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MetALD: Diagnosis and Prognosis With Non-Invasive Tests

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ABSTRACT

Background: Non-invasive tests (NITs) are central to diagnosing and stratifying risk in steatotic liver disease (SLD). However, it remains unclear whether guideline-recommended NIT cut-offs apply to metabolic and alcohol-related liver disease (MetALD).

Aim: Evaluate the diagnostic and prognostic performance of five NITs in patients with MetALD.

Methods: Single-centre study with 423 SLD patients, of whom 102 (24%) had MetALD. Patients were classified using histological or controlled attenuation parameter-defined hepatic steatosis and self-reported alcohol intake. We assessed the circulating markers of FIB-4, LiverRisk score, ELF and ADAPT together with transient elastography (TE) using established cut-offs for advanced fibrosis (≥F3). Liver histology served as reference. Prognostic performance for hepatic decompensation and all-cause mortality was evaluated over a median follow-up of 62 months.

Results: Among circulating NITs in MetALD, ELF and ADAPT both had the highest diagnostic accuracy (AUROC = 0.90), while it was lowest with LiverRisk score (AUROC = 0.74). The indeterminate zone between rule-out and rule-in cut-offs was largest for FIB-4 (34%). TE and circulating NIT concordance was highest for LiverRisk score (81%) to rule-out ≥F3, and highest for ELF (88%) to rule-in ≥F3. All included NITs predicted decompensation-free survival with their corresponding rule-out or rule-in cut-offs. A sequential 2-tier testing strategy (FIB-4 → TE) effectively stratified risk of decompensation. Incorporating a second-tier test (ELF or ADAPT) before TE reduced the number of TE referrals by 43% and 45%, without loss of prognostic performance.

Conclusion: Widely available NITs are applicable for MetALD, where cut-offs can be used to diagnose advanced fibrosis and predict clinical outcomes.

1 | Introduction

Steatotic liver disease (SLD) affects nearly 40% of the adult population, imposing a significant burden on healthcare systems [1]. A significant subgroup of patients with SLD belongs to the newly formed clinical entity of metabolic and alcohol-related liver disease (MetALD) [2]. Patients with MetALD are characterised by hepatic steatosis, the presence of cardiometabolic risk factors (CMRFs) and an alcohol intake between 20–49 and 30–59 g per day for women and men, respectively [3]. As MetALD was unexplored as a separate entity prior to the implementation of the SLD nomenclature, it is unclear if the clinical management of this subgroup is similar to that of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD) [4].

Clinical practice guidelines recommend non-invasive tests (NITs) for the early detection and risk stratification of patients with SLD [5]. Most referral pathways suggest the incorporation of NITs as part of a two- or three-tiered strategy for detecting advanced hepatic fibrosis in at-risk populations [6]. The Fibrosis-4 Index (FIB-4) is recommended as a first-tier test, as it is easily available in most primary care settings. However, applied in a general population setting, guideline-recommended cut-offs show poor accuracy and a high rate of false positives [7, 8]. Furthermore, studies have also suggested considerable variation in the diagnostic performance of FIB-4 across SLD subclasses [9].

LiverRisk score is another first-tier test developed to identify individuals at risk of future liver-related outcomes in the general population [10]. However, its diagnostic and prognostic performance across the spectrum of SLD is less known.

The enhanced liver fibrosis (ELF) test and the ADAPT algorithm, using hepatic fibrogenesis marker PRO-C3, are both proposed as blood-based, second-tier tests [8, 11]. A recent meta-analysis of the ELF test showed that diagnostic performance may differ between patients with MASLD and ALD [12]. ADAPT has been shown to have excellent performance in patients with MASLD [13]. However, since both the ELF test and ADAPT incorporate markers of collagen formation, their diagnostic accuracy may be susceptible to variations in alcohol intake, especially since a single binge drinking episode can lead to a significant acute increase in the hepatic collagen turnover for patients with SLD [14].

Transient elastography (TE) is commonly used in secondary or tertiary care settings to confirm if further diagnostic work-up is needed, or if patients can be referred back to primary care [15]. Key potential sources of false-positive or unreliable TE results include hepatic inflammation due to excessive alcohol intake and severe obesity [16, 17]. Notably, alcohol intake and BMI as a CMRF are both used to subclassify patients with SLD.

As NIT cut-offs for clinical decision making are an integral part of referral pathways as well as management of steatotic liver disease, the diagnostic accuracy and prognostic discrimination for recommended cut-offs are pivotal. However, as studies indicate that factors used to subclassify SLD patients may inherently affect NIT levels, it remains unclear if recommended NIT cut-offs can be consistently applied in MetALD as in other SLD subclasses [18].

We therefore aimed to validate the diagnostic accuracy, prognostic discrimination and sequential use of FIB-4, LiverRisk score, ELF, ADAPT and TE using their recommended cut-offs in MetALD patients with MASLD and ALD as reference subclasses.

2 | Methods

2.1 | Study Design

We used data from two single-centre, prospective studies of SLD patients. The studies were approved by the Ethics Committee for the Region of Southern Denmark (S-20120071, S-20160021, S-20170087), the Danish Data Protection Agency (13/8204, 18/22692) and the Danish Health Data Authority (FSEID-00005798). We used the STARD checklist for study reporting. All study-related procedures were preceded by the participants' informed consent according to the Declaration of Helsinki.

2.2 | Patients

In the first study, patients were recruited from primary care, secondary care and through a community call to screen for alcohol-related liver fibrosis, as previously described [19]. Included patients were between 18 and 75 years of age; all had a history of self-reported excessive alcohol consumption (defined as ≥ 24 g/day for women and ≥ 36 g/day for men) for at least 1 year. Key exclusion criteria were known decompensated cirrhosis, cancer or any other disease with an expected survival of less than a year, competing liver disease from other causes than SLD, biliary obstruction and right heart failure.

In the second study, patients were recruited through an electronic mailbox invitation either due to the presence of risk factors for SLD (history of excessive alcohol intake, obesity, diabetes and/or metabolic syndrome) or as part of a randomly selected group representative of the general population [8]. Alcohol was assessed as the average intake per week in the preceding 3 months prior to study inclusion. In this study, participants were between 30 and 75 years of age but with otherwise similar exclusion criteria as the first study (Table S1).

We classified participants according to the SLD nomenclature by the identification of any histological or ultrasonic signs of hepatic steatosis. For the controlled attenuation parameter, we used the 248 dB/m cut-off to detect steatosis, as recommended by EASL Clinical Practice Guidelines [15]. Patients with histological signs of significant fibrosis (≥ F2), but without signs of steatosis, were still categorised as SLD, if fibrosis development was presumed attributable to a SLD aetiology based on clinical judgement.

We subclassified patients according to their current average self-reported alcohol intake (women/men), defined as the average

intake over the 3 months prior to study inclusion. Patients were classified into MASLD (< 20/< 30 g/day), MetALD (20–30 g/day to 49/59 g/day) and ALD (≥ 50/≥ 60 g/day) contingent on the presence of cardiometabolic risk factors (CMRFs). We used a standardised questionnaire about alcohol intake asked by trained study personnel at baseline. We did not incorporate longitudinal alcohol intake data from medical records, as doing so could introduce attrition bias due to differential follow-up duration and data availability [20].

