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Original Article

Performance of the Enhanced Liver Fibrosis Score, Comparison with Vibration-controlled Transient Elastography 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 Aims: 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 nonalcoholic 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 cutoff 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 ALT, BMI, and HbA1c (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. ***Conclusions:*** Optimal ELF cutoff for ≥F2 is 9.85 and 9.95 for ≥F3. ALT, BMI, and HbA1c (ALBA algorithm) can stratify patients at risk of ≥F2. ELF performance is improved by adding ALBA.

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Keywords: Primary health care; Retrospective evaluation; Liver disease; Diabetes; Nonalcoholic fatty liver disease.

Abbreviations: ALBA, Alanine transaminase, body mass index and alanine transaminase; ALT, Alanine transaminase; APRI, Aspartate transaminase to platelet ratio index; AST, Aspartate transaminase; AUC, Area under the curve; AUDIT, Alcohol use disorders identification test; BMI, Body mass index; CAP, Controlled attenuation parameter; CI, Confidence interval; CVD, Cardio vascular disease; DANA, The difference between the mean fibrosis stage of advanced fibrosis minus the mean fibrosis stage of non-advanced fibrosis; ELF, Enhanced liver fibrosis test; FIB-4, Fibrosis-4 index; GLP-1, Glucagon-like peptide-1; GP, General practitioner; HbA1c, Glycated hemoglobin; IQR, Interquartile range; M, Medium; METAVIR, Meta-analysis of histological data in viral hepatitis; NAFLD, Nonalcoholic fatty liver disease; NASH, Nonalcoholic steohepatitis; NASH CRN, Nonalcoholic steahepatitis Clinical Research Network; NFS, NAFLD fibrosis score; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NPV, Negative predictive value; PPV, Positive predictive value; ROC, Receiver operating characteristic; SD, Standard deviation; T2DM, Type 2 diabetes; VCTE, Vibration-controlled transient elastography; XL, Extra large.

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Introduction

In the UK, liver disease is third commonest cause of premature death.[1] Nonalcoholic 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 (≥6.0 kPa/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 AST to platelet ratio index (APRI) score[15] are less expensive within the NHS, but require measurement of aspartate aminotransaminase (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 cutoff 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 several serum biomarkers available for the detection of liver fibrosis,[25] no one biomarker test is recommended for the detection of ≥F2.

We 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 cutoffs perform in a real-world setting, and estimates the score with the optimum balance of sensitivity and specificity (Youden's index)[26] of ELF for identification of significant (≥F2) and advanced fibrosis (≥F3). We examined whether alanine transaminase (ALT), body mass index (BMI) and glycated hemoglobin (HbA1c), three widely available variables associated with liver disease, can be used as predictors of ≥F2.

Aims

To evaluate:

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

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 developed in the derivation cohort for identifying patients with liver fibrosis. Using the Southampton primary care liver pathway to identify at risk patients (Supplementary File 1), GPs referred patients to the Community Liver Service for VCTE assessment.

Inclusion criteria

Adults (≥18 years of age) 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 1.1 kPa-75.0 kPa.

Exclusion criteria

Individuals with incomplete data, patients entering the pathway with an ELF score <9.0, an alcohol use disorders identification test (AUDIT score of ≥15, indicating alcohol dependence),[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 (Fig. 1).[27,28]

Statistical analysis

Validated cutoff values were used for the ELF scoring system.[17,30,31] Biopsy-confirmed thresholds, using the NASH CRN classification system, were used for the cutoff values for VCTE assessment for fibrosis (kPa) and steatosis (dB/m^2, Supplementary Tables 1–3).[32] Data were stratified by fibrosis stage, medication (statins/no statins), sex (male/female), diabetes status (diabetes/no diabetes), and BMI ≥30 kg/m^2/BMI <30 kg/m^2. Standard descriptive statistics were used to summarize variables: mean and standard deviation (±SD) for continuous variables or median and interquartile range (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 $n \leq 5$, 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 (1) test the independence of associations between variables collected before VCTE assessment and liver fibrosis stage and (2) 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-confirmed VCTE thresholds.[32] The Obuchoswki index is explained in more detail in Supplementary File 2. Youden index analysis[26] was applied to find the optimum

