Performance of the enhanced liver fibrosis (ELF) score, comparison with vibration-controlled transient elastography (VCTE) data, and development of a simple algorithm to predict significant liver fibrosis in a community-based liver service: a retrospective evaluation

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Abstract

Background and objectives

Liver fibrosis is a key risk factor for cirrhosis, hepatocellular carcinoma and end stage liver failure. The National Institute for Health and Care Excellence guidelines for assessment for advanced (≥F3) liver fibrosis in people with non-alcoholic fatty liver disease recommend the use of enhanced liver fibrosis (ELF) test, followed by vibration controlled transient elastography (VCTE). Performance of ELF at predicting significant (≥F2) fibrosis in real-world practice is uncertain.

To assess the accuracy of ELF using VCTE; investigate the optimum ELF cut-off value to identify ≥F2 and ≥F3; and develop a simple algorithm, with and without ELF score, for detecting ≥F2.

Methods

Retrospective evaluation of patients referred to a Community Liver Service for VCTE, Jan-Dec 2020.

Assessment included: body mass index (BMI), diabetes status, alanine aminotransferase (ALT) levels, ELF score and biopsy-validated fibrosis stages according to VCTE.

Results

Data from 273 patients were available. *N*=110 patients had diabetes. ELF showed fair performance for ≥F2 and ≥F3, area under the curve (AUC)=0.70, 95% confidence interval (CI) 0.64-0.76 and AUC=0.72, 95% CI 0.65-0.79 respectively. For ≥F2 Youden's Index for ELF=9.85 and for ≥F3, ELF=9.95. Combining **AL**T, **B**MI and Hb**A**1c (ALBA algorithm) to predict ≥F2 showed good performance (AUC=0.80, 95% CI 0.69-0.92), adding ALBA to ELF improved performance (AUC=0.82, 95% CI 0.77-0.88). Results were independently validated.

Conclusion

Optimal ELF cut-off for ≥F2 is 9.85 and 9.95 for ≥F3. **AL**T, B**M**I and Hb**A**1c (ALBA algorithm) can be used to stratify patients at risk of ≥F2. ELF performance is improved by adding ALBA.

Key words: Primary health care, retrospective evaluation, liver disease, diabetes, non-alcoholic fatty liver disease

Highlights

- Lowering the National Institute for Health and Care Excellence (NICE) recommended enhanced liver fibrosis (ELF) threshold from 10.51 to 9.85 would improve the identification of significant liver fibrosis (≥F2) in a community setting.
- F2 is a risk factor for cirrhosis and overall mortality, and liver fibrosis is an important risk factor for hepatocellular carcinoma.
- Type 2 diabetes is an important risk factor for liver fibrosis and hepatocellular carcinoma, therefore it is important to consider whether liver fibrosis is present in high risk patients, such as individuals with type 2 diabetes.
- In the absence of the enhanced liver fibrosis (ELF) test, the combination of readily available tests (**AL**T, **B**MI and Hb**A**1c [ALBA algorithm]) can be used to identify at risk patients with ≥F2 fibrosis.
- Adding the ALBA simple algorithm to ELF improves the performance of ELF in a Community clinic.

Introduction

In the UK, liver disease is third commonest cause of premature death.[1] Non-alcoholic fatty liver disease (NAFLD) is present, often undiagnosed,[1] in 30% of the UK population[2] and is a risk factor for extrahepatic diseases such as type 2 diabetes, cardiovascular disease, chronic kidney disease,[3 4] and increased long-term risk of developing cancer.[5 6] Evidence shows that as fibrosis stage increases, liver-related mortality increases exponentially.[7] We have shown recently that ~20% of patients with a liver fibrosis stage of ≥F1 (≥6.0kPa/low fibrosis) progressed to advanced fibrosis/cirrhosis during a 5 year period of follow-up.[8] Therefore the detection of liver fibrosis is important because it is a key risk factor for cirrhosis, hepatocellular carcinoma and end stage liver failure.[6 9]

There are a growing number of liver fibrosis assessment services in primary care that use vibration controlled transient elastography (VCTE) to identify patients who require specialist referral to Hepatology services. In 2016, the National Institute of Health and Care Excellence (NICE) NAFLD Guidelines recommended the use of the enhanced liver fibrosis (ELF) test as part of a pathway for the identification of patients at high risk of advanced liver fibrosis.[10] We developed this further[11] and introduced a primary care liver pathway[12] and Community Liver Service for GPs to refer patients with suspected severe liver fibrosis. There are uncertainties regarding the performance of ELF at predicting significant fibrosis (≥F2) in real-world practice and, although recommended by NICE, ELF is not widely available.

Other tests such as the NAFLD Fibrosis score,[13] FIB-4[14] and APRI score[15] are less expensive within the NHS, but require measurement of aspartate amino transaminase (AST), and AST is not routinely measured as part of the normal 'liver function test' panel. Thus, there is a need to offer an alternative method of evaluating patients at risk of liver disease without incurring the additional expense of ELF,[16] or extra requirement and expense of measuring AST. The NICE guidelines recommended ELF cut-off value for predicting advanced fibrosis (≥F3) is 10.51.[17] However, individuals with significant fibrosis (≥F2) are at substantially increased risk of type 2 diabetes, heart disease,[18-21] cirrhosis and overall mortality.[22 23] Detection of ≥F2 is difficult,[24] and although there are a number of serum biomarkers available for the detection of liver fibrosis,[25] no one biomarker test is recommended for the detection of ≥F2.

We have conducted a retrospective evaluation to provide real-world findings for other healthcare providers contemplating implementing a similar service. This retrospective evaluation assesses how ELF test cut-offs perform in a real-world setting, and estimates the score with the optimum balance of sensitivity and specificity (the Youden Index)[26] of ELF for identification of significant (≥F2) and advanced fibrosis (≥F3). We examine whether alanine transaminase (ALT), body mass index (BMI) and glycated haemoglobin (HbA1c), three widely available variables associated with liver disease, can be used as predictors of ≥F2.

Aims

To evaluate:

- The optimum ELF cut-off value for predicting advanced (≥F3/≥9.7kPa) fibrosis.
- Whether ELF can be used to predict significant (≥F2/≥8.2kPa) fibrosis.
- If routinely collected individual patient level data can be used to predict ≥F2; and test whether they improve the performance of ELF to predict ≥F2.
- What factors: (a) are independently associated with ≥F2 liver fibrosis, and (b) predict liver fibrosis ≥F2.

Materials and methods

We used a retrospective cohort of patients (derivation cohort) recruited from the Southampton Community Liver Service between Jan-Dec 2020. An independent cohort (validation cohort) of patients recruited to the Liver Service between Mar-Dec 2021 was used to validate an algorithm that was developed in the derivation cohort for identifying patients with liver fibrosis.

Using the Southampton primary care liver pathway to identify at risk patients (**Supplementary Box 1**), GPs referred patients to the Community Liver Service for VCTE assessment.

Inclusion criteria

Adults (≥18 years) with an ELF score of ≥9.0; an alcohol use disorders identification test (AUDIT)[27] score of <14,[27 28] (indicating low risk, hazardous and harmful alcohol consumption) and VCTE readings between 1.1kPa-75.0kPa.

Exclusion criteria

Individuals with incomplete data, patients entering the pathway who had an ELF score <9.0, an alcohol use disorders identification test (AUDIT score of ≥15 (indicating alcohol dependent),[27 28] and those identified with chronic viral hepatitis, autoimmune liver disease or haemochromatosis.

Data collection

VCTE assessment took place at a primary care site in Southampton. The FibroScan Mini+430 model with automated M and XL probe selection was used. Assessment took 20 minutes and was complete after 10 successive valid (IQR/MED<30%) measurements were obtained.

Data Analysis

Excel, Excel Solver[29] plug-in, SPSS statistics software (version 27), R version 3.4.4 (2018-03-15) were used. Data were cleaned and any incomplete data were excluded from this evaluation. 273/350 patients in the derivation cohort and 115/176 in the validation cohort were eligible for retrospective evaluation. (**Figure 1**).

Statistical analysis

Validated cut-off values were used for the ELF scoring system.[17 30 31] Biopsy validated thresholds, using the NASH CRN classification system, were used for the cut-off values for VCTE assessment for fibrosis (kPa) and steatosis (dB/m^2),[32] (**Supplementary Tables 1-3**).

Data were stratified by fibrosis stage, medication (statins/no statins), sex (male/female), diabetes status (diabetes/no diabetes), and BMI (BMI≥30kg/m^2/BMI<30kg/m^2).

Standard descriptive statistics were used to summarise variables: mean(±SD) for continuous variables or median(IQR) for non-normally distributed variables, and numbers and percentages for categorical variables. The chi-square test for independence (α=0.05) was used to determine the relationship between categorical variables. Two-tailed independent samples t-tests were used to compare the differences between groups and Fisher's exact test was used, when *n*=<5, to determine if there was a significant association. The relationship between F2 and F0-F1 and F3-4 was evaluated using Kruskal-Wallis H test and Mann-Whitney U tests with Bonferonni adjustment. Backward elimination binary logistic regression analysis and receiver operator characteristic (ROC) curve analysis were used to: (a) test the independence of associations between variables collected before VCTE assessment and liver fibrosis stage; and (b) assess the risk prediction ability of variables to identify ≥F2 and ≥F3 as binary outcomes.

The area under the receiver operator curve (AUROC) was used to compare the diagnostic accuracy of ALT, BMI, HbA1c and ELF. The Obuchowski index was used to calculate a weighted AUROC to compare ELF to the biopsy validated VCTE thresholds.[32] The Obuchoswki Index is explained in more detail in **Supplementary Box 2**. Youden index analysis[26] was applied to find the optimal cut-off value of ELF for ≥F2 and ≥F3.

The DANA[33] (difference between the mean fibrosis stage of significant (≥F2) fibrosis minus the mean fibrosis stage of non-significant (F0-F1) fibrosis) was applied according to the prevalence of fibrosis stages.

Individual predictor variables

ALT,[34] BMI[35] and HbA1c[36-38] are known to be associated with liver fibrosis, AUROC was used to evaluate their combined performance in predicting significant (≥F2) and advanced (≥F3) fibrosis.

Algorithm

We combined BMI, HbA1c with ALT to develop an algorithm to predict the probability of a patient having ≥F2. A full description of the methodology is included in **Supplementary Box 3**.

Validation data

Data from different patients referred to the Community Liver Service in 2021 were used to develop an independent validation cohort, in order to validate the algorithm that was developed from the derivation cohort. A description of the methodology is included in **Supplementary Box 4**.

Results

Patient characteristics (**Table 1**)

Derivation cohort

Median(IQR) age was 57 years (47-64), 55.3% were men. Mean(±SD) VCTE reading and CAP scores were 9.0kPa(±7.8) and 319.2dB/m^2(±58.1) respectively. 24% (*n*=65) were consuming alcohol harmful and hazardous levels,[27 28] 61.2% (*n*=167) had a BMI≥30kg/m^2 and 40.3% (*n*=110) had diabetes.

Validation cohort

Median(IQR) age was 61 years (50-69), 55.7% were men. Mean(±SD) VCTE reading and CAP scores were 8.6kPa(±6.2) and 315.6dB/m^2(±52.0) respectively. 22.6% (*n*=26) were consuming alcohol harmful and hazardous levels,[27 28] 0.9% (*n*=70) had a BMI≥30kg/m^2 and 26.9% (*n*=31) had diabetes.

Prevalence of liver fibrosis

42/273 patients (15.4%) were identified as having advanced fibrosis/cirrhosis (F4/≥13.6kPa); 12.8% (*n*=35) severe fibrosis (F3/9.7kPa-13.5kPa); 9.2% (*n*=25) moderate fibrosis (F2/8.2kPa-9.6kPa) and 62.6% (*n*=171) no-low fibrosis (F0-F1/<6.0kPa/≥6.0kPa-8.1kPa). Characteristics of patients by fibrosis stage are presented in **Supplementary Table 4**.