CMRFs were defined according to the established criteria for metabolic syndrome, which were applied as per the SLD nomenclature guidance [3]. Blood pressure, BMI, waist circumference, fasting blood glucose, glycated haemoglobin, plasma triglycerides and HDL were measured at inclusion. By review of the patients' medication log, we identified any drugs to treat hypertension, type 2 diabetes or dyslipidaemia whereby they fulfilled the CMRF criteria.

2.3 | Histological Assessment

Liver biopsies for histology were all performed percutaneously with a 17-G Menghini suction needle (Hepafix, Braun, Germany) on the same day as other investigations. The predefined quality assessment of biopsies included a length > 10 mm and > 5 portal tracts, in the absence of histological evidence of cirrhosis. Staging of liver fibrosis was done according to the Kleiner fibrosis score, ranging from no fibrosis (F0) to cirrhosis (F4). Advanced fibrosis was defined as F3 or above (≥ F3). All biopsies were evaluated by a single experienced pathologist, blinded to the clinical data of the participants. Liver biopsies were performed in all patients up until 2016, where a change to the study protocol led to only patients with a TE ≥ 6 kPa were biopsied as the negative predictive value of ≥ F3 was 100% below this value [19]. Hence, only patients with available liver histology were included in the diagnostic accuracy analyses.

2.4 | Non-Invasive Tests and Cut-Offs

For diagnosing ≥ F3 and risk stratifying for outcomes, we applied low rule-out (to avoid false negatives) and high rule-in (to avoid false positives) cut-offs for FIB-4, ELF, ADAPT, LiverRisk score and TE based on recommendations from clinical practice guidelines and the literature [5, 15, 21].

FIB-4 was calculated based on blood samples from the day of the investigations. FIB < 1.30 was used as rule-out for participants aged < 65 and < 2.00 for ≥ 65 years of age, whereas FIB-4 ≥ 2.67 was the rule-in cut-off [5].

For LiverRisk score we used the recommended cut-offs with the upper boundary of the low-risk group (< 10) and the lower boundary of the high-risk group (≥ 15) [10].

The ELF test was analysed according to the manufacturer's instructions on an Advia Centaur XP (Siemens Healthcare Diagnostics Inc.). We used a cut-off < 9.8 to rule-out advanced fibrosis and ELF ≥ 11.3 to rule-in [22]. Since only a small proportion (3%) of patients from our cohort had ELF < 7.7, this cut-off was not applied [19].

To calculate ADAPT, we used NordicPRO-C3 measured in serum samples from a fasting state. In the first study, NordicPRO-C3 was measured with ELISA kits, while it was being measured on the Roche COBAS e602 platform in the second study. NordicPRO-C3 quantification from the two platforms was harmonised by using a conversion factor provided by the manufacturer (Nordic Bioscience A/S) to align values with cut-offs recommended in clinical practice guidelines. Cut-offs for ADAPT are part of the recent clinical practice guideline for MASLD, which recommends ADAPT < 4.46 to rule-out and ≥ 7.15 to rule-in advanced fibrosis [15]. Similar to ELF, few patients in our cohort had ADAPT values below the guideline-recommended rule-out cut-off (< 4.46). Hence, we selected an ADAPT < 6.33 to rule-out ≥ F3, since a previous study showed a high negative predictive value for this cut-off in a similar population [13].

TE was performed on the day of investigations in a fasting state by experienced study staff with the M- or XL-probe. We used the cut-offs for TE of < 10 kPa to rule-out and ≥ 15 kPa to rule-in advanced disease, as per Baveno VII recommendations [21].

2.5 | Longitudinal Follow-Up

We manually reviewed electronic medical records to identify any hepatic decompensation or death occurring during follow-up until September 2022. We followed participants from the time of inclusion until death, lost to follow-up or until September 2022. Participants who were lost to follow-up were censored on the date of the latest available medical record. We used the Baveno VII criteria to define hepatic decompensation as overt ascites, overt hepatic encephalopathy or variceal bleeding [21].

2.6 | Statistics

We present normally distributed continuous variables as means with standard deviations (SD) and compare groups using Student's *t*-test. For non-normally distributed continuous variables, we report medians and interquartile ranges (IQR), with Wilcoxon rank sum test to compare groups.

To evaluate diagnostic performance among circulating NITs, we calculated the area under the receiver operating characteristic curve (AUC) for advanced fibrosis (≥ F3). AUCs were compared using De-Long's test across all NITs, with head-to-head comparisons made only if statistically significant differences in AUCs were detected. We computed sensitivity, specificity, positive and negative predictive values, as well as positive and negative likelihood ratios for all NITs based on the rule-out and rule-in cut-offs. We also calculated the corresponding cut-offs for 90% sensitivity and 90% specificity for all circulating NITs.

For the comparison of diagnostic accuracy, we conducted complete case analyses of all circulating NITs available. TE was not

TABLE 1 | Baseline characteristics for all patients with available non-invasive tests and reliable transient elastography measurements.

	MetALD	MASLD	ALD
	***n* = 102**	***n* = 227**	***n* = 94**
Age, years	60 (9)	57 (10)	57 (9)
Sex, male	78 (76%)	163 (72%)	78 (83%)
Alcohol intake last week, g/day	43 (34–51)	0 (0–2)	69 (7–96)
Alcohol abstinence, *n*	—	155 (69%)	—
Years of alcohol abstinence[a] (< 1, 1–5, 6–10, 11–20, 21–30, > 30)	—	93/15/5/5/3/3	—
Cardiometabolic risk factors			
BMI, kg/m^2	29.0 (25.7–31.5)	29.7 (26.0–34.0)	27.8 (24.2–32.3)
Waist circumference, cm	108 (100–116)	114 (101–125)	104 (96–118)
BMI ≥ 25 kg/m^2 or waist circumference > 94/> 80 cm, *n*	62 (78%)	107 (74%)	61 (72%)
Diabetes, yes	17 (17%)	61 (27%)	8 (9%)
Impaired glycaemic control, *n*	68 (87%)	117 (82%)	71 (85%)
Triglycerides (mmol/L)	1.4 (0.9–1.9)	1.4 (1.0–2.0)	1.3 (0.9–1.9)
Triglycerides ≥ 1.70 mmol/L, *n*	40 (51%)	61 (44%)	41 (49%)
HDL-cholesterol (mmol/L)	1.4 (1.2–1.8)	1.2 (1.0–1.4)	1.4 (1.2–1.8)
HDL-cholesterol ≤ 1.0/≤ 1.3 mmol/L, *n*	21 (27%)	66 (48%)	25 (31%)
Hypertension, *n*	88 (86%)	181 (82%)	75 (82%)
Number of CMRFs, *n*	3 (2–4)	4 (2–5)	3 (2–4)
Biochemical			
ALT, U/L	42 (29–60)	32 (23–48)	40 (28–58)
AST, U/L	43 (31–61)	32 (26–47)	45 (30–77)
ALP, U/L	76 (63–96)	86 (67–111)	78 (67–107)
GGT, U/L	118 (57–302)	67 (35–165)	135 (65–282)
Biomarkers			
FIB-4	1.7 (1.3–2.7)	1.5 (0.9–2.3)	1.7 (1.3–3.1)
LiverRisk score	8 (6–12)	7 (6–9)	8 (6–12)
ELF	9.6 (8.6–10.6)	9.6 (9.0–10.6)	9.2 (8.7–10.3)
ADAPT	6.14 (4.96–7.60)	6.54 (5.32–8.47)	6.00 (4.84–7.43)
TE, kPa[b]	8.5 (5.1–12.1)	10.2 (6.7–20.4)	8.8 (5.5–17.1)
Histology			
Patients with liver biopsy, *n*	78 (76%)	213 (94%)	73 (78%)
Fibrosis stage (0/1/2/3/4)	2/23/34/9/10	10/64/71/26/42	3/21/26/12/11
Advanced fibrosis (≥ F3), *n*	19 (24%)	68 (32%)	23 (32%)

