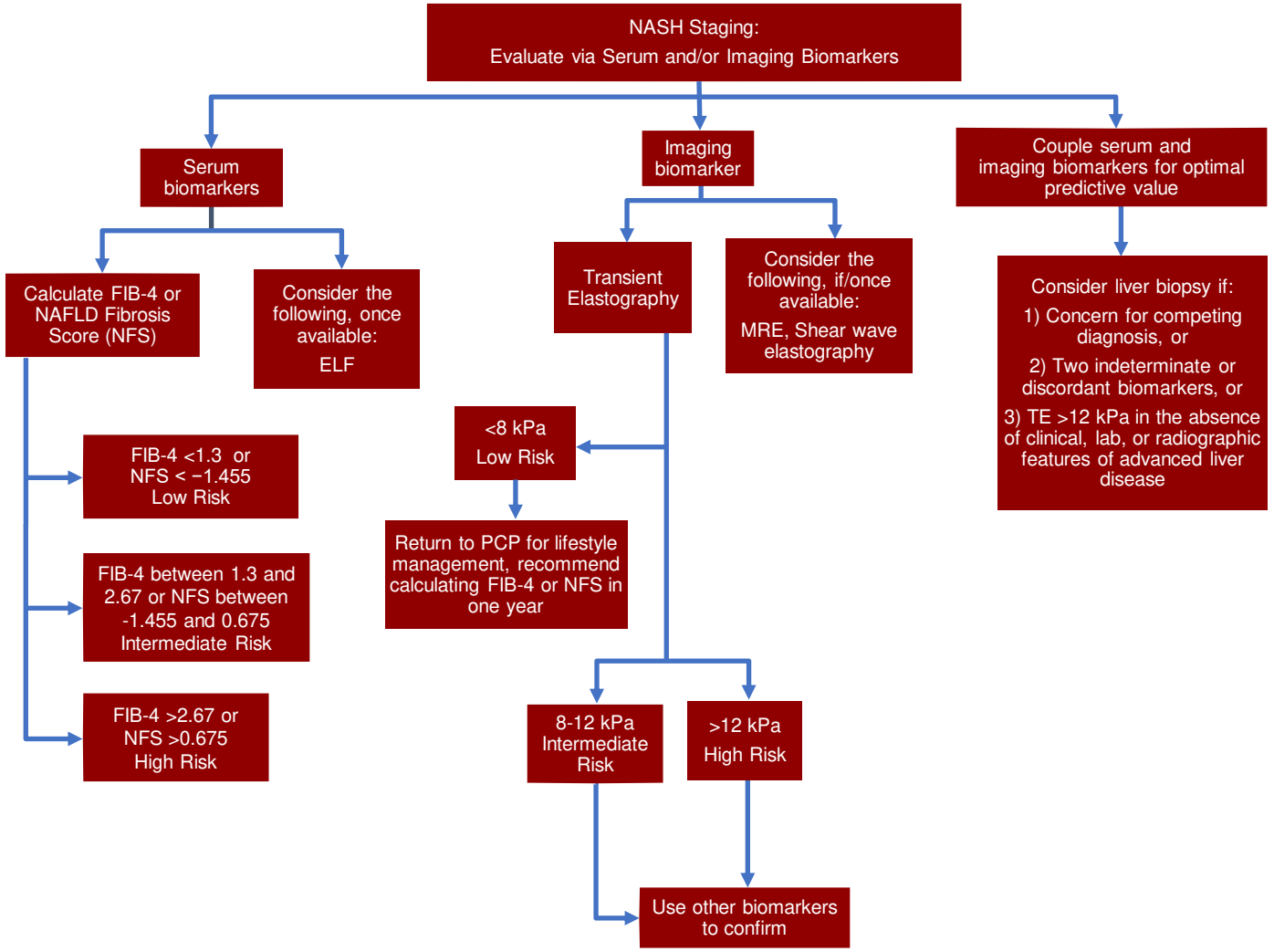
Papagianni M, et al. *World J Hepatol*. 2015;7:638–48; Golabi P, et al. *Expert Rev Gastroenterol Hepatol*. 2016;10:63–71.