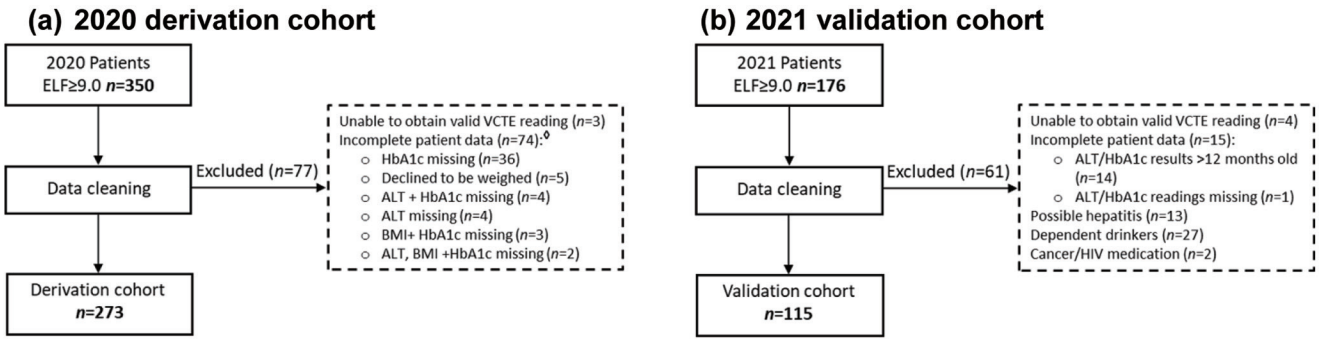

Fig. 1. Flowchart showing patients who were eligible for analysis. ◊84% of patients excluded from analysis because of incomplete data were also categorized as dependent drinkers (patients who scored ≥15 on the alcohol use disorders identification test [AUDIT]).[2728] ELF, enhanced liver fibrosis; VCTE, vibration controlled transient elastography; HbA1c, glycated haemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; BMI, body mass index.

cutoff 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 nonsignificant (F0-F1) fibrosis) was applied according to the prevalence of fibrosis stages.

Individual predictor variables

ALT,[34] BMI[35] and HbA1c[36–38] are 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 method is included in Supplementary File 3.

Validation data

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

Results

Patient characteristics are presented in Table 1

Derivation cohort

Median (IQR) age was 57 years (47–64), 55.3% were men. Mean (±SD) VCTE reading and controlled attenuation parameter (CAP) scores were 9.0 kPa (±7.8) and 319.2 dB/m^2 (±58.1), respectively. 24% (*n*=65) were consuming alcohol at harmful and hazardous levels,[27,28] 61.2% (*n*=167) had a BMI ≥30 kg/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 8.6 kPa (±6.2) and 315.6 dB/m^2 (±52.0), respectively. Up to 22.6% (*n*=26) were consuming alcohol at harmful and hazardous levels,[27,28] 60.9% (*n*=70) had a BMI ≥30 kg/m^2 and 26.9% (*n*=31) had diabetes.

Prevalence of liver fibrosis

Forty-two of the two hundred and seventy-three patients (15.4%) were identified as having advanced fibrosis/cirrhosis (F4/≥13.6 kPa), with 12.8% (*n*=35) having severe fibrosis (F3/9.7 to 13.5 kPa), 9.2% (*n*=25) having moderate fibrosis (F2/8.2 kPa to 9.6 kPa) and 62.6% (*n*=171) having no to low fibrosis (F0 to F1/<6.0 kPa/≥6.0 kPa to 8.1 kPa). The characteristics of patients by fibrosis stage are shown in Supplementary Table 4.

Factors associated with ≥F2 liver fibrosis

ELF, BMI ≥30 kg/m^2, ALT ≥40 IU/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). The results for data stratified by sex, BMI, diabetes status, and medication are shown in Supplementary Tables 6–9 respectively.

Predictors of ≥F2

Median (IQR) BMI of patients with F0-F1 was 30.0 kg/m^2 (26.0–32.8) and 32.0 kg/m^2 (29.3–38.9) in patients with F2 (p=0.003). Mean (SD) HbA1c of patients with F0–F1 was 39.9 mmol/mol (12.0) and 48.5 mmol/mol (15.7) in patients with F2. In total, 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 ≥30 kg/m^2 (p=0.016) (Supplementary Tables 10a and b).

ELF

As a predictor of significant (≥F2/≥8.2 kPa) or advanced fibrosis (≥F3/≥9.7 kPa) ELF showed a fair performance, AUC=0.70, 95% confidence interval (CI: 0.64–0.76 and AUC=0.72, 95% CI: 0.65–0.79 respectively (Fig. 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.[32]

Individual variables

ALT alone showed a poor performance for predicting both

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)	
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 (<6.0 kPa), *n* (%)	113	41.4	47	40.9
F1 (6.0–8.2 kPa), *n* (%)	58	21.2	29	25.2
F2 (8.2–9.6 kPa), *n* (%)	25	9.2	10	8.7
F3 (9.7–13.5 kPa), *n* (%)	35	12.8	14	12.2
F4 (≥13.6 kPa), *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);[27,28] [B]0.7% (*n*=2) declined to complete the AUDIT. IQR, interquartile range; SD, standard deviation; kg, kilogram; BMI, body mass index; kg/m^2, kilogram per square meter; HbA1c, glycated hemoglobin; mmol/mol, millimoles per mole; ALT, alanine transaminase; IU/L, international units per liter; VCTE, vibration-controlled transient elastography; kPa, kilopascals; CAP, controlled attenuation parameter; dB/m^2, decibel per square meter; 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.