Note: Data are presented as mean (SD) or median (IQR) for continuous measures, and *n* (%) for categorical measures.
[a]Duration of abstinence missing for 31 MASLD patients.
[b]Majority of TE measurements were performed with the M-probe, whereas the XL-probe was used in 56 MASLD, 19 MetALD and 15 ALD patients.

part of the diagnostic accuracy analyses as a TE > 6 kPa served as the determinant of referral for liver biopsy in most patients. We used Cohen's kappa to assess concordance to rule-out advanced fibrosis for all NITs.

For time-to-event data, we considered decompensation-free survival as our primary prognostic outcome of interest. Here, we applied univariable Cox regression analysis of models with rule-out and rule-in cut-offs for NITs. We tested the proportional

hazard assumption of Cox regression by inspection of the Schoenfeld residuals. We compared the prognostic performance between NIT models with Harrel's *C* test statistic. As a sensitivity analysis, we performed competing risk regression with hepatic decompensation as the outcome of interest and death as the competing event.

We assessed both a 2-step and 3-step sequential testing strategy to identify patients at risk of hepatic decompensation during follow-up. The 2-step approach consisted of FIB-4 and TE, whereas the 3-step approach was FIB-4, ELF and TE or FIB-4 ADAPT and TE. The age-adjusted rule-out cut-off for FIB-4 was used to identify low-risk patients, where patients with a FIB-4 between 1.30 and 2.66 or 2.00 and 2.66 were referred to ELF or ADAPT in the 3-step approach. We applied the rule-out cut-offs for ELF (<9.8) and ADAPT (<6.33) to categorise as low risk, or for referral to TE, if values were above the rule-out cut-offs. Patients with a FIB-4 ≥ 2.67 were referred directly to TE. Patients with TE were considered as low risk (<10 kPa), grey zone (≥10 to 14.9 kPa) and high risk (≥15 kPa).

We used STATA 18 (StataCorp TX, US) for all analyses and considered *p*-values <0.05 as statistically significant results.

3 | Results

3.1 | Baseline Characteristics

We included 423 SLD patients: 24% with MetALD, 54% with MASLD and 22% with ALD (Table 1). Of these, 74% were recruited from primary care or secondary care in the first study, whereas the remaining 26% were recruited through electronic mailbox invitation in the second study. Across SLD subclasses, most patients were men (76%), with a mean age of 58 years (±9). The median number of CMRFs was 3 in MetALD and ALD but 4 in MASLD patients. Baseline levels of FIB-4, LiverRisk score, ELF, ADAPT and TE were similar across the SLD subgroups. Liver histology was available in 366 patients, with a the prevalence of advanced fibrosis ranging from 25% in MetALD to 32% in MASLD.

3.2 | Diagnostic Performance of Non-Invasive Tests for the Detection of Advanced Fibrosis

The AUC for diagnosing ≥F3 in MetALD was numerically highest with ELF or ADAPT and lowest for LiverRisk score but with no statistically significant difference between NITs ($p = 0.053$) (Figure 1). This finding was consistent in MASLD and ALD, where ELF also had the highest performance in both subclasses (Figure S1).

We calculated the diagnostic accuracy of the four NITs with rule-out and rule-in cut-offs for biopsy-verified advanced fibrosis (Table 2). For patients with MetALD, the rule-out sensitivity was highest with ELF <9.8 and lowest for LiverRisk score <10. For rule-in cut-offs in MetALD, specificity was numerically highest for ELF ≥11.3 and lowest for ADAPT ≥7.15. 90% sensitivity and 90% specificity cut-offs are available in Table S2.

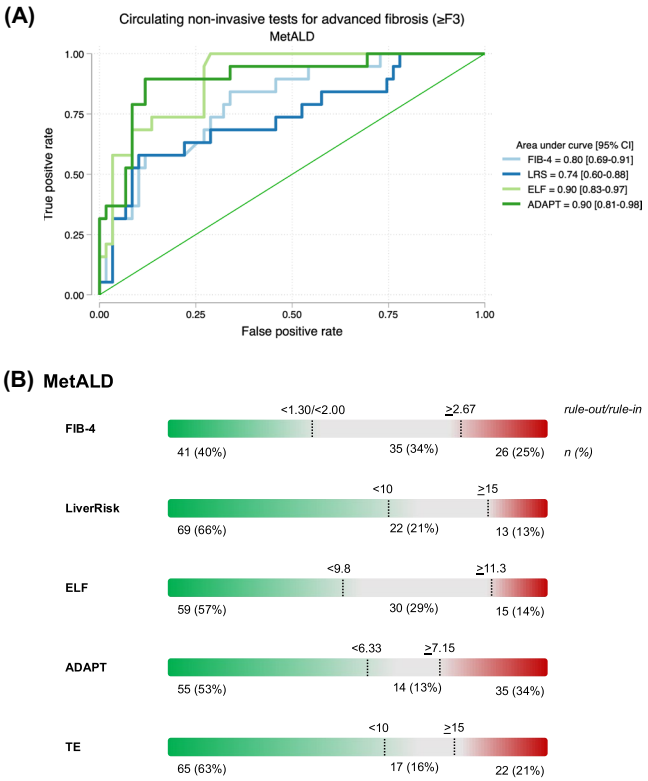


FIGURE 1 | (A) Complete case analysis of diagnostic area under the curve (AUC) for advanced fibrosis in MetALD for circulating NITs. In MetALD, the AUC were numerically similar where only LiverRisk score had an AUC <0.80. (B) Applying the proposed rule-out and rule-in cut-offs resulted in fewest patients in the indeterminate zone for ADAPT (13%), while most where in indeterminate zone with age-dependent FIB-4 rule-out and rule-in (34%).

Applying rule-out and rule-in cut-offs simultaneously in MetALD with all five NITs led to fewest patients in the indeterminate zone with ADAPT and most indeterminate patients with FIB-4 (Figure 1). The size of numerical indeterminate zone for NITs was similar for patients with MASLD and ALD (Figure S1).