NAFLD/NASH Screening Algorithm



Available at: https://chronicliverdisease.org/disease_focus/NASH-Leadership.cfm. Accessed May 21, 2020.

NAFLD/NASH Staging Algorithm



Available at: https://chronicliverdisease.org/disease_focus/NASH-Leadership.cfm. Accessed May 21, 2020.

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Guidelines

AASLD Guidance Statements[1]

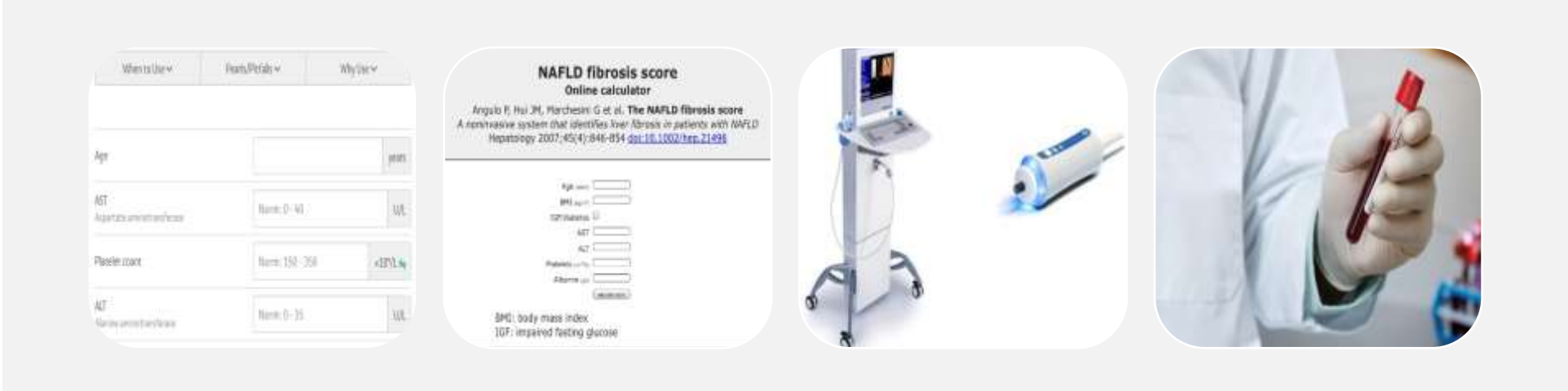
- **NFS** or **FIB-4** Index are clinically useful tools for identifying NAFLD patients with higher likelihood of having bridging fibrosis (F3) or cirrhosis (F4)
- **Vibration controlled transient elastography (VCTE)** or Magnetic resonance elastography **(MRE**) are clinically useful tools for identifying advanced fibrosis in patients with NAFLD
- Clinical decision aids such as **NFS or fibrosis-4 index (FIB-4) or vibration controlled transient elastography (VCTE)** can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis)

EASL Guideline Statements[2]

- **Biomarkers and scores of fibrosis**, as well as **transient elastography**, are acceptable, noninvasive procedures for the identification of cases at low risk of advanced fibrosis/cirrhosis
- The combination of **biomarkers/scores and transient elastography** might confer additional diagnostic accuracy and might save a number of diagnostic liver biopsies
- The identification of advanced fibrosis or cirrhosis by **serum biomarkers/scores and/or elastography** is less accurate and needs to be confirmed by liver biopsy, according to the clinical context

1. Chalasani N, et al. *Hepatology*. 2018;67:328-357. 2. "The management of non-alcoholic fatty liver disease, EASL–EASD–EASO Clinical Practice Guidelines" *Journal of Hepatology*. 2016;64:1388-402.