Factors associated with ≥F2 *liver fibrosis*

ELF, BMI≥30kg/m^2, ALT≥40IU/L and HbA1c were all positively associated with significant (≥F2) fibrosis (*p*=0.001, *p*=<0.001, *p*=0.005 and *p*=0.002 respectively. (**Supplementary Table 5**).

Results for data stratified by sex, BMI, diabetes status and medication are presented in **Supplementary Tables 6, 7, 8 and 9** respectively.

Predictors of ≥F2

Median (IQR) BMI of patients with F0-F1 was 30.0kg/m^2 (26.0-32.8) and 32.0kg/m^2 (29.3-38.9) in patients with F2 (*p*=0.003). Mean (SD) HbA1c of patients with F0-F1 was 39.9mmol/mol (12.0) and 48.5mmol/mol (15.7) in patients with F2. 26.3% (*n*=45) of F0-F1 patients and 64.0% (*n*=16) of F2 patients were diabetes positive (*p*<0.001) and, 50.3% (*n*=86) of patients with F0-F1 and 76% (*n*=19) of patients with F2 had a BMI≥30kg/m^2 (*p*=0.016) (**Supplementary Tables 10a and 10b).**

ELF

As a predictor of significant (≥F2/≥8.2kPa) or advanced fibrosis (≥F3/≥9.7kPa) ELF showed a fair performance, area under the curve (AUC)=0.70, 95% confidence interval (CI) 0.64-0.76 and AUC=0.72, 95% CI 0.65-0.79 respectively (**Figure 2**). Applying the Obuchowski index showed a slight improvement in the estimated accuracy of ELF for identifying ≥F2 and ≥F3 (0.773 and 0.789 respectively), **Supplementary Table 11**. Youden's Index calculated ELF=9.85 for ≥F2 and ELF=9.95 for ≥F3.

The 2020 and 2021 DANA scores (**Supplementary Table 12**) show that the prevalence of fibrosis is not evenly distributed across the five fibrosis stages, when compared to the uniform prevalence distribution DANA of 2.5.

Missed cases are defined as patients whose VCTE reading showed they had significant fibrosis (≥F2) and their ELF score was <9.0 (2020 Community Liver Service threshold), <9.8 (manufacturers of ELF threshold for severe fibrosis)[39] or <10.51 (threshold proposed by NICE).[17] **Table 2** shows that when ELF<10.51 there are *n*=20 missed cases for F2, *n*=24 missed cases for F3 and *n*=25 missed cases for F4.

Individual variables

ALT alone showed a poor performance for predicting both ≥F2 and ≥F3, AUC=0.65, 95% CI 0.59-0.72 and AUC=0.67, 95% CI 0.61-0.74 respectively. BMI alone showed a fair performance for predicting both ≥F2 and ≥F3, AUC=0.72, 95% CI 0.66-0.78 and AUC=0.71, 95% CI 0.64-0.78 respectively. HbA1c alone showed a fair performance for ≥F2, AUC=0.70, 95% CI 0.63-0.77 and a lesser performance for ≥F3 AUC=0.68, 95% CI 0.61-0.76, (**Supplementary Figure 1**).

Combining variables

Since each of the individual variables (ALT, BMI and HbA1c) did not show good diagnostic performance for identifying liver fibrosis, we tested the effect of combining these variables. Diagnostic performance for identifying ≥F2 and ≥F3 improved when we combined ALT, BMI and HbA1c, showing a good performance for identifying ≥F2 (AUC=0.80, 95% CI 0.74-0.85 and a fair performance for identifying ≥F3 (AUC=0.78, 95% CI 0.72-0.84). Adding ELF to the three variables increased the performance of ≥F3 to good (AUC=0.82, 95% CI 0.76-0.88) and increased the performance of ≥F2 (AUC=0.82, 95% CI 0.76-0.87) (**Figure 3**). Although there was a trend towards an improvement in AUC with the addition of ELF, the differences in AUC were not statistically significant.

***AL**T, **B**MI and Hb**A**1c (ALBA) Algorithm*

The derivation cohort (*n*=273) was used to create the ALBA algorithm (**Table 1(a)**).

The equation for predicting ≥F2 is:

((ALT–28.826)*0.002638)+((BMI–23.291)*0.02152)+((HbA1c–28.462)*0.009975)

Applying the ALBA algorithm to the derivation data-set also showed a good performance for predicting ≥F2 (AUC=0.80, 95% CI 0.69-0.92) (**Figure 4a**).

Validation cohort

The validation cohort (*n*=115) was used to validate the ALBA algorithm **(Table 1(b))**. Applying the ALBA algorithm to the validation cohort showed AUC=0.75, 95% CI 0.66-0.85 (**Figure 4b**).

ALBA and ELF

Diagnostic performance for identifying ≥F2 improved when we combined the ALBA algorithm and ELF. AUC=0.82, 95% CI 0.77-0.88 for the derivation cohort and AUC= 0.76, 95% CI 0.67-0.86 for the validation cohort (**Figures 4c and 4d**).

Discussion

Summary

Our results show that when compared to validated VCTE cut-off values for the stages of liver fibrosis,[32] the NICE recommended cut-off value (ELF≥10.51)[17] for predicting advanced fibrosis (≥F3) is too high. Youden's index shows the optimum cut-off value for ≥F3 in this population is an ELF=9.95, and for ≥F2 is an ELF=9.85. The NICE cut-off value therefore should be viewed as a recommendation as our study, and others,[40 41] show that the ELF cut-off value should be set according to the population it is being used for. To evaluate the performance of ELF for identifying ≥F2 and ≥F3, we used the novel and under-utilised Obuchowski index, as well as the more standard area under the curve (AUC). We found the Obuchowski index shows a slightly higher performance than does AUC, although this increase does not change the performance classification of ELF. We have shown that referrals to the Community Liver Service have a high proportion of patients with obesity (BMI≥30kg/m^2) and type 2 diabetes, which led to the development of the ALBA algorithm, as an alternative method of evaluating patients at risk of liver disease. We validated the ALBA algorithm, compared the performance with ELF, and found that both offered a fair performance for predicting ≥F2. Importantly, combining ELF with ALBA improved the performance of both for predicting ≥F2. Our simple ALBA algorithm was not designed to replace existing validated markers of fibrosis, but it could be a tool for GPs, who do not have access to these costly tests, to use in order to assess whether a patient is at risk of ≥F2.

Strengths and limitations

This study has shown that routinely available data can be used to assess a patient for ≥F2. This study has also provided data to demonstrate that liver disease is highly prevalent among patients with diabetes and/or BMI≥30kg/m^2.[42 43 44]

There were limitations to this study. This evaluation did not differentiate between NAFLD and alcohol related liver disease. Our sample size was small and there may have been some slight overfitting. Our data was not evenly distributed across the five fibrosis stages but did represent a more realistic prevalence of fibrosis in a community setting. We did not have measurements of AST available, therefore we were unable to calculate other liver fibrosis scores such as the Fibrosis-4[14] score for comparison with ELF or ALBA. Finally, VCTE assessment is a validated non-invasive test used to measure liver stiffness,[32] and although liver biopsy continues to remain the gold standard in the assessment for liver disease,[45] it is invasive, costly and prone to sampling error.[46] Moreover, liver biopsy is not feasible within a large Community-based Liver Service that does not have the capability of monitoring patients for any length of time post-liver biopsy procedure.

Comparison with existing literature

Previous studies have focussed on patients with established NAFLD or screening for patients with advanced fibrosis/cirrhosis.[47 48] However it is early detection of NAFLD and early stage of liver fibrosis (F2), an established risk factor for cirrhosis and overall mortality,[49 50] that is key to helping prevent, control and manage disease progression.

Our findings revealed that 40.3% of patients referred to the Community Liver Service had diabetes, six times higher than the prevalence of diabetes in the UK.[51] Diabetes is known to be important risk factor for NAFLD,[52] yet liver function tests are not recommended in the NICE guidelines for diabetes.[53] NAFLD is one of the most common causes of hepatocellular carcinoma and is likely to continue as the incidence of both obesity and type 2 diabetes continue to increase.[54]

Implications for practice

Health care providers considering implementing a liver service should consider what would be a suitable ELF threshold to achieve the desired performance.[41] This evaluation provided the Southampton Clinical Commissioning Group with the evidence needed to refine the primary care liver pathway ELF cut-off value, referral for VCTE assessment is now set to ELF≥9.5.

Importantly, 12.8% (*n*=25) of patients discharged back to their GP were found to have F2, a stage of liver fibrosis which puts them at an increased risk of type 2 diabetes and heart disease.[18-21] At this present time, because we do not know what specific factors will predict disease progression, these patients need to be managed by their GP on the assumption that their liver fibrosis will progress over time.[8]

This study has shown that in the absence of access to non-invasive blood tests, the ALBA algorithm can be used to predict the probability of a patient having ≥F2, a stage of fibrosis that can be treated with low doses of prescribed GLP-1 receptor agonists.[22 23] We have further shown that combining ALBA and ELF improves risk prediction for ≥F2. Finally, this study highlights the disproportionate number of patients with diabetes and/or a BMI≥30kg/m^2 who have liver fibrosis, which lends further weight to targeting these known high risk groups in screening for liver disease.

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Ethical approval

This retrospective evaluation of the Southampton Community Liver Service used routinely collected data. All the data collection and analysis was conducted by the clinical team involved in delivering patient care. This evaluation was approved by the clinical lead for Hepatology services at University Hospital Southampton and was registered for clinical audit (registration number: ZAUD7162) but not subject to review by an independent ethics committee and individual patient consent was not sought. All activities were performed in accordance with the guidelines of the Helsinki Declaration.

Conflict of interest

The authors have no conflict of interests related to this publication.

Patient and Public involvement

No patient public involvement was used for this retrospective analysis.

Tables

Table 1: Characteristics of patients in the (a) derivation cohort and (b) validation cohort

Patient characteristics	(a) Derivation cohort (*n*=273)		(b) Validation cohort (*n*=115)	
	n	%	n	%
Men sex, *n* (%)	151	55.3	64	55.7
Minority ethnic groups, *n* (%)	65	23.8	19	16.5
Median age, years (IQR)	57	47-64	61	50-69
Mean ELF score, (SD)[F]	9.9	0.8	10.2	0.6
Mean weight, kg (SD)	90.2	20.2	93.7	19.9
Median BMI, kg/m^2 (IQR)	30.8	27.7-35.2	31.6	27.4-36.4
BMI≥30 kg/m^2, *n* (%)	167	61.2	70	60.9
Diabetes positive, *n* (%)[¶]	110	40.3	31	26.9
Mean HbA1c, mmol/mol, (SD)	43.2	14.1	45.4	14.6
ALT≥40 IU/L, *n* (%)	153	56.0	58	50.4
Mean ALT, IU/L (SD)	52.47	37.4	44.1	24.0
Mean VCTE reading, kPa (SD)	9.0	7.8	8.6	6.2
Mean CAP score, dB/m^2 (SD)	319.2	58.1	315.6	52.0
High alcohol, *n* (%)[B]*	65	24.0	26	22.6
Smoker, *n* (%)	45	16.5	No data	
Fibrosis stage:				
F0 (<6.0kPa), *n* (%)	113	41.4	47	40.9
F1 (6.0kPa-8.2kPa), *n* (%)	58	21.2	29	25.2
F2 (8.2kPa-9.6kPa), *n* (%)	25	9.2	10	8.7
F3 (9.7kPa-13.5kPa), *n* (%)	35	12.8	14	12.2
F4 (≥13.6kPa), *n* (%)	42	15.4	15	13.0
≥F2, *n* (%)	102	37.4	40	34.8
≥F3, *n* (%)	77	28.2	31	26.9
Steatosis grade:				
S0 (<302 dB/m^2), *n* (%)	90	33.0	42	37.2
S1 (≥302 dB/m^2), *n* (%)	56	20.5	26	23.0
S2 (≥331 dB/m^2, *n* (%)	15	5.5	4	3.5
S3 (≥337 dB/m^2, *n* (%)	112	41.0	41	36.3
Medication:				
Antidepressants, *n* (%)	75	27.5	23	20
Antihypertensives, *n* (%)	116	42.5	53	46.1
Anticoagulants, *n* (%)	36	13.2	10	8.7
GLP-1 agonist, *n* (%)	13	4.8	2	1.7
Statins, *n* (%)	88	32.2	39	33.9
AIIR blockers, *n* (%)	22	8.1	7	6.1