3.3 | Concordance for Rule-Out and Rule-In Cut-Offs Between Non-Invasive Tests

In patients with MetALD, concordance of ruling out ≥F3 for blood-based NITs with TE was highest for LiverRisk score (81%) and lowest for FIB-4 (65%) (Figure 2). Despite good concordance between LiverRisk score and TE, six patients with ≥F3 MetALD had a LiverRisk score <10 but TE ≥10 kPa. For the other circulating NITs, the number of patients below the rule-out but with a TE ≥10 kPa was 1 for both FIB-4 and ADAPT, and none for ELF. Importantly, none with advanced fibrosis had biomarker levels below both rule-out cut-offs for the circulating NITs and TE.

Findings for blood-based NIT and TE concordance were comparable with MASLD (Figure S2) and ALD (Figure S3) except for LiverRisk score where 44 of 68 (65%) of ≥F3 MASLD patients had a LiverRisk score <10.

TABLE 2 | Diagnostic accuracy of recommended rule-in and rule-out cut-offs for FIB-4, ELF, ADAPT, LiverRisk score and TE to predict advanced fibrosis in patients with MetALD, MASLD and ALD.

≥ F3 across SLD subclasses (% prevalence)	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	LR (+) [95% CI]	LR (−) [95% CI]	Correctly classified (%)
MetALD (24%)							
Rule-out							
FIB-4 < 1.30/< 2.00[a]	95 [74–100]	41 [28–54]	34 [22–48]	96 [80–100]	1.6 [1.3–2.0]	0.1 [0.0–0.9]	45
LiverRisk < 10	68 [43–87]	64 [51–76]	37 [21–55]	87 [73–95]	1.9 [1.2–3.0]	0.5 [0.2–1.0]	65
ELF < 9.8	100 [82–100]	62 [49–74]	45 [30–61]	100 [91–100]	2.7 [1.9–3.7]	0.0	72
ADAPT < 6.33	95 [74–100]	54 [41–67]	39 [25–55]	97 [85–100]	2.1 [1.5–2.8]	0.1 [0.0–0.7]	65
Rule-in							
FIB-4 ≥ 2.67	58 [33–80]	79 [66–88]	46 [26–67]	86 [74–94]	2.7 [1.5–5.0]	0.5 [0.3–0.9]	73
LiverRisk ≥ 15	42 [20–67]	92 [82–97]	62 [32–86]	84 [73–92]	5.1 [1.9–13.8]	0.6 [0.4–0.9]	79
ELF ≥ 11.3	58 [33–80]	93 [84–98]	73 [45–92]	88 [77–95]	8.8 [3.2–24.5]	0.5 [0.3–0.8]	85
ADAPT ≥ 7.15	89 [67–99]	70 [57–81]	49 [31–66]	96 [85–99]	3.0 [2.0–4.6]	0.1 [0.0–0.6]	77
MASLD (32%)							
Rule-out							
FIB-4 < 1.30/2.00	79 [68–88]	60 [52–68]	48 [39–58]	86 [78–92]	2.0 [1.6–2.5]	0.3 [0.2–0.6]	66
LiverRisk < 10	26 [17–39]	81 [74–87]	40 [26–56]	70 [63–77]	1.4 [0.8–2.4]	0.9 [0.8–1.1]	64
ELF < 9.8	87 [76–94]	72 [64–79]	59 [49–69]	92 [85–96]	3.1 [2.3–4.0]	0.2 [0.1–0.3]	77
ADAPT < 6.33	88 [78–95]	60 [52–68]	51 [41–60]	92 [84–96]	2.2 [1.8–2.7]	0.2 [0.1–0.4]	69
Rule-in							
FIB-4 ≥ 2.67	49 [36–61]	91 [85–95]	72 [57–84]	79 [72–85]	5.4 [3.1–9.6]	0.6 [0.4–0.7]	77
LiverRisk ≥ 15	7 [2–16]	94 [89–98]	38 [14–68]	68 [62–75]	1.3 [0.5–3.9]	1.0 [0.9–1.1]	67
ELF ≥ 11.3	44 [32–57]	97 [92–99]	86 [70–95]	79 [72–84]	12.8 [5.2–31.5]	0.6 [0.5–0.7]	80
ADAPT ≥ 7.15	75 [63–85]	70 [61–77]	54 [43–64]	86 [78–91]	2.5 [1.9–3.3]	0.4 [0.2–0.5]	71

(Continues)

TABLE 2 | (Continued)

≥ F3 across SLD subclasses (% prevalence)	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	LR (+) [95% CI]	LR (−) [95% CI]	Correctly classified (%)
ALD (32%)							
Rule-out							
FIB-4 < 1.30/2.00	83 [61–95]	40 [26–55]	39 [25–54]	83 [63–95]	1.4 [1.0–1.9]	0.4 [0.2–1.1]	53
LiverRisk < 10	70 [47–87]	66 [51–79]	48 [31–66]	82 [67–93]	2.0 [1.3–3.3]	0.5 [0.2–0.9]	67
ELF < 9.8	83 [61–95]	72 [58–84]	58 [39–75]	90 [76–97]	3.0 [1.8–4.8]	0.2 [0.1–0.6]	75
ADAPT < 6.33	83 [61–95]	62 [47–75]	50 [33–67]	89 [73–97]	2.2 [1.5–3.2]	0.3 [0.1–0.7]	69
Rule-in							
FIB-4 ≥ 2.67	65 [43–84]	82 [69–91]	62 [41–81]	84 [70–93]	3.6 [1.9–7.0]	0.4 [0.2–0.8]	77
LiverRisk ≥ 15	39 [20–61]	90 [78–97]	64 [35–87]	76 [63–86]	3.9 [1.5–10.4]	0.7 [0.5–1.0]	74
ELF ≥ 11.3	30 [13–53]	94 [83–99]	70 [35–93]	75 [62–85]	5.1 [1.4–17.9]	0.7 [0.6–1.0]	74
ADAPT ≥ 7.15	74 [52–90]	76 [62–87]	59 [39–76]	86 [73–95]	3.1 [1.8–5.3]	0.3 [0.2–0.7]	75

[a]Age-specific rule-out cut-off FIB-4 with < 1.30 if age < 65 and < 2.00 if age ≥ 65 years.

For ruling in advanced fibrosis, blood-based NIT and TE concordance was generally higher than rule-out, ranging from 88% with ELF and TE to 82% for ADAPT and TE. Applying both rule-in cut-offs simultaneously led to a low number of false positives ranging from one patient with ELF and TE to four patients with FIB-4 and TE or ADAPT and TE.

Agreement for rule-out and rule-in cut-offs for NITs was also assessed by Cohen's kappa (Tables S3 and S4). For MetALD, inter-NIT agreement tended to be similar between rule-out and rule-in cut-offs except for rule-out for FIB-4, where agreement was lower (from $\kappa = 0.217$ with FIB-4 and ELF to $\kappa = 0.393$ with FIB-4 and LRS). In patients with MetALD, the highest kappa was observed between rule-in for FIB-4 and ADAPT ($\kappa = 0.609$), whereas the lowest was between rule-out for LiverRisk score and TE ($\kappa = 0.424$).