4 NITs have been Selected for Immediate Exploration to Identify Patients for Treatment ‡



FIB-4 | **NFS** | **FibroScan** | **ELF**

FIB-4 and NFS are better at ruling-out than ruling-in advanced fibrosis (F3/4)

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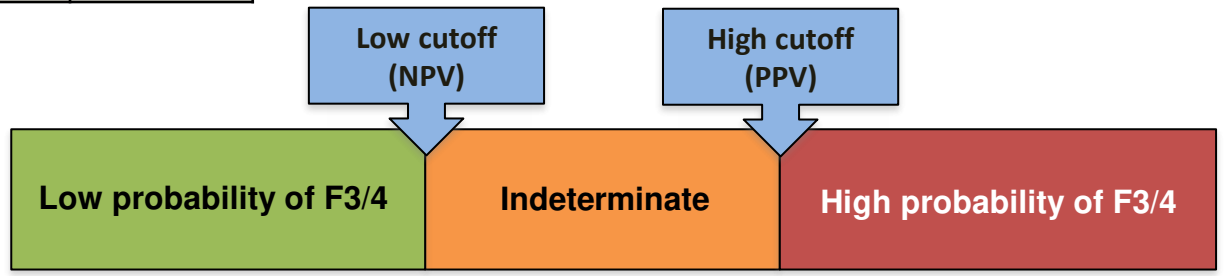
Parameter
Age
AST
ALT
Platelet count
BMI
Albumin
Impaired fasting glucose/diabetes?

NAFLD fibrosis score

FIB-4 Score

NAFLD fibrosis score[1]	Effect	NPV or PPV, %
<-1.455	Rules out fibrosis	88 to 93
>0.676	Predicts fibrosis	82 to 90

FIB-4 Score[2,3]	Effect	NPV or PPV, %
<1.3	Rules out fibrosis	95
>3.25	Predicts fibrosis	75



1. Angulo P, et al. Hepatology 2007;45:846–54;
2. Sterling RK, et al. Hepatology 2006;43:1317–25;
3. McPherson S, et al. Gut 2010;59:1265–69

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; NPV: negative predictive value; PPV: positive predictive value

VCTE and AST/ALT Ratio

- VCTE results plus NAFLD fibrosis score and FIB-4 scoring
- AST/ALT ratio[a,b]
  - AST ↑ = increased risk of fibrosis and active disease
  - Biggest component of the NAFLD fibrosis score and FIB-4

NAFLD Fibrosis Score Formula[b]	FIB-4 Formula[b]
−1.675 + 0.037 × age (y) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × **AST/ALT ratio** -- 0.013 × platelet (× 10^9/L) -- 0.66 × albumin (g/dL)	Age (y) × **AST** (IU/L)/platelet (10^9/L) × **ALT** (IU/L)^2

a. Sattar N, et al. *BMJ*. 2014;349:g4596; b. Cheah MCC, et al. *J Clin Trans Hepatol*. 2017;5:261-271.

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Enhanced Liver Fibrosis (ELF) Score

- 3 direct biomarkers of fibrosis combined into one score:
  - Hyaluronic acid
  - Procollagen III N terminal peptide (PIIINP)
  - Tissue inhibitor of metalloproteinase 1 (TIMP1)
- Good at diagnosing severe fibrosis in patients with HBV, HCV, and HIV
- Not as much validation in subjects with NAFLD
- Significant overlap with normal ranges, which may confound interpretation of results in mild to moderate fibrosis range
- Used in NASH trials as a surrogate marker for fibrosis; preliminary results encouraging

ELF Score	Severity of Liver Fibrosis	Fibrosis Stage	AUROC
< 7.7	None to mild	≥F2	0.82
≥ 7.7 – < 9.8	Moderate	≥F3	0.90
≥ 9.8	Severe	≥F4	0.87
≥ 11.3	Cirrhosis		