[F]ELF measures three direct markers of fibrosis: hyaluronic acid (HA), procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1); [¶]Diabetes = HbA1c reading of >48 mmol/mol; *High alcohol; a score of 8-14 (harmful/hazardous) on the alcohol use disorders identification test (AUDIT);[1 2] [B]0.7% (*n*=2) declined to complete the AUDIT. IQR, interquartile range; SD, standard deviation; kg, kilogramme; BMI, body mass index; kg/m^2, kilogram per square metre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per litre; VCTE, vibration controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square metre; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis; S0, no steatosis; S1, mild steatosis; S2, moderate steatosis; S3, severe steatosis; GLP-1 agonist, glucagon-like peptide-1 receptor agonist; AIIR blockers, angiotensin II receptor blockers.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table 2: Number of patients below the selected ELF score thresholds and their VCTE confirmed fibrosis stage

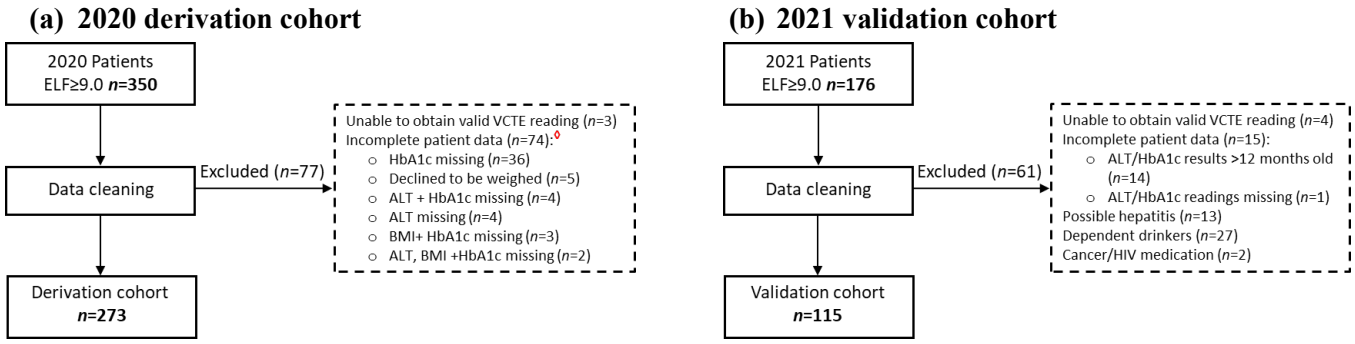
Fibrosis stage with VCTE thresholds[a]	Total patients	ELF<9.0		ELF<9.8		ELF<10.51	
		n	%	*n*	%	*n*	%
F2/≥8.2kPa to 9.6kPa	25	1	4.0	8	32.0	20	80.0
F3/≥9.7kPa to 13.5kPa	35	1	2.9	9	25.7	24	68.6
F4/≥13.6kPa	42	0	-	12	28.6	25	59.5

VCTE, vibration controlled transient elastography; [a]Eddowes[1] biopsy validated cut off thresholds; ELF, enhanced liver fibrosis; kPa, kilopascal; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis.

[1]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730.

Figures

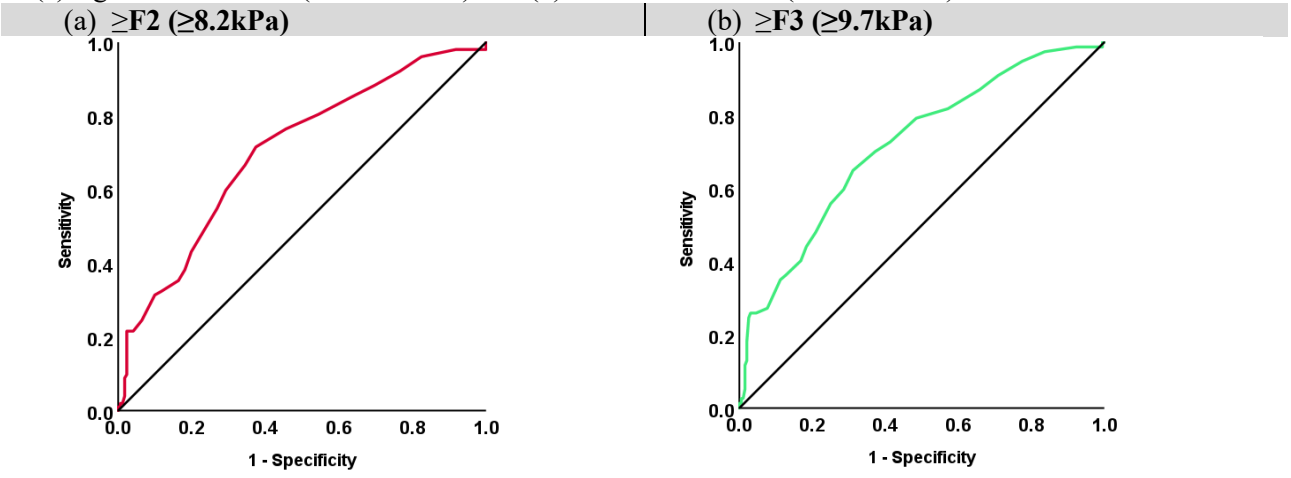
Figure 1: Flow chart showing patients who were eligible for analysis



◊ 84% of patients excluded from analysis because of incomplete data were also categorized as dependent drinkers (patients who scored ≥15 on the alcohol use disorders identification test [AUDIT]);[1 2] ELF, enhanced liver fibrosis; VCTE, vibration controlled transient elastography; HbA1c, glycated haemoglobin; mmol/mol; ALT, alanine transaminase; BMI, body mass index.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Figure 2: Area under the curve (AUC) receiver-operating characteristics (ROC) for ELF for the diagnosis of (a) significant fibrosis (≥F2/≥8.2kPa) and (b) advanced fibrosis (≥F3/≥9.7kPa)

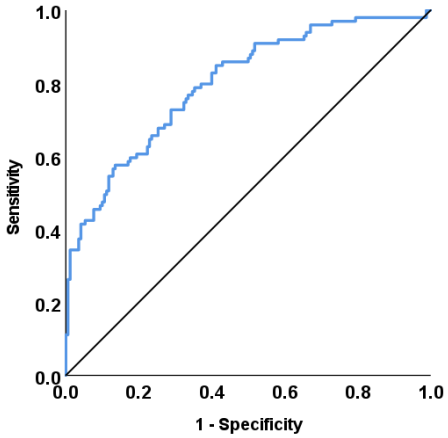


CI, confidence interval; kPa, kilopascal; F2, significant fibrosis; F3, severe fibrosis.

Figure 3: Area under the curve (AUC) receiver-operating characteristics (ROC) for the prediction of significant (≥F2/≥8.2kPa) and advanced fibrosis (≥F3/≥9.7kPa) using (a) ALT, BMI and HbA1c and (b) ALT, BMI, HbA1c and ELF

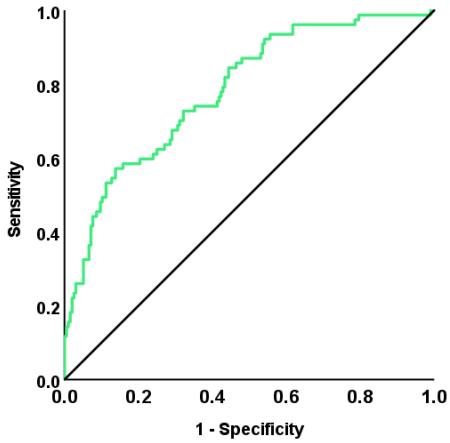
(a) ALT, BMI and HbA1c

≥F2 (≥8.2kPa)



AUC = 0.80 (95% CI 0.74-0.85)

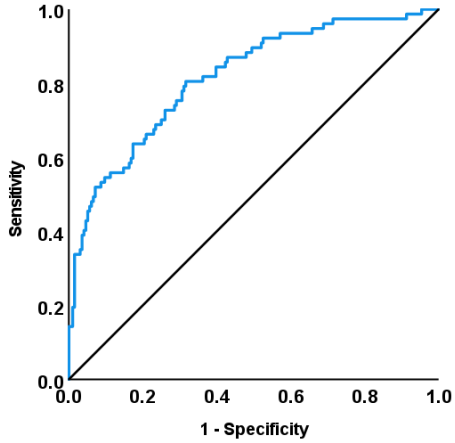
≥F3 (≥9.7kPa)



AUC = 0.78 (95% CI 0.72-0.84)

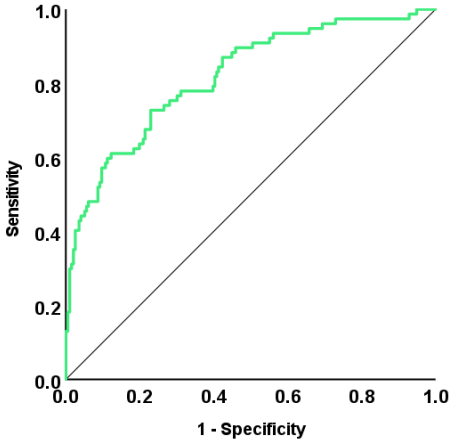
(b) ALT, BMI, HbA1c and ELF

≥F2 (≥8.2kPa)



AUC = 0.82 (95% CI 0.76-0.87)

≥F3 (≥9.7kPa)

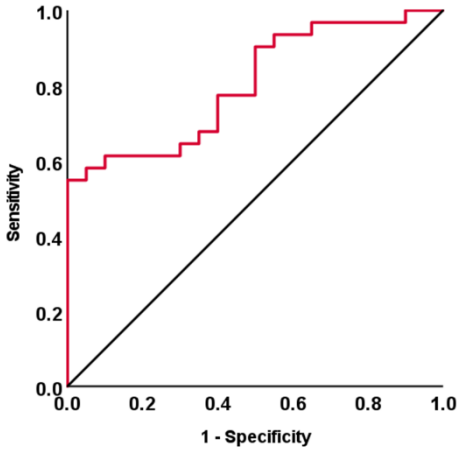


AUC = 0.82 (95% CI 0.76-0.88)

ALT, alanine transaminase; BMI, body mass index; HbA1c, glycated haemoglobin; ELF; enhanced liver fibrosis; kPa, kilopascals; CI, confidence interval; F2, moderate fibrosis; F3, severe fibrosis.