3.4 | Clinical Outcomes During Follow-Up

The median follow-up time was 61 months (IQR: 51–88 months) for 311 patients with clinical outcome data. During this time, 53 patients (17%) developed hepatic decompensation, and 80 (26%) died, 43 without a prior decompensation. None of the patients were liver transplanted. The type of first decompensation was primarily ascites ($n = 31$), followed by hepatic encephalopathy ($n = 14$) and variceal bleeding ($n = 8$). The median time from inclusion to decompensation was 26 months (IQR: 10–44 months).

3.5 | Comparison of Prognostic Performance for Non-Invasive Tests

In patients with MetALD, rule-out and rule-in cut-offs for all NITs were prognostic for decompensation-free survival in univariable Cox regression (Table 3). In contrast to the other NIT cut-offs in MASLD and ALD, the rule-in cut-off for LiverRisk score in MASLD and the rule-out cut-off for FIB-4 in ALD were not associated with the outcome of decompensation-free survival.

Harrel's *C* with continuous NIT values in MetALD was numerically highest for FIB-4 (*C*-statistic = 0.817) and lowest with LRS (*C*-statistic = 0.767) but with no significant difference between NITs. In MASLD, TE had the highest Harrel's *C* while this was ELF in ALD.

In competing risk regression for hepatic decompensation, the prognostic findings were robust except for the age-adjusted rule-out cut-off for FIB-4 in ALD together with the rule-in for the LiverRisk score in MASLD (Table S6).

3.6 | Sequential Testing Strategies Identify Patients At-Risk of Hepatic Decompensation

In patients with MetALD, sequential testing strategies using age-adjusted FIB-4 as a first-tier test, followed by either ELF or ADAPT as second-tier tests, and TE as the final tier, effectively stratified risk for hepatic decompensation.

Using the two-tier strategy (FIB-4 followed by TE), a high-risk group with a 55% incidence of hepatic decompensation was

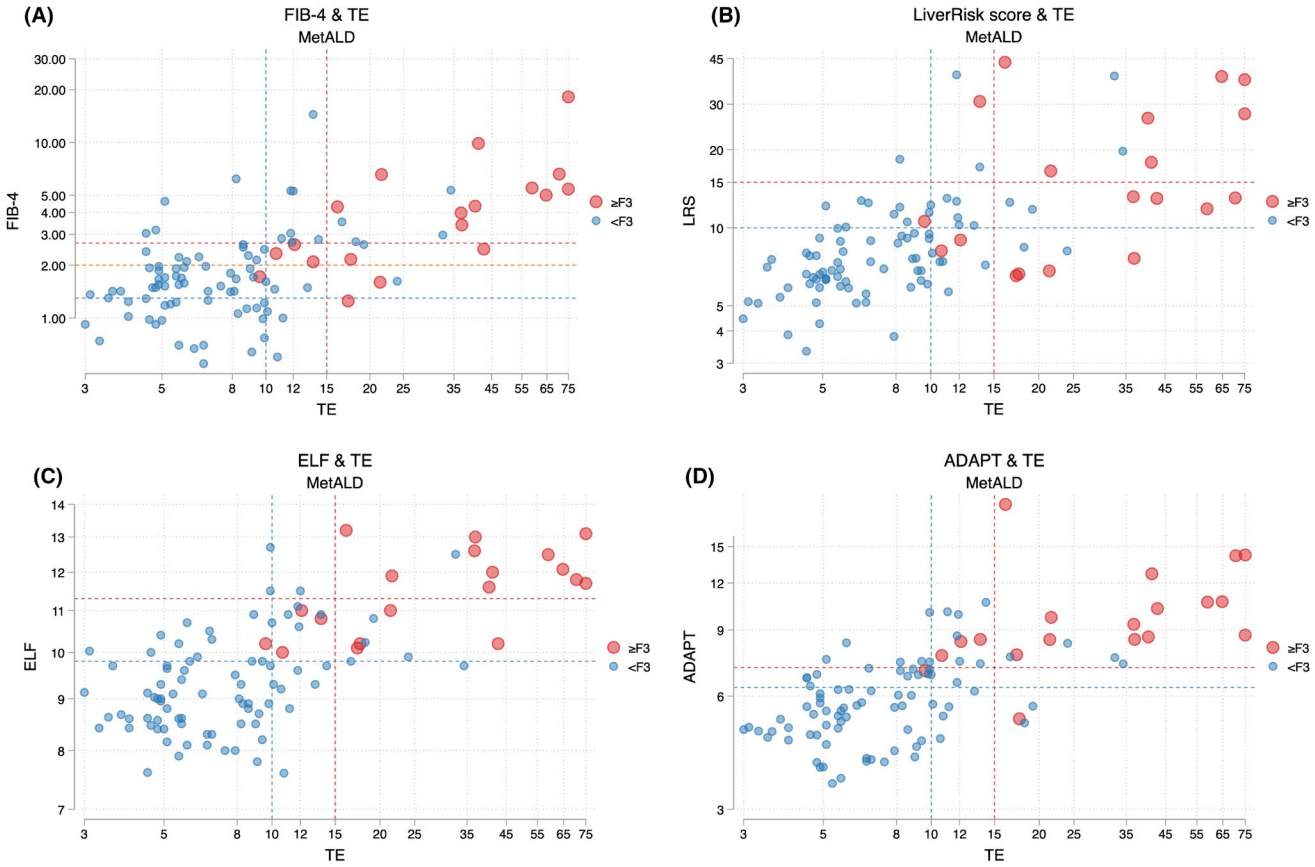


FIGURE 2 | Concordance plots of rule-out (blue dashed lines) and rule-in (red dashed lines) cut-offs for circulating non-invasive tests with transient elastography in metabolic and alcohol-related liver disease. Applied rule-out cut-offs: FIB-4 < 1.30/< 2.00 (yellow dashed line), LiverRisk score < 10, ELF < 9.8, ADAPT < 6.33 and TE < 10 kPa. Concordance with TE and blood-based NIT to rule-out in MetALD was 56% with FIB-4 (A), 81% with LiverRisk score (B), 79% with ELF (C), 78% for ADAPT (D). Applied rule-in cut-offs: FIB-4 ≥ 2.67, LiverRisk score ≥ 15, ELF ≥ 11.3, ADAPT ≥ 7.15 and TE ≥ 15 kPa. Concordance with TE and blood-based NIT to rule-in for MetALD was 83% with FIB-4 (A), 84% with LiverRisk score (B), 88% with ELF (C) and 82% for ADAPT (D). Red circle marks patients with advanced fibrosis (≥ F3), while blue circle show patients with non-advanced fibrosis (< F3). All axes are log-transformed and broken.

identified (Figure 3A), corresponding to a HR = 47.5 (95% CI: 6.1–368.2) compared with those classified as low risk. The three-tier pathways of FIB-4 → ELF → TE and FIB-4 → ADAPT → TE yielded similar prognostic discrimination.