Lichtinghagen R, et al. J Heaptol 2013; Yoo EJ, et al. Liver Int 2013

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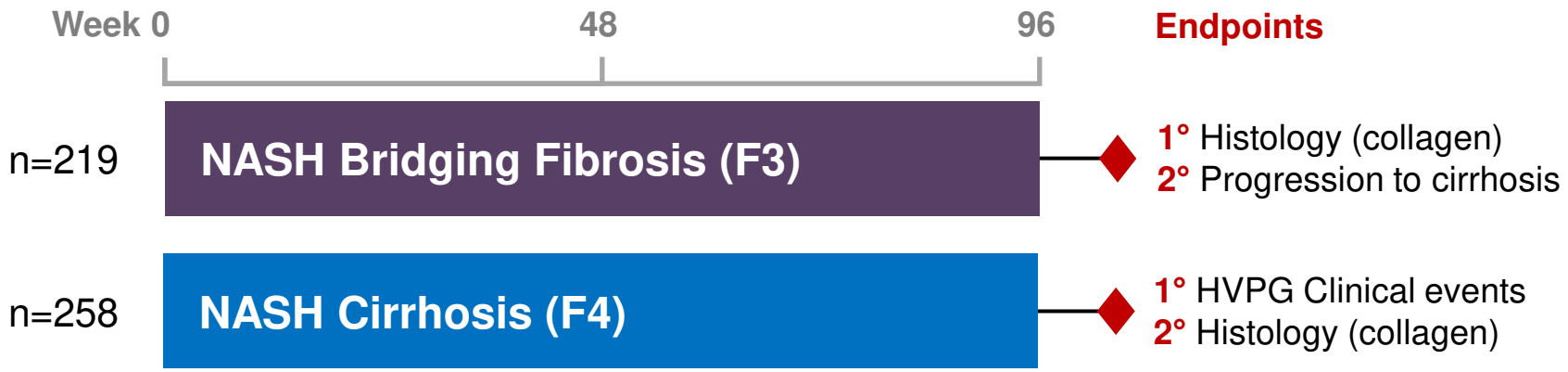
Simtuzumab (SIM) in NASH and F3–F4 Fibrosis



- Studies terminated at Week 96 due to lack of efficacy
- Clinical data, serum, and liver tissue for biomarker discovery/validation

HVPG, hepatic venous pressure gradient.
Harrison S, et al. EASL 2017, Oral PS-094

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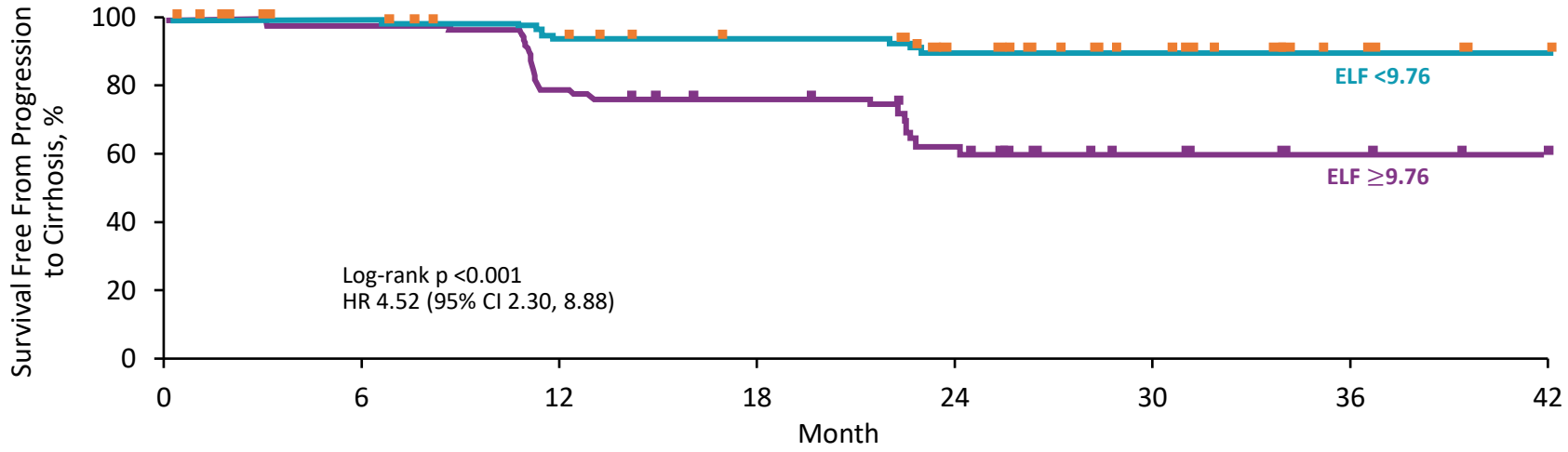
ELF Predicts Progression More Accurately than Biopsy