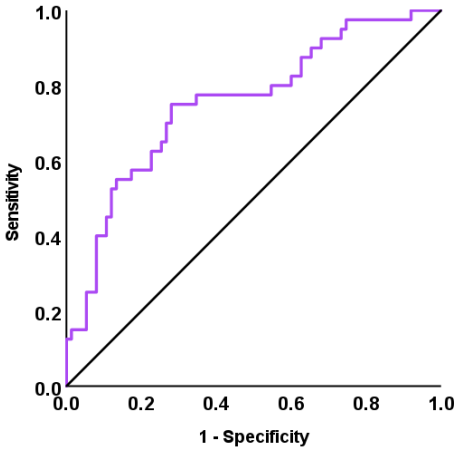
Figure 4a and 4b: Area under the curve (AUC) receiver-operating characteristics (ROC) for the prediction of significant fibrosis (≥F2/≥8.2kPa) using the ALBA algorithm on (a) the derivation data and (b) the validation data

(a) Derivation data



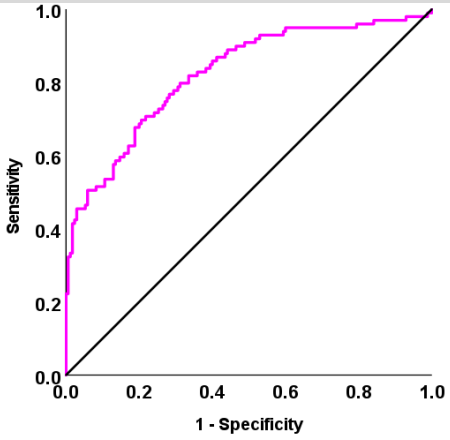
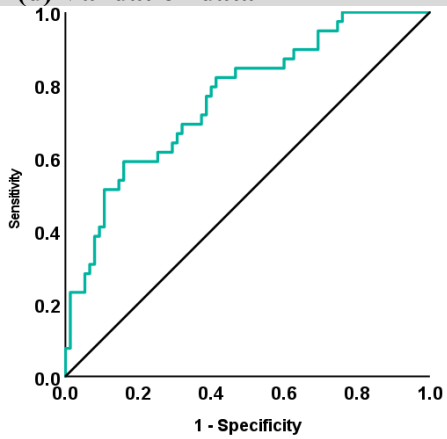
AUC = 0.80, (95% CI 0.69-0.92)

(b) Validation data



AUC = 0.75 (95% CI 0.66-0.85)

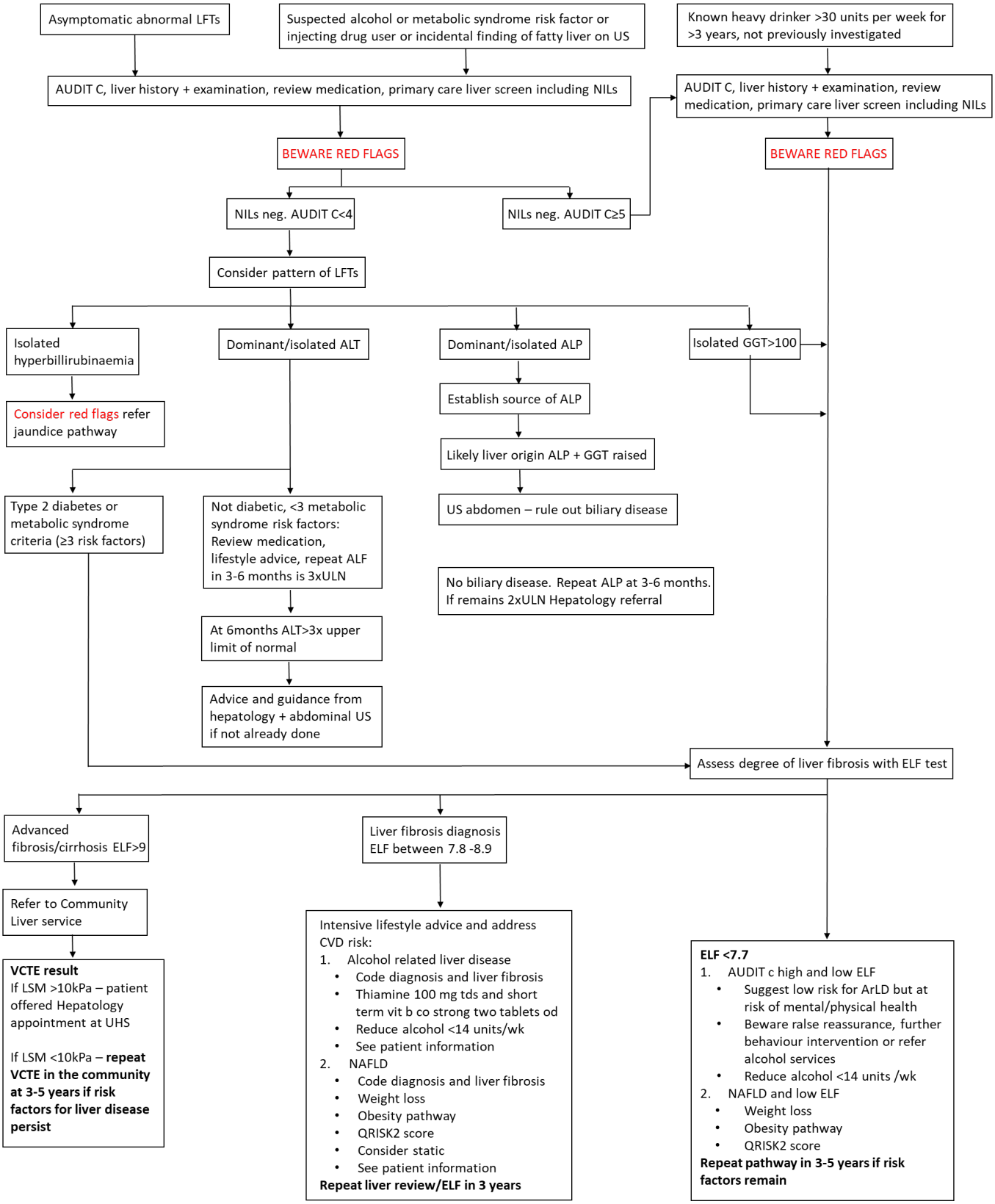
Figure 4c and 4d: Area under the curve (AUC) receiver-operating characteristics (ROC) using the ALBA algorithm and ELF together to predict significant fibrosis (≥F2/≥8.2kPa)

(c) Derivation data	**(d) Validation data**
	
AUC = 0.82, (95% CI 0.77-0.88)	AUC= 0.76, (95% CI 0.67-0.86)

ELF, enhanced liver fibrosis; kPa, kilopascal; CI, confidence interval, F2, moderate fibrosis.

Supplementary information

Box S1: Primary care liver pathway (abridged)



Full details of the Southampton primary care liver pathway can be found at:
https://drive.google.com/file/d/1hiyM8wEYfLQv8P_ImMylA3NVtT9rW6iR/view

Box S2: Obuchowski Index[1]

The Obuchowski Index calculates the accuracy of a diagnostic test when the gold standard is measured on a continuous, ordinal or nominal scale. The Obuchowski index is a weighted average of the area under the

receiver operating characteristic (AUROC) values obtained for all possible pairs of fibrosis stages (i.e. 10 pairs for the five [F0–F4] fibrosis stages) to be differentiated. It estimates the probability that a test will correctly rank two randomly chosen patients with different stages of fibrosis.[2] The Obuchowski Index is a rank based measure that can be calculated without constructing a receiver operating characteristic curve (ROC), although they can be interpreted similarly, they are not associated with ROC curves.[3]

[1]Obuchowski NA. Estimating and comparing diagnostic tests' accuracy when the gold standard is not binary. Acad Radiol. 2005 Sep;12(9):1198-204. doi: 10.1016/j.acra.2005.05.013. PMID: 16099683.
2Choi KJ, Jang JK, Lee SS, et al. Development and Validation of a Deep Learning System for Staging Liver Fibrosis by Using Contrast Agent-enhanced CT Images in the Liver. *Radiology* 2018;289(3):688-97. doi: 10.1148/radiol.2018180763 [published Online First: 2018/09/05]
[3]Nguyen P. nonbinROC: Software for Evaluating Diagnostic Accuracies with Non-Binary Gold Standards. *Journal of Statistical Software* 2007;21(10) doi: 10.18637/jss.v021.i10.

Table S1: ELF[a] test thresholds and predicted severity of liver fibrosis

ELF test thresholds	Severity of Liver fibrosis
<7.7[b]	None to mild
≥ 7.7 to < 9.8	Moderate
≥9.8 to 10.5	Severe
≥10.51[c]	Advanced
≥11.3	Cirrhosis

ELF, enhanced liver fibrosis; [a]ELF thresholds proposed by the manufacturers of ELF;[1] [b]The National Institute for Health and Care Excellence (NICE) excludes fibrosis when ELF≤7.8;[2] [c]NICE recommended cut-off value for advanced (F3/F4) fibrosis. [2]
[1]https://www.siemens-healthineers.com/en-uk/laboratory-diagnostics/assays-by-diseases-conditions/liver-disease/elf-test/literature-compendium-vol-1.
[2]https://www.nice.org.uk/ guidance/ng49/chapter/Recommendations.

Table S2: VCTE cut-off values and liver stage fibrosis[1]

VCTE cut off values	Liver fibrosis stage
<6.0kPa	F0 (no fibrosis)
≥6.0kPa to 8.1kPa	F1 (mild fibrosis)
≥8.2kPa to 9.6kPa	F2 (moderate fibrosis)
≥9.7kPa to 13.5kPa	F3 (severe fibrosis)
≥13.6kPa	F4 (advanced fibrosis/cirrhosis)

VCTE, vibration controlled transient elastography; kPa, kilopascal.

[1]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730.

Table S3: CAP cut-off values and grade of steatosis[1]

CAP cut-off values	Steatosis grade
<302 dB/m^2	S0 (no steatosis)
≥302 dB/m^2	S1 (mild steatosis)
≥331 dB/m^2	S2 (moderate steatosis)
≥337 dB/m^2	S3 (severe steatosis)

CAP, controlled attenuation parameter; dB/m^2, decibel per square metre.

[1]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730.

Box S3: Development of algorithm

Software used: SPSS statistics (version 27); Microsoft Excel and Microsoft Solver Excel plug-in.

Method

1. 2020 data set (*n*=273) screened for outliers. Excluded data:
   - ALT >221 UL/L (*n*=3)
   - HbA1c >140 mmol/mol (*n*=1)
   - Total for algorithm training data ***n*=269**
2. A 'fitting the risk model' was adopted for this algorithm.
3. Binary logistic regression analysis was used to find the predicted probability and group membership of the three predictor variables: ALT, BMI and HbA1c. The dependent variable used was ≥F2 (≥8.2kPa).
4. The regression analysis output was plotted on a graph (**Figure 1**).
5. The aim was to develop an equation that replicated the regression analysis on the graph, using ALT, BMI and HbA1c.
6. We arrived at the following equation: ((patient ALT score – ALT y-intercept)*ALT multiplier$^{\Phi}$)+ ((patient BMI score – BMI y-intercept)* BMI multiplier$^{\Phi}$)+ ((patient HbA1c score – HbA1c y-intercept)*HbA1c multiplier$^{\Phi}$) $^{\Phi}$multiplier comes from Excel Solver analysis of the training data set.
7. The y-intercept of the best fit lines from the training data: ALT, BMI and HbA1c was calculated (**Figure 2**).
8. Excel Solver computed the multiplier for each of the three variables.
9. The missing values were added to the algorithm: ((patient ALT score – 28.826)*0.002638)+ ((patient BMI score – 23.291)* 0.02152)+((patient HbA1c score – 28.462)*0.009975).
10. The algorithm was applied to the complete training data set (*n*=269).
11. The results of the algorithm were plotted on the graph (**Figure 1)** for comparison with the logistic regression output.

Figure 1: Comparison of the predicted probability of group membership for ≥F2 using the calculated regression analysis and the ALBA algorithm

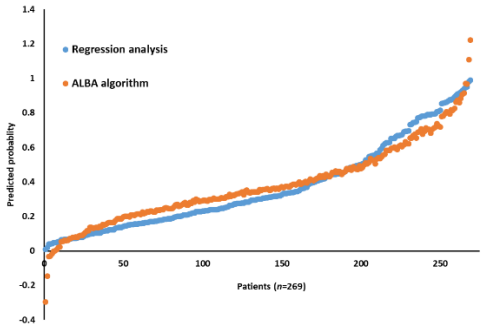
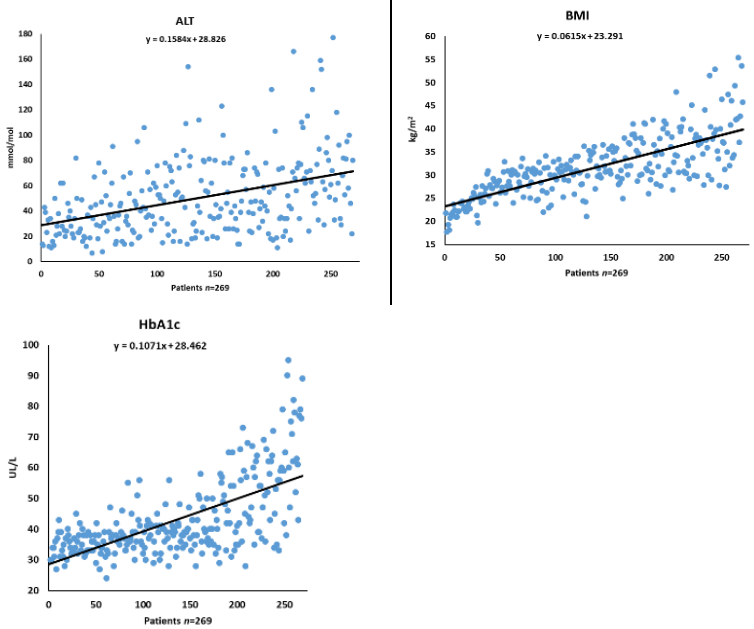


Figure 2: y-intercept of the best fits lines for ALT, BMI and HbA1c



ALT, alanine transaminase; HbA1c, glycated haemoglobin; BMI, body mass index; F2, moderate fibrosis; kPa, kilopascals.