Second-tier tests in the 3-step strategy led to a reduction in patients needing referral for TE for risk stratification by 43% for ELF (20 out of 47) and 45% for ADAPT (21 out of 47). However, both second-tier NITs reclassified one patient who developed decompensation as low risk, who would have been considered high risk in the 2-step strategy.

In the ELF-based pathway, patients in the high-risk group had a 55% incidence of decompensation (HR: 24.7, 95% CI: 5.4–112.5) (Figure 3B). In the ADAPT-based pathway, 61% of high-risk patients experienced hepatic decompensation (HR: 28.0, 95% CI: 6.2–126.9) (Figure 3C).

Findings were similar in MASLD (Figure S4A–C) and ALD (Figure S4D–F), where the 2-step strategy and 3-step strategy with either ELF or ADAPT risk stratified patients. However, 4 out of 14 events in the ALD group occurred in the low-risk group, regardless of the testing strategy.

4 | Discussion

Our study confirms that recommended cut-offs for diagnosing advanced fibrosis are applicable in the new MetALD subclass. The diagnostic accuracy also translates into prognostic discrimination as the rule-in and rule-out cut-offs could identify patients who would later experience the composite of hepatic decompensation and death. A two-step sequential testing strategy with FIB-4 and TE led to the identification of a MetALD patient subgroup with a high risk of later hepatic decompensation. Incorporation of ELF or ADAPT as second-tier tests in a 3-step algorithm reduced almost half of all TEs needed for risk stratification.

Non-invasive diagnosis of advanced fibrosis is central in the new paradigm of hepatology, emphasising early detection of asymptomatic liver disease for timely intervention [23]. Our novel findings include the diagnostic and prognostic validation of NITs from the same biopsy-confirmed cohorts of MetALD patients with MASLD and ALD as references. This contrasts with recent studies focused mainly on the compatibility between MASLD and the former non-alcoholic fatty liver disease (NAFLD) [24]. With a special attention to MetALD, some other studies have

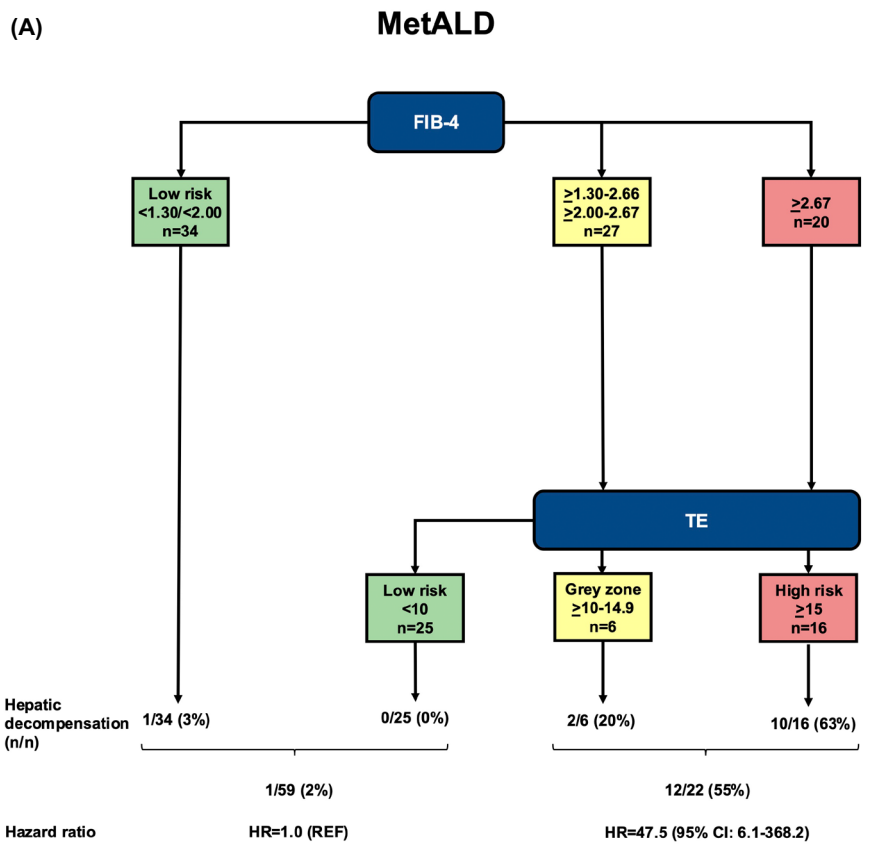
TABLE 3 | Univariable Cox regression models with Harrel's *C*-statistic and number of events for decompensation-free survival according to NIT rule-out and rule-in cut-offs. For the MetALD group, there were 18 deaths and 13 hepatic decompensations. The table shows hazard ratios of NITs with their corresponding 95% confidence intervals. For FIB-4 rule-out, an age-adjusted cut-off (< 1.30 for age < 65 years and < 2.00 for ≥ 65 years) was used. For Harrel's *C*, the point estimate with the corresponding 95% is presented from the continuous NIT values why it is identical in the rule-out and rule-in rows.

	MetALD			
	HR [95% CI]	***p***	***C*-statistic [95% CI]**	**Events, *n*/*N***
Rule-out				
FIB-4 < 1.30/< 2.00	*Reference*		0.817 [0.713–0.921]	4/34 (12%)
FIB-4 ≥ 1.30/≥ 2.00	3.489 [1.174–10.374]	0.025		17/47 (36%)
ELF < 9.8	*Reference*		0.784 [0.687–0.881]	8/41 (20%)
ELF > 9.8	2.441 [1.010–5.899]	0.029		13/32 (41%)
ADAPT < 6.33	*Reference*		0.803 [0.693–0.913]	6/44 (14%)
ADAPT > 6.33	5.129 [1.984–13.256]	< 0.001		15/29 (52%)
LRS < 10	*Reference*		0.767 [0.649–0.885]	7/48 (15%)
LRS ≥ 10	5.194 [2.086–12.930]	< 0.001		11/25 (44%)
TE < 10	*Reference*		0.781 [0.663–0.899]	7/48 (15%)
TE ≥ 10	6.111 [2.436–15.328]	< 0.001		14/25 (56%)
Rule-in				
FIB-4 < 2.67	*Reference*		0.817 [0.713–0.921]	8/54 (15%)
FIB-4 ≥ 2.67	7.821 [3.204–19.092]	< 0.001		13/19 (68%)
ELF < 11.3	*Reference*		0.784 [0.687–0.881]	12/61 (20%)
ELF ≥ 11.3	7.823 [3.141–19.482]	< 0.001		9/12 (75%)
ADAPT < 7.15	*Reference*		0.803 [0.693–0.913]	6/52 (12%)
ADAPT ≥ 7.15	11.282 [4.309–29.542]	< 0.001		15/21 (71%)
LRS < 15	*Reference*		0.767 [0.649–0.885]	12/63 (19%)
LRS ≥ 15	7.494 [3.137–17.903]	< 0.001		9/10 (90%)
TE < 15	*Reference*		0.781 [0.663–0.899]	9/56 (16%)
TE ≥ 15	9.402 [3.721–23.755]	< 0.001		12/17 (71%)

looked into the diagnostic accuracy of NITs across SLD subclasses or non-invasive pathways to stratify for significant fibrosis [25, 26]. However, here the diagnostic accuracy has not been linked to whether it also reflects relevant prognostic outcomes such as the development of hepatic decompensation.