Patients with NASH and bridging fibrosis (n=219) or compensated cirrhosis (n=258) enrolled in two Phase 2b SIM studies

Progression to Cirrhosis According to Baseline ELF



Predictors of Progression to Cirrhosis

Parameter	Adjusted HR (95% CI)	*P*-value
Baseline ELF	3.20 (2.33, 4.39)	<0.001
Change in ELF	1.60 (1.19, 2.16)	<0.01
Ishak stage 4 vs 3	0.87 (0.47, 1.59)	0.64

Higher baseline ELF and greater change in ELF were associated with increased risk of progression to cirrhosis

Harrison, AASLD 2017, Poster 2122

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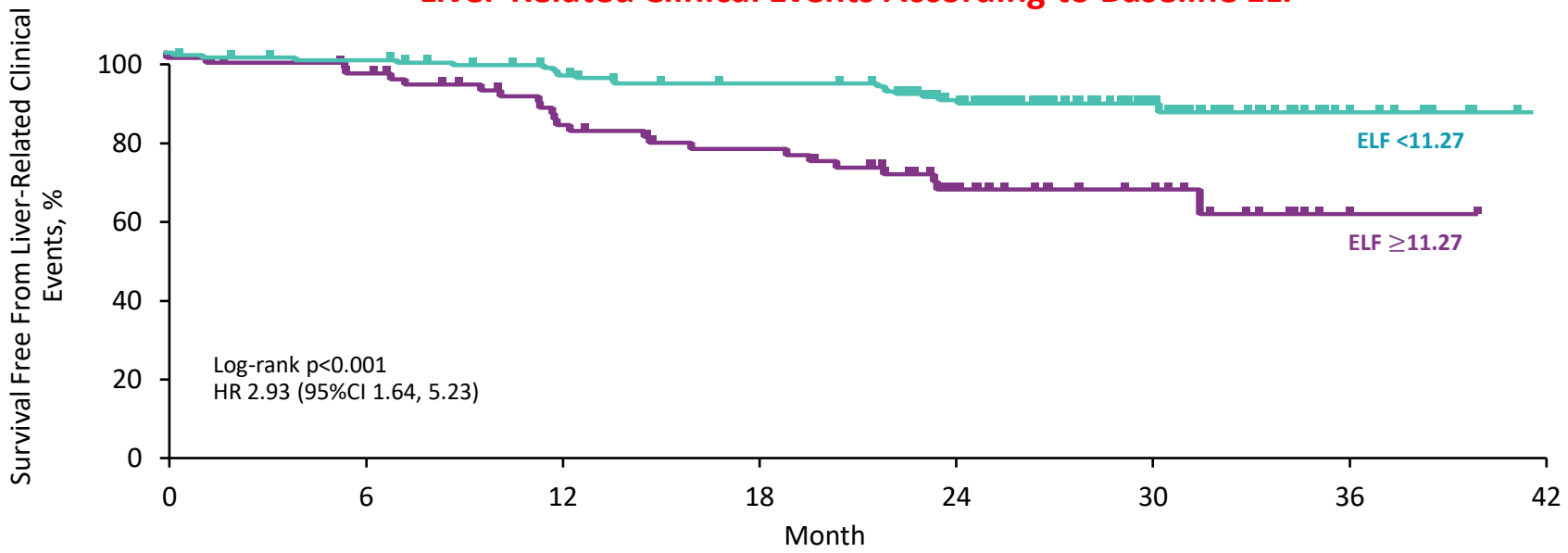
ELF Predicts Progression More Accurately than Biopsy