References

Guidance from the following literature was used to help with constructing our algorithm:

Davies MJ, Gray LJ, Ahrabian D, et al. A community-based primary prevention programme for type 2 diabetes mellitus integrating identification and lifestyle intervention for prevention: a cluster randomised controlled trial. Southampton (UK): NIHR Journals Library; 2017 Jan. Programme Grants for Applied Research, No. 5.2. Chapter 3, Developing the risk score. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409312/

Kebede Deribe, Lyndsey Florence, Abebe Kelemework, Tigist Getaneh, Girmay Tsegay, Jorge Cano, Emanuele Giorgi, Melanie J Newport, Gail Davey, Developing and validating a clinical algorithm for the diagnosis of podoconiosis, Transactions of The Royal Society of Tropical Medicine and Hygiene, Volume 114, Issue 12, December 2020, Pages 916–925, https://doi.org/10.1093/trstmh/traa074

Chava L Ramspek, Kitty J Jager, Friedo W Dekker, Carmine Zoccali, Merel van Diepen, External validation of prognostic models: what, why, how, when and where?, Clinical Kidney Journal, Volume 14, Issue 1, January 2021, Pages 49–58, https://doi.org/10.1093/ckj/sfaa188

Box S4: Validation cohort

Method

1. 2021 data set (*n*=176) was screened, the following data was excluded:
   - Incomplete patient data (*n*=15)
   - Possible hepatitis (*n*=13)
   - Dependent drinkers (*n*=27) (patients who scored ≥15 on the alcohol use disorders identification test [AUDI])[1 2]

- Cancer/HIV medication (*n*=2)
- Unable to obtain valid VCTE reading (*n*=4)

Total for validation cohort data ***n*=115**

2. The ALT, BMI and HbA1c readings of the validation cohort were fed into the ALBA algorithm: ((patient ALT score – 28.826)*0.002638)+ ((patient BMI score – 23.291)* 0.02152)+((patient HbA1c score – 28.462)* 0.009975).
3. If the total of the ALBA algorithm was ≥0.5 then the patient was predicted to be 'positive' for ≥F2.
4. If the total of the ALBA algorithm as <0.5 then the patient was predicted to be 'negative' for ≥F2.
5. The patient's predicted positive or negative value was then compared to the patient's actual F2 status.
6. The number of correct predicted values was then calculated for the validation cohort.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S4: Characteristics of patients by fibrosis stage[a]

Characteristics of patients (n=273)	F0 (40.1%) (*n*=113)		F1 (22.8%) (*n*=58)		F2 (8.9%) (*n*=25)		F3 (13.0%) (*n*=35)		F4 (15.3%) (*n*=42)	
Men sex, *n* (%)	62	54.9	34	58.6	14	56.0	18	51.4	23	54.8
Minority ethnic groups, *n* (%)	33	29.2	15	25.9	7	28.0	4	11.4	6	14.3
Median age, years (IQR)	57	44-65	56	50-64	58	45-63	55	45-61	58	53-65
Mean ELF score, (SD)	9.8	0.6	9.7	0.8	9.9	0.7	10.2	0.7	10.6	1.1
Mean weight, kg (SD)	82.2	16.8	91.3	19.2	96.9	20.5	92.5	19.0	105.7	21.5
Median BMI, kg/m^2 (IQR)	29.5	24.6-32.6	30.7	28.0-34.0	32.0	29.3-38.9	31.6	30.0-36.3	36.4	30.3-40.3
BMI≥30 kg/m^2, *n* (%)	54	47.8	32	55.2	19	76.0	27	77.1	35	85.3
Diabetes positive, *n* (%)[¶]	26	23.0	19	32.8	16	64	19	54.3	30	71.4
Mean HbA1c, mmol/mol (SD)	38.9	9.2	41.7	16.2	48.5	15.7	47.0	14.6	50.6	16.0
ALT≥40 IU/L, *n* (%)[$]	44	38.9	37	63.8	15	60.0	23	65.7	34	81.0
Mean ALT, IU/L (SD)	42.6	30.3	50.4	24.2	52.1	32.1	68.5	57.9	68.7	42.6
Mean VCTE reading, kPa (SD)	4.5	0.9	6.9	0.6	8.7	0.4	11.2	1.1	22.8	12.0
Mean CAP score, dB/m^2 (SD)	289.8	60.3	321.9	50.2	348.6	38.1	335.9	45.5	363.5	34.7
High alcohol, *n* (%)[B]*	23	20.4	14	25.0	6	24.0	8	22.9	14	33.3
Smoker, *n* (%)	16	14.2	8	13.8	7	28.0	8	22.9	6	14.3
Steatosis grade:										
S0 (<302 dB/m^2), *n* (%)	51	54	20	34.5	2	8.0	7	20.0	2	4.8
S1 (≥302 dB/m^2), *n* (%)	22	19.5	14	24.1	6	24.0	6	17.1	7	16.7
S2 (≥331 dB/m^2, *n* (%)	6	5.3	2	5.2	3	12.0	3	8.6	0	-
S3 (≥337 dB/m^2, *n* (%)	24	21.2	21	36.2	14	56.0	20	57.1	33	78.6
Medication:										
Antidepressants, *n* (%)	26	23	14	24.1	6	24.0	14	40.0	15	35.7
Statins, *n* (%)	35	31	14	24.1	15	60.0	10	28.6	14	33.3
Antihypertensives, *n* (%)	38	33.6	21	36.2	13	52.0	15	42.9	29	69.0
AIIR blockers, *n* (%)	4	3.5	8	10.3	7	28.0	0	-	5	11.9
Statins and antihypertensives, *n* (%)	27	23.9	12	20.7	11	44.0	7	20.0	13	31.0
Anticoagulants, *n* (%)	17	15.0	6	10.3	5	20.0	4	11.4	4	9.5
GLP-1 agonist, *n* (%)	1	0.9	2	3.4	2	8.0	4	11.4	4	9.5

[a]Biopsy validated thresholds were used for the cut-off values for fibrosis stage and steatosis grade;[1] [¶]Diabetes = HbA1c reading of >48 mmol/mol; [B]High alcohol; a score of 8-14 (harmful/hazardous) on the alcohol use disorders identification test (AUDIT);[2 3] *0.7% (*n*=2) declined to complete the AUDIT; IQR, interquartile range; SD, standard deviation; kg, kilogramme; BMI, body mass index; kg/m^2, kilogram per square metre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per litre; VCTE, vibration controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square metre; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis; S0, no steatosis; S1, mild steatosis; S2, moderate steatosis; S3, severe steatosis; GLP-1 agonist, glucagon-like peptide-1 receptor agonist; AIIR blockers, angiotensin II receptor blockers.

[1]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730.
[2]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.

[3]https://auditscreen.org/about/scoring-audit

Table S5: Patient characteristics and their relationship with significant (≥F2) liver fibrosis

Variable	Reference group	≥F2 OR	≥F2 95% CI	*p*-value[Æ]
Men	Women	0.878	0.434-1.775	0.718
Minority ethnic groups	White European	0.688	0.297-1.593	0.383
Age (1 year increment)		0.992	0.961-1.025	0.645
ELF (0.10 increment)		2.180	1.387-3.426	**0.001**
BMI≥30kg/m^2	BMI<30kg/m^2	1.150	1.087-1.217	**<0.001**
ALT≥40 IU/L	ALT<40 IU/L	1.017	1.005-1.029	**0.005**
HbA1c (1 mmol/mol increment)		1.042	1.015-1.069	**0.002**
High alcohol[Φ]	Low alcohol[◊]	1.903	0.860-4.211	0.112
Smoker	Non-smoker	2.409	0.962-6.032	0.060
Anti-depressants	No anti-depressants	0.901	0.422-1.922	0.788
Statins	No statins	1.061	0.471-2.391	0.887
Anti- hypertensives	No anti-hypertensives	1.731	0.733-4.087	0.211
AIIR blocker	No AIIR blockers	1.240	0.410-3.747	0.703
Anti-coagulants	No anti-coagulants	0.573	0.208-1.579	0.281
GLP-1 agonist	No GLP-1 agonist	2.457	0.511-11.810	0.262

[Æ]p-values refer to backward elimination binary logistic regression analysis using the alpha level of 5%; Boldfaced indicates significant *p*-values; [Φ]High alcohol; a score of 8-14 (harmful/hazardous) on the alcohol use disorders identification test (AUDIT);[1 2] [◊]Low alcohol; a score of <7 (low risk) on the AUDIT;[1 2] CI, confidence interval; OR, odds ratio; F2, moderate fibrosis; ELF, enhanced liver fibrosis; BMI, body mass index; kg/m^2, kilogram per square metre; ALT, alanine transaminase; IU/L, international units per litre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; AIIR blockers, angiotensin II receptor blockers; GLP-1 agonist, glucagon-like peptide-1 receptor agonist.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S6: Characteristics of patients stratified by sex

Characteristics (*n*=273)	Men (55.3%/*n*=151)		Women (44.7%/*n*=122)		*p*-value
Minority ethnic groups, *n* (%)	42	27.8	23	18.9	0.084[Æ]
Median age, years (IQR)	55	44-63	59	51-65	0.044[ʊ]
Mean ELF score, (SD)	9.9	0.8	10.0	0.9	0.091[•]
Mean weight, kg (SD)	93.9	19.0	85.7	20.9	0.001[•]
Median BMI, kg/m^2 (IQR)	30.1	27.1-33.8	31.9	28-31.2	0.008[•]
BMI≥30kg/m^2, *n* (%)	85	56.3	82	67.2	0.066[Æ]
Diabetes positive, *n* (%)[¶]	63	41.7	47	38.5	0.592[Æ]
Mean HbA1c, mmol/mol (SD)	43.0	12.9	43.6	15.5	0.724[•]
ALT≥40 IU/L, *n* (%)	93	61.6	60	49.2	0.040[Æ]
Mean ALT, IU/L (SD)	56.1	35.4	48.0	39.4	0.074[•]
Mean VCTE reading, kPa (SD)	9.1	7.6	8.9	8.2	0.842[•]
Mean CAP score, dB/m^2 (SD)	324.6	57.5	312.6	58.3	0.092[•]
High alcohol, *n* (%)[B*]	52	34.7	13	10.7	<0.0001[Æ]
Smoker, *n* (%)	21	13.9	24	19.7	0.202[Æ]
Fibrosis stage:					
F0 (<6.0kPa), *n* (%)	62	41.1	51	41.8	0.901[Æ]
F1 (6.0kPa-8.2kPa), *n* (%)	34	22.5	24	19.7	0.568[Æ]
F2 (8.2kPa-9.6kPa), *n* (%)	14	9.3	11	9.0	0.942[Æ]