The high prevalence of risk factors for SLD, but with only a smaller proportion of patients having advanced liver fibrosis, makes multiple-tier testing an attractive strategy for case finding. Clinical practice guideline algorithms recommend affordable and widely available NITs, such as FIB-4, as part of first-tier testing, while more costly and more specialised NITs (ELF, ADAPT and TE) may be used as part of second- and third-tier testing to identify high-risk individuals [5]. Overall, circulating NITs demonstrated high negative predictive values at their respective rule-out thresholds, indicating strong performance in excluding advanced fibrosis. In contrast, the positive predictive values at the rule-in cut-offs were modest, reflecting limited accuracy in confirming advanced fibrosis when used alone. Since information from several NITs is often combined in clinical decision making, we tested the concordance of rule-out for blood-based NITs with TE. Our findings showed that few cases of advanced fibrosis were missed with the combination of blood-based NITs and TE.

Of note with the LiverRisk score, this had a lower diagnostic accuracy in MASLD compared to all four other NITs. Of special interest was the finding that for the majority of patients with ≥ F3 MASLD and a high TE, the LiverRisk score was below the rule-out cut-off < 10. The low accuracy of the LiverRisk score in MASLD is in line with another study of tertiary care patients [27]. In sum, these findings warrant further investigation into how the LiverRisk score may be applied if used in non-general population settings.



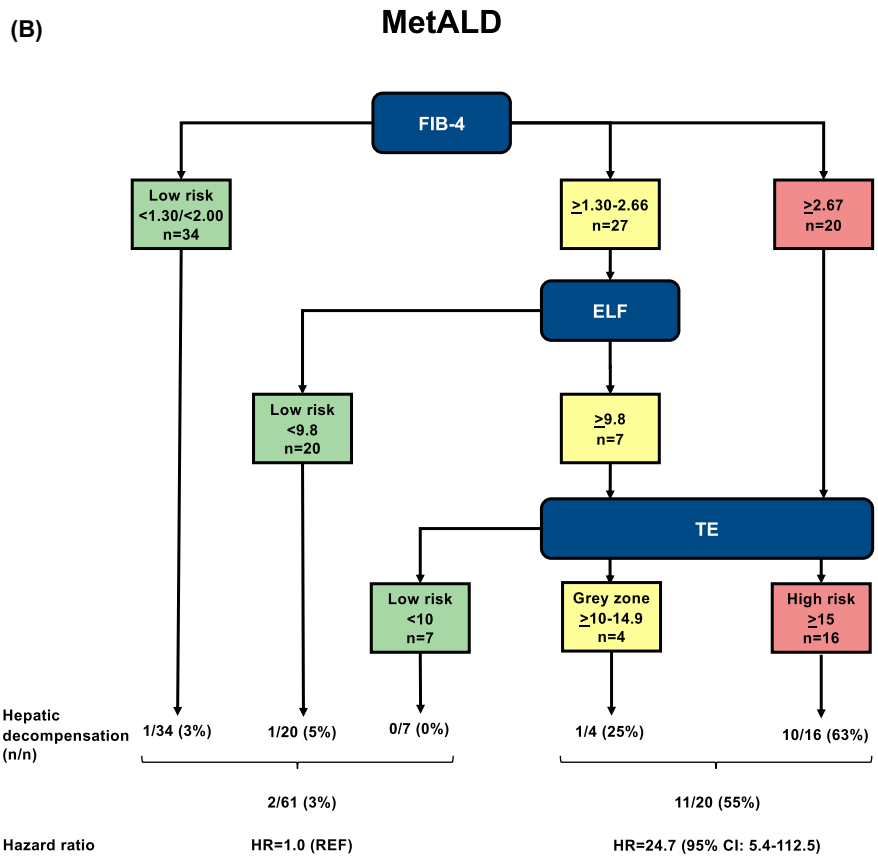


FIGURE 3 | Classification trees for risk stratification of hepatic decompensation for MetALD with FIB-4 → TE (A), FIB-4 → ELF → TE (B) and FIB-4 → ADAPT → TE (C). Both the two-step and three-step sequential testing strategy identified a subgroup of patients at increased risk of decompensation with ELF or ADAPT as second-tier tests.

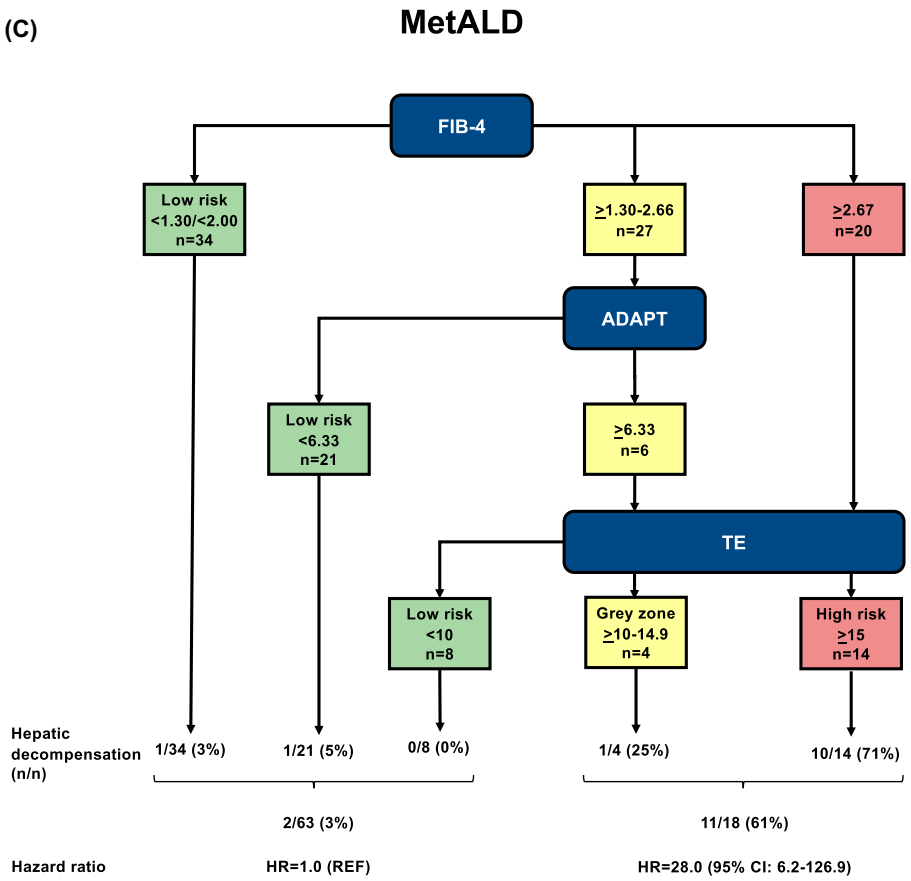


FIGURE 3 | (Continued)

The MASLD subclass also tended to have higher liver stiffness measurements and a slightly higher prevalence of advanced fibrosis on biopsies. For the participants from study one, who were recruited from primary or secondary care, all had a history of excessive alcohol intake; the more severe disease stage in MASLD may represent a sick quitter effect [28].