Liver-Related Clinical Events According to Baseline ELF



Predictors of Liver-Related Clinical Events

Parameter	Adjusted HR (95% CI)	*P*-value
Baseline ELF	2.40 (1.70, 3.38)	<0.001
Change in ELF	1.53 (1.09, 2.14)	0.01
Ishak stage 6 vs 5	0.89 (0.47, 1.68)	0.71

Higher baseline ELF and greater change in ELF were associated with liver-related clinical events

Harrison, AASLD 2017, Poster 2122

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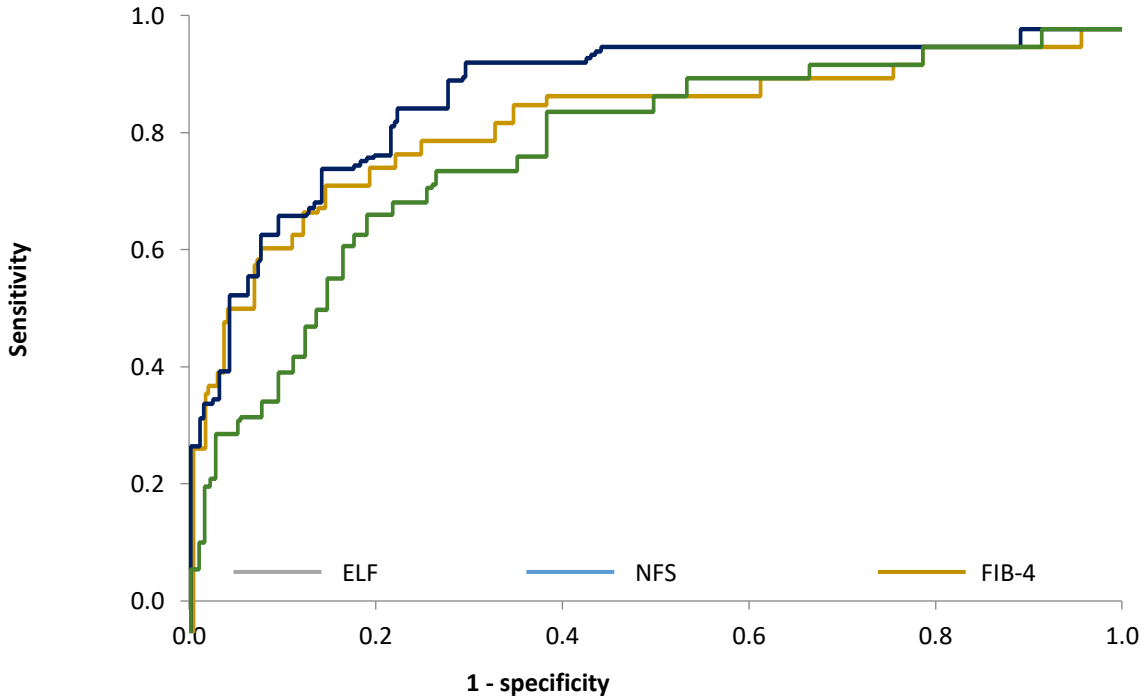
ELF Score Accurately Detects Advanced Fibrosis (F3/F4) in NAFLD

Diagnostic accuracy of Enhanced Liver Fibrosis (ELF) score was evaluated to predict advanced fibrosis in 188 patients with NAFLD

Predictive Value of NITs for Diagnosis of Advanced Fibrosis



	AUROC (95% CI)
ELF score	0.89 (0.83-0.95)*
NFS	0.80 (0.72-0.88)
FIB-4	0.85 (0.77-0.93)

*P<0.05 vs. NFS using comparison of AUROC according to DeLong et al.

ELF score showed good diagnostic accuracy for detection or exclusion of advanced fibrosis in NAFLD

ELF test is a noninvasive fibrosis panel composed of hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinase-1 (TIMP1)
Staufer, EASL 2018, FRI-445