F3 (9.7kPa-13.5kPa), *n* (%)	18	11.9	17	13.9	0.621[Æ]
F4 (≥13.6kPa), *n* (%)	23	15.2	19	15.6	0.938[Æ]
>F2, *n* (%)	55	36.4	47	38.5	0.721[Æ]
>F3, *n* (%)	41	27.2	36	29.5	0.667[Æ]
Steatosis grade:					
S0 (<302 dB/m^2), *n* (%)	42	27.8	50	41.0	0.022[Æ]
S1 (≥302 dB/m^2), *n* (%)	31	21.2	23	18.9	0.632[Æ]
S2 (≥331 dB/m^2), *n* (%)	8	5.3	7	5.7	0.874[Æ]
S3 (≥337 dB/m^2), *n* (%)	63	45.7	43	35.2	0.081[Æ]
Medication:					
Antidepressants, *n* (%)	26	17.2	49	40.2	<0.0001[Æ]
Statins, *n* (%)	52	34.4	36	29.5	0.386[Æ]
Antihypertensives, *n* (%)	60	39.7	56	45.9	0.305[Æ]
AIIR blockers, *n* (%)	10	6.6	12	9.8	0.332[Æ]
Statins and antihypertensives, *n* (%)	40	26.5	30	24.6	0.721[Æ]
Anticoagulants, *n* (%)	22	14.6	14	11.5	0.453[Æ]
GLP-1 agonist, *n* (%)	4	2.6	9	7.4	0.088[◊]

[Æ]p-values refer to a Chi-square test for independence using an alpha level of 5%; [ʊ]p-values refer to a Mann-Whitney U test used as the non-parametric alternative test to the independent sample t-test; [•]p-values refer to a two-tailed independent samples t-test using a CI of 95%; [¶]Diabetes; HbA1c reading of >48 mmol/mol; [B]High alcohol; a score of 8-14 (harmful/hazardous) on the alcohol use disorders identification test (AUDIT);[1] [2] [*]0.7% (*n*=2) declined to complete the AUDIT; [◊]Fisher's exact test was used to determine if there was a significant association.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S7: Characteristics of patients stratified by BMI<and ≥30kg/m^2

Characteristics N=273	**≥30kg/m^2** (61.2%/*n*=167)		**<30kg/m^2** (38.8%/*n*=106)		***p*-value**
Men sex, *n* (%)	85	52.1	66	62.3	0.066[Æ]
Minority ethnic groups, *n* (%)	32	19.2	33	31.1	0.024[Æ]
Median age, years (IQR)	58	48-64	57	43-65	0.998[•]
Mean ELF score, (SD)	10.0	0.8	9.9	0.8	0.149[•]
Mean weight, kg (SD)	100.6	17.6	75.0	13.0	<0.0001[•]
Median BMI, kg/m^2 (IQR)	34.2	31.1-38.0	26.2	23.8-28.1	<0.0001[•]
Diabetes positive, *n* (%)[¶]	80	47.9	30	28.3	0.001[Æ]
Mean HbA1c, mmol/mol (SD)	44.4	13.2	41.3	15.2	0.075[•]
ALT≥40 IU/L, *n* (%)	94	56.3	59	55.7	0.919[Æ]
Mean ALT, IU/L (SD)	53.6	41.0	50.1	31.0	0.517[•]
Mean VCTE reading, kPa (SD)	10.0	7.8	7.5	7.7	0.011[•]
Mean CAP score, dB/m^2 (SD)	333.9	55.0	296.2	55.6	<0.0001[•]
High alcohol, *n* (%)[B*]	35	21.1	30	28.6	0.160[Æ]
Smoker, *n* (%)	28	16.8	17	16.0	0.874[Æ]
Fibrosis stage:					
F0 (<6.0kPa), *n (*%)	54	32.3	59	55.7	<0.0001[Æ]
F1 (6.0kPa-8.2kPa), *n (*%)	32	19.2	26	24.5	0.291[Æ]
F2 (8.2kPa-9.6kPa), *n (*%)	19	11.4	6	5.7	0.110[Æ]
F3 (9.7kPa-13.5kPa), *n (*%)	27	16.2	8	7.5	0.038[Æ]
F4 (≥13.6kPa), *n (*%)	35	21.0	7	6.6	0.001[Æ]
≥F2, *n (*%)	81	48.5	21	19.8	<0.0001[Æ]
≥F3, *n (*%)	62	37.1	15	14.2	<0.0001[Æ]
Steatosis grade:					

S0 (<302 dB/m^2), *n* (%)	40	24.4	52	49.1	<0.0001[Æ]
S1 (≥302 dB/m^2), *n* (%)	27	16.2	28	26.4	0.040[Æ]
S2 (≥331 dB/m^2), *n* (%)	12	7.2	3	2.8	0.174[◊]
S3 (≥337 dB/m^2), *n* (%)	88	52.7	24	22.6	<0.0001[Æ]
Medication:					
Antidepressants, *n* (%)	48	28.7	27	25.5	0.555[Æ]
Statins, *n* (%)	59	35.3	29	27.4	0.170[Æ]
Antihypertensives, *n* (%)	80	47.9	36	34.0	0.023[Æ]
AIIR blockers, *n* (%)	17	10.2	5	4.7	0.117[◊]
Statins and antihypertensives, *n* (%)	49	29.3	21	19.8	0.079[Æ]
Anticoagulants, *n* (%)	24	14.4	12	11.3	0.468[Æ]
GLP-1 agonist medication, *n* (%)	12	7.2	1	0.9	0.019[◊]

[Æ]p-values refer to a Chi-square test for independence using an alpha level of 5%; [•]p-values refer to a two-tailed independent samples t-test using a CI of 95; [¶]Diabetes = HbA1c reading of >48 mmol/mol; [B]High alcohol; a score of 8-14 (harmful/ hazardous) on the alcohol use disorders identification test (AUDIT);[1 2] *0.7% (*n*=2) declined to complete the AUDIT; [◊]Fisher's exact test was used to determine if there was a significant association. IQR, interquartile range; SD, standard deviation; kg, kilogramme; BMI, body mass index; kg/m^2, kilogram per square metre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per litre; VCTE, vibration controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square metre; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis; S0, no steatosis; S1, mild steatosis; S2, moderate steatosis; S3, severe steatosis; GLP-1 agonist, glucagon-like peptide-1 receptor agonist; AIIR blockers, angiotensin II receptor blockers.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S8: Characteristics of patients stratified by diabetes status

Characteristics *n*=273	**Diabetes[¶]** (40.3%/*n*=110)		**No diabetes** (59.7%/*n*=163)		***p*-value**
Men sex, *n* (%)	63	57.3	88	54.0	0.592[Æ]
Minority ethnic groups, *n* (%)	28	25.5	37	22.7	0.600[Æ]
Median age, years (IQR)	58	50-64	57	44-64	0.326[•]
Mean ELF score, (SD)	10.1	0.7	9.8	0.9	0.007[•]
Mean weight, kg (SD)	95.5	19.8	86.7	19.8	0.001[•]
Median BMI, kg/m^2 (IQR)	32.1	29.6-36.9	30.1	26.0-33.8	<0.0001[•]
BMI≥30 kg/m^2, *n* (%)	80	72.7	87	53.4	0.001[Æ]
Mean HbA1c, mmol/mol (SD)	54.4	15.8	35.7	4.8	<0.0001[•]
ALT≥40 IU/L, *n* (%)[$]	71	64.5	82	50.3	0.020[Æ]
Mean ALT, IU/L (SD)	57.0	36.5	49.4	37.8	0.100[•]
Mean VCTE reading, kPa (SD)	11.6	8.6	7.3	6.8	<0.0001[•]
Mean CAP score, dB/m^2 (SD)	339.0	47.0	305.9	61.2	<0.0001[•]
High alcohol, *n* (%)[B]*	23	21.1	42	25.9	0.362[Æ]
Smoker, *n* (%)	14	12.7	31	19.0	0.169[Æ]
Fibrosis stage:					
F0 (<6.0kPa), *n* (%)	26	23.6	87	53.4	<0.0001[Æ]
F1 (6.0kPa-8.2kPa), *n* (%)	19	17.3	39	23.9	0.187[Æ]
F2 (8.2kPa-9.6kPa), *n* (%)	16	14.5	9	5.5	0.011[Æ]
F3 (9.7kPa-13.5kPa), *n* (%)	19	17.3	16	9.8	0.071[Æ]
F4 (≥13.6kPa), *n* (%)	30	27.3	12	7.4	<0.0001[Æ]
≥F2, *n* (%)	65	59.1	37	22.7	<0.0001[Æ]
≥F3, *n* (%)	49	44.5	28	17.2	<0.0001[Æ]
Steatosis grade:					
S0 (<302 dB/m^2), *n* (%)	21	19.1	71	43.6	<0.0001[Æ]

S1 (≥302 dB/m^2), *n* (%)	21	19.1	34	20.9	0.721[Æ]
S2 (≥331 dB/m^2), *n* (%)	5	4.5	10	6.1	0.788[◊]
S3 (≥337 dB/m^2), *n* (%)	63	57.3	49	30.1	<0.0001[Æ]
Medication:					
Antidepressants, *n* (%)	36	32.7	39	23.9	0.110[Æ]
Statins, *n* (%)	55	62.5	33	20.2	<0.0001[Æ]
Antihypertensives, *n* (%)	61	55.5	55	33.7	<0.0001[Æ]
AIIR blockers, *n* (%)	8	7.3	14	8.6	0.695[Æ]
Statins and antihypertensives, *n* (%)	42	38.2	28	17.2	<0.0001[Æ]
Anticoagulants, *n* (%)	16	14.5	20	12.3	0.586[Æ]
GLP-1 agonist medication, *n* (%)	13	11.8	0	-	-

[Æ]p-values refer to a Chi-square test for independence using an alpha level of 5%. [•] p-values refer to a two-tailed independent samples t-test using a CI of 95%. [¶]Diabetes = HbA1c reading of >48 mmol/mol. [B]High alcohol; a score of 8-14 (harmful/ hazardous) on the alcohol use disorders identification test (AUDIT);[1 2] *0.7% (*n*=2) declined to complete the AUDIT; [◊]Fisher's exact test was used to determine if there was a significant association. IQR, interquartile range; SD, standard deviation; kg, kilogramme; BMI, body mass index; kg/m^2, kilogram per square metre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per litre; VCTE, vibration controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square metre; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis; S0, no steatosis; S1, mild steatosis; S2, moderate steatosis; S3, severe steatosis; GLP-1 agonist, glucagon-like peptide-1 receptor agonist; AIIR blockers, angiotensin II receptor blockers.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S9 Characteristics of patients stratified by statin prescribing

Characteristics (*n*=273)	**Statins (*n*=88)**		**No statins (*n*=185)**		***p*-value**
Men sex, *n* (%)	52	59.1	99	53.5	0.386[Æ]
Minority ethnic groups, *n* (%)	17	19.3	48	25.9	0.229[Æ]
Median age, years (IQR)	61	55-68	55	43-62	<0.0001[ʊ]
Mean ELF score, (SD)	10.1	0.7	9.9	0.9	0.068[•]
Mean weight, kg (SD)	92.4	18.8	89.2	20.9	0.250[•]
Median BMI, kg/m^2 (IQR)	31.4	28.4-36.3	30.6	26.9-35.2	0.193[•]
BMI≥30kg/m^2, *n* (%)	59	67.0	108	58.4	0.170[Æ]
Diabetes positive, *n* (%)[¶]	55	62.5	55	29.7	<0.0001[Æ]
Mean HbA1c, mmol/mol (SD)	49.3	17.4	40.3	11.1	<0.0001[•]
ALT≥40 IU/L, *n* (%)	37	42.0	116	62.7	0.001[Æ]
Mean ALT, IU/L (SD)	41.4	23.1	57.7	41.6	0.001[•]
Mean VCTE reading, kPa (SD)	9.9	9.4	8.6	6.9	0.222[•]
Mean CAP score, dB/m^2 (SD)	329.8	60.1	314.2	56.2	0.038[•]
High alcohol, *n* (%)[B*]	15	17.0	50	27.3	0.064[Æ]
Smoker, *n* (%)	11	12.5	34	18.4	0.221[Æ]
Fibrosis stage:					
F0 (<6.0kPa), *n* (%)	35	39.8	78	42.2	0.708[Æ]
F1 (6.0kPa-8.2kPa), *n* (%)	14	15.9	44	23.8	0.137[Æ]
F2 (8.2kPa-9.6kPa), *n* (%)	15	17.0	10	5.4	0.002[Æ]
F3 (9.7kPa-13.5kPa), *n* (%)	10	11.4	25	13.5	0.619[Æ]
F4 (≥13.6kPa), *n* (%)	14	15.9	28	15.1	0.868[Æ]
≥F2, *n* (%)	39	44.3	63	34.1	0.101[Æ]
≥F3, *n* (%)	24	27.3	53	28.6	0.868[Æ]
Steatosis grade:					
S0 (<302 dB/m^2), *n* (%)	21	23.9	71	38.4	0.018[Æ]