Participants in the ALD subclass tended to reduce their alcohol intake in the week prior to study entry, with the 25th percentile reporting a consumption of only 7 g/day. In contrast, participants classified as MetALD reported a median intake of 43 g/day during the same period. These findings suggest that our MetALD cohort is largely representative of individuals with ongoing alcohol consumption, rather than those with only a prior history of excessive intake. As a second important objective, we also tested if the diagnostic cut-offs for NITs held prognostic potential. All NITs were predictors of decompensation-free survival in MetALD, with Harrel's *C* ranging from 0.767 with LRS to 0.817 with FIB-4. This indicates that baseline measurements of these NITs can serve an important role to inform patients about their long-term prognosis and can at the same time be utilised to tailor management and clinical follow-up.

Sequential testing pathways with FIB-4 → TE or with either ELF or ADAPT as the second-tier test (FIB-4 → ELF → TE or FIB-4 → ADAPT → TE) could identify a high risk population where around half would develop hepatic decompensation during follow-up. This finding is in line with a previous study of MASLD patients [29]. Reducing the number of false positives directed for TE investigations is an important aspect of referral pathways, since TE measurements require trained personnel and are only done in a limited number of clinical settings. In contrast, the blood-based NITs are widely available as they can be analysed on commercial platforms. Having similar prognostic performance, our 3-step strategy could reduce the number of patients referred to TE by 43% and 45% for ELF and ADAPT respectively. In clinical practice, the incorporation of ELF or ADAPT could be part of a reflex testing scheme where testing would be triggered by an elevated FIB-4.

Important in this regard is the fact that we were unable to apply the guideline-recommended rule-out cut-offs for both ELF (< 7.7) and ADAPT (< 4.46). For ELF, the < 7.7 cut-off is derived from a cohort of hepatitis C patients compared against healthy controls [30]. However, in line with the current study, a recent meta-analysis across liver disease aetiologies showed a higher rule-out cut-off may be more optimal [12]. ADAPT was in our study based upon converted PRO-C3 concentrations measured with ELISA kits and on the COBAS e602 platform. With the transition of PRO-C3 to Roche COBAS e801 platform that is globally available with high accuracy and precision, ADAPT cut-offs may need future refinement, pending direct platform comparisons [31].

A limitation of our single-centre study is the high prevalence of advanced fibrosis across all SLD subgroups, reflecting the nature of the cohort, predominantly recruited based on the presence of SLD risk factors and from secondary care centres. Our findings may therefore not be generalisable to the background population with a lower prevalence of advanced fibrosis. For both cohorts used in this study, TE was the gatekeeper NIT for liver biopsy referral. Though the TE threshold for performing the biopsies was low (≥ 6 kPa), it may have introduced spectrum bias. Finally, SLD subclassification was solely based on the clinical history of self-reported alcohol intake. The combination of phosphatidylethanol and self-report may have enhanced the diagnostic subclassification [32, 33].

This study was also characterised by several methodological strengths. First of all, the majority of included patients were liver biopsied, allowing us to compare the diagnostic accuracy of NITs with the current reference standard for staging disease severity in asymptomatic chronic liver disease. The systematic recording and evaluation of hepatic decompensation episodes also gave more granular insights into the prognostic value of the NITs, using the recommended Baveno VII criteria in contrast to less reliable disease codes from registries.

In conclusion, our study validates recommended cut-offs for FIB-4, LiverRisk score, ELF, ADAPT and TE. The NITs can be applied to the new MetALD subclass for diagnosing advanced fibrosis and prognostic discrimination as part of a sequential test strategy.

Author Contributions

Nikolaj Torp: conceptualization, formal analysis, investigation, writing – original draft. **Mads Israelsen:** conceptualization, formal analysis, writing – original draft, investigation, supervision. **Stine Johansen:** investigation, data curation. **Georg Semmler:** investigation, writing – review and editing. **Camilla Dalby Hansen:** investigation, writing – review and editing. **Katrine Tholstrup Bech:** investigation, writing – review and editing. **Mette Lehmann Andersen:** investigation, writing – review and editing. **Katrine Holtz Thorhauge:** investigation, data curation, writing – review and editing. **Peter Andersen:** investigation, software, writing – review and editing. **Helle Lindholm Schnefeld:** investigation, writing – review and editing. **Johanne Kragh Hansen:** investigation, writing – review and editing. **Ellen Lyngbeck Jensen:** investigation, writing – review and editing. **Emil Deleuran Hansen:** investigation, writing – review and editing. **Ida Villesen:** investigation, resources, writing – review and editing. **Katrine Prier Lindvig:** investigation, data curation, writing – review and editing. **Diana Julie Leeming:** resources, writing – review and editing. **Morten Karsdal:** resources, writing – review and editing. **Emmanuel A. Tsochatzis:** methodology, writing – review and editing. **Maja Thiele:** methodology, investigation, data curation, writing – review and editing, funding acquisition. **Aleksander Krag:** conceptualization, methodology, supervision, funding acquisition, writing – review and editing.

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Nikolaj Torp is a guarantor of the article and takes the responsibility for the integrity of the work as a whole.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: During the preparation of this work the author(s) used ChatGPT from OpenAI in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Conflicts of Interest

M.T. received speaker's fee from Echosens, Madrigal, Takeda and Novo Nordisk; advisory fee from Boehringer Ingelheim, Astra Zeneca, Novo Nordisk and GSK; research grant from GSK; and co-founder of Evido. J.K.H. received speaker's fee from Norgine. C.D.H. received speaker's fee from Novo Nordisk. E.A.T. received advisory fees from Boehringer Ingelheim, Siemens, Novo Nordisk, MSD, Madrigal and speaker fees from Abbvie, Dr. Falk, Boehringer Ingelheim, Echosens and Novo Nordisk. D.J.L. and M.K. are employed by and own stock in Nordic Bioscience A/S. A.K. has served as speaker for Novo Nordisk, Norgine and Siemens; participated in advisory boards for Siemens, Boehringer Ingelheim, Novo Nordisk and GSK all outside the submitted work; has received research support from Norgine, Siemens, Nordic Bioscience, AstraZeneca and Echosens; and is a board member and co-founder of evido.health. K.P.L. received speaker's fee from Siemens Healthcare and Novo Nordisk; and is a board member and co-founder of evido.health. K.H.T. is employed by evido.health and received advisory fee from Evidera. Remaining authors declare no conflicts of interest.

Data Availability Statement

Data are available in a pseudonymised manner upon request to nikolaj.torp@rsyd.dk after approval from the Danish Data Protection Agency.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1.**