S1 (≥302 dB/m^2), *n* (%)	17	19.3	38	20.5	0.814[Æ]
S2 (≥331 dB/m^2, *n* (%)	4	4.5	11	5.9	0.635[◊]
S3 (≥337 dB/m^2, *n* (%)	46	52.3	66	35.7	0.009[Æ]
Medication:					
Antidepressants, *n* (%)	32	36.4	43	23.2	0.023[Æ]
Antihypertensives, *n* (%)	70	79.5	46	24.9	<0.0001[Æ]
AIIR blockers, *n* (%)	13	14.8	9	4.9	0.005[Æ]
Statins and antihypertensives, *n* (%	70	79.5	-	-	-
Anticoagulants, *n* (%)	25	28.4	11	5.9	<0.0001[Æ]
GLP-1 agonist, *n* (%)	11	12.5	2	1.1	<0.0001[◊]

[Æ]p-values refer to a Chi-square test for independence using an alpha level of 5%. [ʊ] p-values refer to a Mann-Whitney U test used as the non-parametric alternative test to the independent sample t-test. [•]p-values refer to a two-tailed independent samples t-test using a CI of 95%. [¶]Diabetes = HbA1c reading of >48 mmol/mol or GP record states diabetes. [B]High alcohol; a score of 8-14 (harmful/ hazardous) on the alcohol use disorders identification test (AUDIT);[1 2] [*]0.7% (*n*=2) declined to complete the AUDIT; [◊]Fisher's exact test was used to determine if there was a significant association. IQR, interquartile range; SD, standard deviation; kg, kilogramme; BMI, body mass index; kg/m^2, kilogram per square metre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per litre; VCTE, vibration controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square metre; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis; S0, no steatosis; S1, mild steatosis; S2, moderate steatosis; S3, severe steatosis; GLP-1 agonist, glucagon-like peptide-1 receptor agonist; AIIR blockers, angiotensin II receptor blockers.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S10a: A comparison of the characteristics of patients with no-low fibrosis (F0-F1) versus patients with moderate fibrosis (F2)

Characteristics	**F0-F1 (n=171)**		**F2 (8.9%) (*n*=25)**		***p*-value[•]**
Men sex, *n* (%)	96	56.1	14	56.0	0.989
Minority ethnic groups, *n* (%)	48	28.1	7	28.0	0.994
Median age, years (IQR)	57	46-64	58	45-63	0.926
Mean ELF score, (SD)	9.8	0.7	9.9	0.7	**0.048**
Mean weight, kg (SD)	85.4	18.2	96.8	20.5	**0.013**
Median BMI, kg/m^2 (IQR)	30.0	26.0-32.8	32.0	29.3-38.9	**0.003**
BMI≥30kg/m^2, *n* (%)	86	50.3	19	76.0	**0.016**
Diabetes positive, *n* (%)[¶]	45	26.3	16	64.0	**<0.0001**
Mean HbA1c, mmol/mol (SD)	39.9	12.0	48.5	15.7	**0.005**
ALT≥40 IU/L, *n* (%)	81	47.4	15	60.0	0.239
Mean ALT, IU/L (SD)	45.3	28.5	52.1	32.1	0.317
Mean VCTE reading, kPa (SD)	5.3	1.4	8.7	0.4	**<0.0001**
Mean CAP score, dB/m^2 (SD)	300.7	59.0	348.6	38.1	**<0.0001**
High alcohol, *n* (%)[B]*	37	21.6	6	24.0	0.813
Smoker, *n* (%)	24	14.0	7	28.0	0.075
Antidepressants, *n* (%)	40	23.4	6	24.0	0.947
Antihypertensives, *n* (%)	59	34.5	13	52.0	0.091
Anticoagulants, *n* (%)	23	13.5	5	20.0	0.383
Statins, *n* (%)	49	28.7	15	60.0	**0.002**

[¶]Diabetes = HbA1c reading of >48 mmol/mol. *0.7% (*n*=2) declined to complete the alcohol AUDIT. [B]High alcohol; a score of 8-14 (harmful/hazardous) on the alcohol use disorders identification test (AUDIT);[1 2] [*]0.7% (*n*=2) declined to complete the AUDIT; [•]p-values refer Mann-Whitney test with Bonferonni adjustment; Boldfaced indicates significant *p*-values. IQR, interquartile range; SD, standard deviation; kg, kilogramme; BMI, body mass index; kg/m^2, kilogram per square metre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per litre; VCTE, vibration controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square metre; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S10b: A comparison of the characteristics of patients with advanced fibrosis (≥F3) versus patients with moderate fibrosis (F2)

Characteristics	**≥F3 (n=77)**		**F2 (8.9%) (*n*=25)**		***p*-value**
Men sex, *n* (%)	41	53.2	14	56.0	0.811
Minority ethnic groups, *n* (%)	10	13	7	28.0	0.082
Median age, years (IQR)	58	49-63	58	45-63	0.978
Mean ELF score, (SD)	10.4	1.0	9.9	0.7	**0.037**
Mean weight, kg (SD)	99.6	21.3	96.8	20.5	0.670
Median BMI, kg/m^2 (IQR)	34.4	30.1-39.9	32.0	29.3-38.9	0.453
BMI≥30kg/m^2, *n* (%)	62	80.5	19	76.0	0.629
Diabetes positive, *n* (%)[¶]	49	63.6	16	64.0	0.974
Mean HbA1c, mmol/mol (SD)	49.0	15.4	48.5	15.7	0.750
ALT≥40 IU/L, *n* (%)	57	74	15	60.0	0.183
Mean ALT, IU/L (SD)	68.6	49.8	52.1	32.1	0.114
Mean VCTE reading, kPa (SD)	17.5	10.5	8.7	0.4	**<0.0001**
Mean CAP score, Db/m^2 (SD)	351.0	42.1	348.6	38.1	0.643
High alcohol, *n* (%)[B]*	22	28.6	6	24.0	0.658
Smoker, *n* (%)	14	18.2	7	28.0	0.294
Antidepressants, *n* (%)	29	37.7	6	24.0	0.213
Antihypertensives, *n* (%)	44	57.1	13	52.0	0.654
Anticoagulants, *n* (%)	8	10.1	5	20.0	0.213
Statins, *n* (%)	24	31.2	15	60.0	**0.010**

[¶]Diabetes = HbA1c reading of >48 mmol/mol. *0.7% (*n*=2) declined to complete the alcohol AUDIT. [B]High alcohol; a score of 8-14 (harmful/hazardous) on the alcohol use disorders identification test (AUDIT);[1 2] *0.7% (*n*=2) declined to complete the AUDIT; *p*-values refer Mann-Whitney test with Bonferonni adjustment; boldfaced indicates significant *p*-values; IQR, interquartile range; SD, standard deviation; kg, kilogramme; BMI, body mass index; kg/m^2, kilogram per square metre; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per litre; VCTE, vibration controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square metre; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis.

[1]Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88(6):791-804.
[2]https://auditscreen.org/about/scoring-audit

Table S11: Evaluation of the diagnostic performance of ELF using area under the curve (AUC) and the Obuchowski index (full calculations shown in **Box S5a**)

	AUC	**Obuchowski index**
Fibrosis stage		
≥F2	0.70 (95% CI 0.64-0.76)	0.773
≥F3	0.72 (95% CI 0.65-0.79)	0.789

AUC, area under the curve; Obuchowski index, a weighted average of the area under the receiver operating characteristic curve values obtained for all possible pairs of fibrosis stages (i.e. 10 pairs for the five [F0–F4] fibrosis stages) to be differentiated. The Obuchowski index is a rank based measure that can be calculated without constructing a receiver operating characteristic curve (ROC), although they can be interpreted similarly, they are not associated with ROC curves.[3] The penalty function used was: 0.25 when the difference between stages was 1, 0.5 when the difference was 2, 0.75 when the difference was 3, and 1.0 when the difference was 4.[4] F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis.

[1]Poynard T, Halfon P, Castera L, et al. Standardization of ROC curve areas for diagnostic evaluation of liver fibrosis markers based on prevalences of fibrosis stages. *Clin Chem* 2007;53(9):1615-22. doi: 10.1373/clinchem.2007.085795.
[2]Obuchowski NA. Estimating and comparing diagnostic tests' accuracy when the gold standard is not binary. Acad Radiol. 2005 Sep;12(9):1198-204. doi: 10.1016/j.acra.2005.05.013. PMID: 16099683.
[3]Nguyen P. nonbinROC: Software for Evaluating Diagnostic Accuracies with Non-Binary Gold Standards. *Journal of Statistical Software* 2007;21(10) doi: 10.18637/jss.v021.i10.
[4]Lambert J, Halfon P, Penaranda G, Bedossa P, Cacoub P, Carrat F. How to measure the diagnostic accuracy of noninvasive liver fibrosis indices: the area under the ROC curve revisited. Clin Chem. 2008 Aug;54(8):1372-8. doi: 10.1373/clinchem.2007.097923. Epub 2008 Jun 6. PMID: 18539647.

Table S12: Comparison of the difference in significant (≥F2) and non-significant (F0-F1) fibrosis means (DANA) in the 2020 and 2021 datasets (full calculations shown in **Box S5b**)

	No. of patients	Mean fibrosis stage: Non-significant fibrosis (F0-F1)	Mean fibrosis stage: Significant fibrosis (≥F2)	Observed DANA score	Difference between observed and uniform* DANA scores
2020 derivation data	273	0.338	3.165	2.827	0.327
2021 validation data	115	0.381	3.126	2.745	0.245

DANA score, difference in significant (≥2) minus non-significant fibrosis (F0-F1) means; *Uniform DANA score calculated as 2.5;[1] ELF, enhanced liver fibrosis; F0, no fibrosis; F1, low fibrosis; F2 moderate fibrosis; F3 severe fibrosis; F4 advanced fibrosis/cirrhosis.

[1]Poynard T, Halfon P, Castera L, et al. Standardization of ROC curve areas for diagnostic evaluation of liver fibrosis markers based on prevalences of fibrosis stages. *Clin Chem* 2007;53(9):1615-22. doi: 10.1373/clinchem.2007.085795.

Box S5: Calculations for (a) Obuchowski index and (b) DANA

(a) Obuchowski index[1]

Software used: R version 3.4.4 (2018-03-15) with statistical code package ordROC[2]

Method

1. Eddowes[3] biopsy validated VCTE thresholds was our reference standard measurement (F0=<6.0 kilopascal (kPa); F1=6.0kPa-8.2kPa; F2=≥8.2kPa-<9.6kPa; F3=≥9.7kPa <13.5kPa and F4=≥13.6kPa).
2. ELF was the diagnostic test we were evaluating. The cut-off thresholds published by the manufacturers of ELF[4] were used to predict the fibrosis stage of patients: <7.7=none to mild; ≥7.7-<9.8=moderate; ≥9.8-10.5=severe; ≥10.51[5]=advanced and ≥11.3=cirrhosis.
3. Each pairwise comparison (VCTE compared to ELF) required a weighting (penalty) to take into account the distance between fibrosis stages (F0-F4). We adopted the penalty function proposed by Lambert et al,[6] which was a penalty proportional to the difference in METAVIR units between stages: 0.25 when the difference between stages was 1, 0.5 when the difference was 2, 0.75 when the difference was 3, and 1.0 when the difference was 4.
4. We ran the statistical code package ordROC on our data (see **Box S5a** below for output) to estimate the overall accuracy of ELF to identify: (i) liver fibrosis (F0-F4); (ii) significant fibrosis (≥F2) and (iii) severe-advanced fibrosis/cirrhosis (F3/F4) and found that the estimated overall accuracy of ELF to identify liver fibrosis is 0.813, 0.773 and 0.789 respectively, for the given penalty function (as point 3 above).

Therefore, of two randomly chosen patients with differing fibrosis stages and with the given penalty function, the ELF test has an 81.3%, 77.3% and 78.9% chance of identifying fibrosis in patients with F0-F4, ≥F2 and F3/F4 respectively.

[1]Obuchowski NA. Estimating and comparing diagnostic tests' accuracy when the gold standard is not binary. Acad Radiol. 2005 Sep;12(9):1198-204. doi: 10.1016/j.acra.2005.05.013.
[2]Nguyen P. nonbinROC: Software for Evaluating Diagnostic Accuracies with Non-Binary Gold Standards. *Journal of Statistical Software* 2007;21(10) doi: 10.18637/jss.v021.i10.
[3]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2019;156(6):1717-30. doi: 10.1053/j.gastro.2019.01.042.
[4]Siemens-Healthineers https://cdn0.scrvt.com/39b415fb07de4d9656c7b516d8e2d907/8f5cdbb2d5ed0014/ea3e1c380937/DX_ELF_Literature_Compendium_Vol1_Rev04-V4.pdf.
[5]https://www.nice.org.uk/guidance/ng49/chapter/Recommendations.ELF, enhanced liver fibrosis.
[6]Lambert J, Halfon P, Penaranda G, Bedossa P, Cacoub P, Carrat F. How to measure the diagnostic accuracy of noninvasive liver fibrosis indices: the area under the ROC curve revisited. Clin Chem. 2008 Aug;54(8):1372-8. doi: 10.1373/clinchem.2007.097923. Epub 2008 Jun 6. PMID: 18539647.

Box S5a: OrdROC output data

(i) ELF predicting ≥F3 and VCTE

```
> f3f4<-read.csv("f3f4.csv", header=TRUE)
> library(nonbinROC)
> attach(f3f4)
> penalty <- matrix(c(0,0,0,0,0, 0.25,0,0,0,0, 0.5,0.25,0,0,0, 0.75,0.5,0.25,0,0, 1,0.75,0.5,0.25,0),nrow = 5)
> ordROC(VCTE, ELF, penalty = penalty)
$`Pairwise Accuracy`
   Pair  Estimate Standard.Error
1  1 vs 2 0.5952381    0.11604266
2  1 vs 3 0.5714286    0.04852616
3  1 vs 4 0.5649351    0.08551880
4  1 vs 5 0.7226891    0.07835426
5  2 vs 3 0.6666667    0.10540926
6  2 vs 4 0.5303030    0.12676667
7  2 vs 5 0.6274510    0.12204800
```

8 3 vs 4 0.6363636 0.07041788
9 3 vs 5 0.7941176 0.06151912
10 4 vs 5 0.6577540 0.09350551
$`Penalty Matrix`
1 2 3 4 5
1 0 0.25 0.50 0.75 1.00
2 0 0.00 0.25 0.50 0.75
3 0 0.00 0.00 0.25 0.50
4 0 0.00 0.00 0.00 0.25
5 0 0.00 0.00 0.00 0.00
$`Overall Accuracy`
Estimate Standard.Error
1 0.7894491 0.03207889

(ii) ELF predicting ≥F2 and VCTE > f2f3f4<-read.csv("f2f3f4.csv", header=TRUE)
> library(nonbinROC)
> attach(f2f3f4)
> penalty <- matrix(c(0,0,0,0,0, 0.25,0,0,0,0, 0.5,0.25,0,0,0, 0.75,0.5,0.25,0,0, 1,0.75,0.5,0.25,0),nrow = 5)
> ordROC(VCTE, ELF, penalty = penalty)
$`Pairwise Accuracy`
Pair Estimate Standard.Error
1 1 vs 2 0.5241546 0.06937839
2 1 vs 3 0.5115090 0.06529201
3 1 vs 4 0.5677258 0.06166766
4 1 vs 5 0.6695652 0.05969210
5 2 vs 3 0.5359477 0.08122507
6 2 vs 4 0.5405983 0.07790468
7 2 vs 5 0.6407407 0.07324759
8 3 vs 4 0.5814480 0.07388662
9 3 vs 5 0.6852941 0.06675932
10 4 vs 5 0.6096154 0.06962065
$`Penalty Matrix`
1 2 3 4 5
1 0 0.25 0.50 0.75 1.00
2 0 0.00 0.25 0.50 0.75
3 0 0.00 0.00 0.25 0.50
4 0 0.00 0.00 0.00 0.25
5 0 0.00 0.00 0.00 0.00
$`Overall Accuracy`
Estimate Standard.Error
1 0.7733856 0.02217227

b. The difference between significant (≥F2) and non-significant (F0-F1) fibrosis stages (DANA)
We applied Poynard et al's method.[1]
Patients from the 2020 Community Liver Service (derivation cohort) with VCTE assessment (n=273), the stage prevalences were: F0=41.4%; F1=21.2%; F2=9.2%; F3=12.8%; F4=15.4%.
The mean fibrosis stage in METAVIR units for significant fibrosis was 3.165 vs 0.338 for non-significant fibrosis:

[Mean of (F2 + F3 + F4)/(F2+F3+F4)]
(0.092 x 2) + (0.128 x 3) + (0.154 x 4)/(0.092 + 0.128 + 0.154)
(0.184) + (0.384) + (0.616)/0.374
= 3.165
[Mean of (F1 + F0)/(F1+F0)]
(0.212 x 1) + (0.414 x 0)/(0.212 + 0.414)
0.212/0.626
=0.338

Patients from the 2021 Community Liver Service (validation cohort) with VCTE assessment (*n*=115), the stage prevalences were: F0=40.9%; F1=25.2%; F2=8.7%; F3=12.2%; F4=13.0%.
The mean fibrosis stage in METAVIR units for significant fibrosis was 3.126 vs 0.381 for non-significant fibrosis:

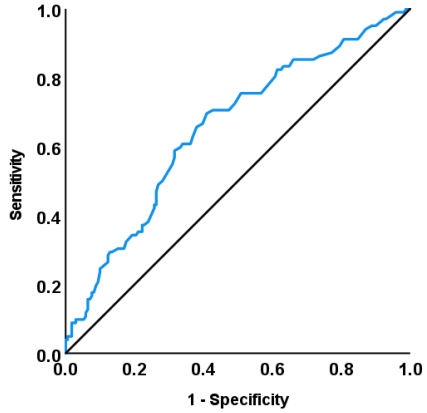
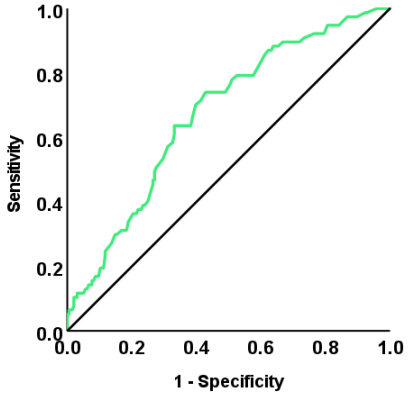
[Mean of (F2 + F3 + F4)/(F2+F3+F4)]
(0.087 x 2) + (0.122 x 3) + (0.130 x 4)/(0.087 + 0.122 + 0.130)
(0.174) + (0.366) + (0.520)/0.339
= 3.126
[Mean of (F1 + F0)/(F1+F0)]
(0.252 x 1) + (0.409 x 0)/(0.252 + 0.409)
0.252/66.1
=**0.381**

The uniform prevalence distribution of fibrosis stages was defined by a prevalence of 0.20 for each of the five stages of fibrosis (F0-F4). The mean fibrosis stage in METAVIR units is 3 for significant fibrosis vs 0.5 for non-significant fibrosis. Therefore the uniform prevalence distribution is **2.5.**

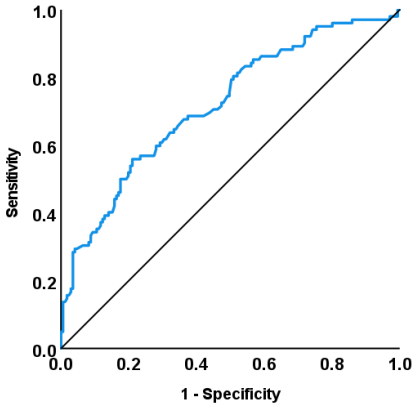
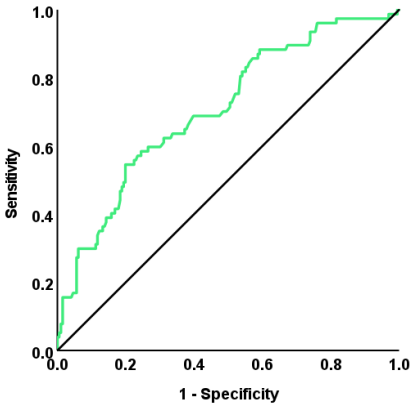
[1] Poynard T, Halfon P, Castera L, et al. Standardization of ROC curve areas for diagnostic evaluation of liver fibrosis markers based on prevalences of fibrosis stages. *Clin Chem* 2007;53(9):1615-22. doi: 10.1373/clinchem.2007.085795.

Figure S1: Area under the curve (AUC) receiver-operating characteristics (ROC) for the prediction of significant fibrosis (≥F2/≥8.2kPa) and advanced fibrosis (≥F3/≥9.7kPa) using (a) ALT; (b) BMI and (HbA1c)

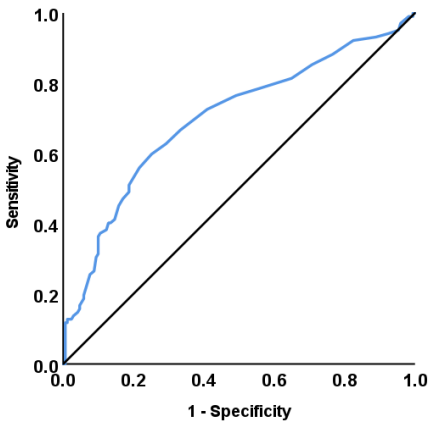
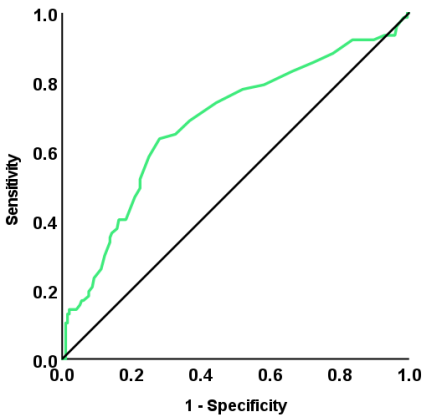
(a) ALT

≥F2 (≥8.2kPa)	≥F3 (≥9.7kPa)
	
AUC = 0.65 (95% CI 0.59-0.72)	AUC = 0.67 (95% CI 0.61-0.74)

(b) BMI

≥F2 (≥8.2kPa)	≥F3 (≥9.7kPa)
	
AUC = 0.72 (95% CI 0.66-0.78)	AUC = 0.71 (95% CI 0.64-0.78)

(c) HbA1c

≥F2 (≥8.2kPa)	≥F3 (≥9.7kPa)
	

AUC = 0.70 (95% CI 0.63-0.77)	AUC = 0.68 (95% CI 0.61-0.76)

F2, moderate fibrosis; F3, severe fibrosis; ALT, alanine transaminase; BMI, body mass index; HbA1c, glycated haemoglobin; CI,

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