≥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: 0.610.76 (Supplementary Fig. 1).

Combining variables

As each of the individual variables (ALT, BMI, and HbA1c)

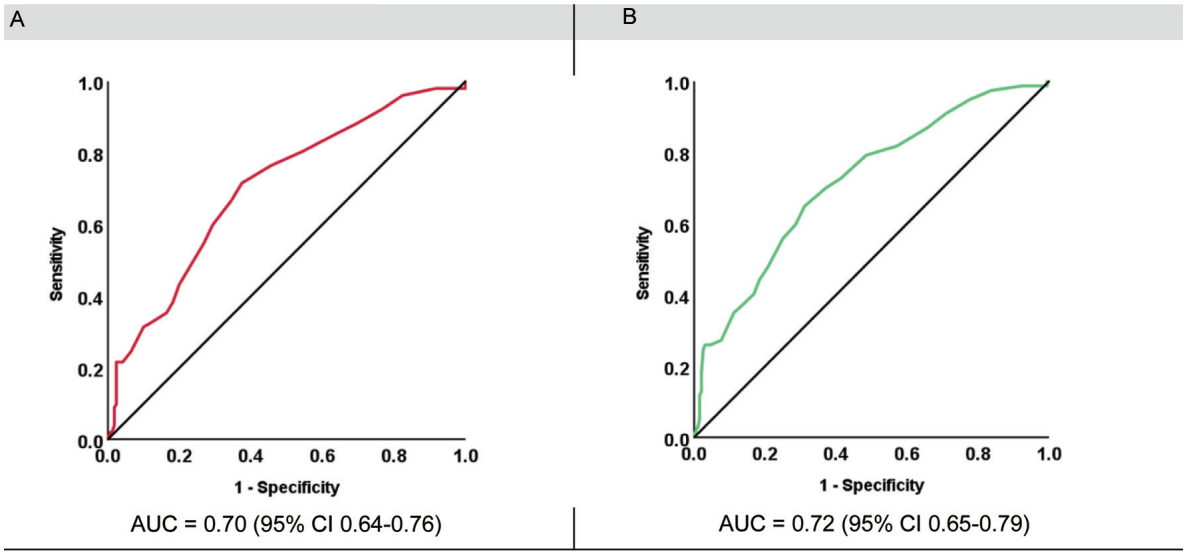

Fig. 2. Area under the curve (AUC) receiver operating characteristics (ROC) for enhanced liver fibrosis (ELF) for the diagnosis of (A) significant fibrosis (≥F2/≥8.2 kPa) and (B) advanced fibrosis (≥F3/≥9.7 kPa). CI, confidence interval; kPa, kilopascal; F2, significant fibrosis; F3, severe fibrosis.

did not show a 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, which had 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, Fig. 3A). 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, Fig. 3B). Although there was a trend toward an improvement in AUC with the addition of ELF, the differences in AUC were not statistically significant.

ALT, BMI, and HbA1c (ALBA) algorithm

The derivation cohort (*n*=273) was used to create the ALBA algorithm (Table 1). The equation for predicting ≥F2 was:

(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, Fig. 4A).

Validation cohort

The validation cohort (Table 1), *n*=115, was used to validate the ALBA algorithm. Applying the ALBA algorithm to the validation cohort for predicting ≥F2 showed AUC=0.75, 95% CI: 0.66–0.85 (Fig. 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 (Fig. 4C, D respectively).

Discussion

Summary

Our results show that when compared to validated VCTE cutoff values for the stages of liver fibrosis,[32] the National Institute for Health and Care Excellence (NICE) recommended cutoff value (ELF≥10.51)[17] for predicting advanced fibrosis (≥F3) is too high. Youden's index shows the optimum cutoff value for ≥F3 in this population is an ELF=9.95, and for ≥F2 is an ELF=9.85. The NICE cutoff value therefore should be viewed as a recommendation as our study, and others,[40,41] show that the ELF cutoff 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 underutilized Obuchowski index and the more standard 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≥30 kg/m^2) and type 2 diabetes, which led to the development of the ALBA algorithm, as an alternative method of evaluating patients at risk

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/≥8.2 kPa to 9.6 kPa	25	1	4.0	8	32.0	20	80.0
F3/≥9.7 kPa to 13.5 kPa	35	1	2.9	9	25.7	24	68.6
F4/≥13.6 kPa	42	0	-	12	28.6	25	59.5

VCTE, vibration-controlled transient elastography; [a]Eddowes *et al*[32] biopsy-validated cutoff thresholds; ELF, enhanced liver fibrosis; kPa, kilopascal; F0, no fibrosis; F1, low fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, advanced fibrosis/cirrhosis.

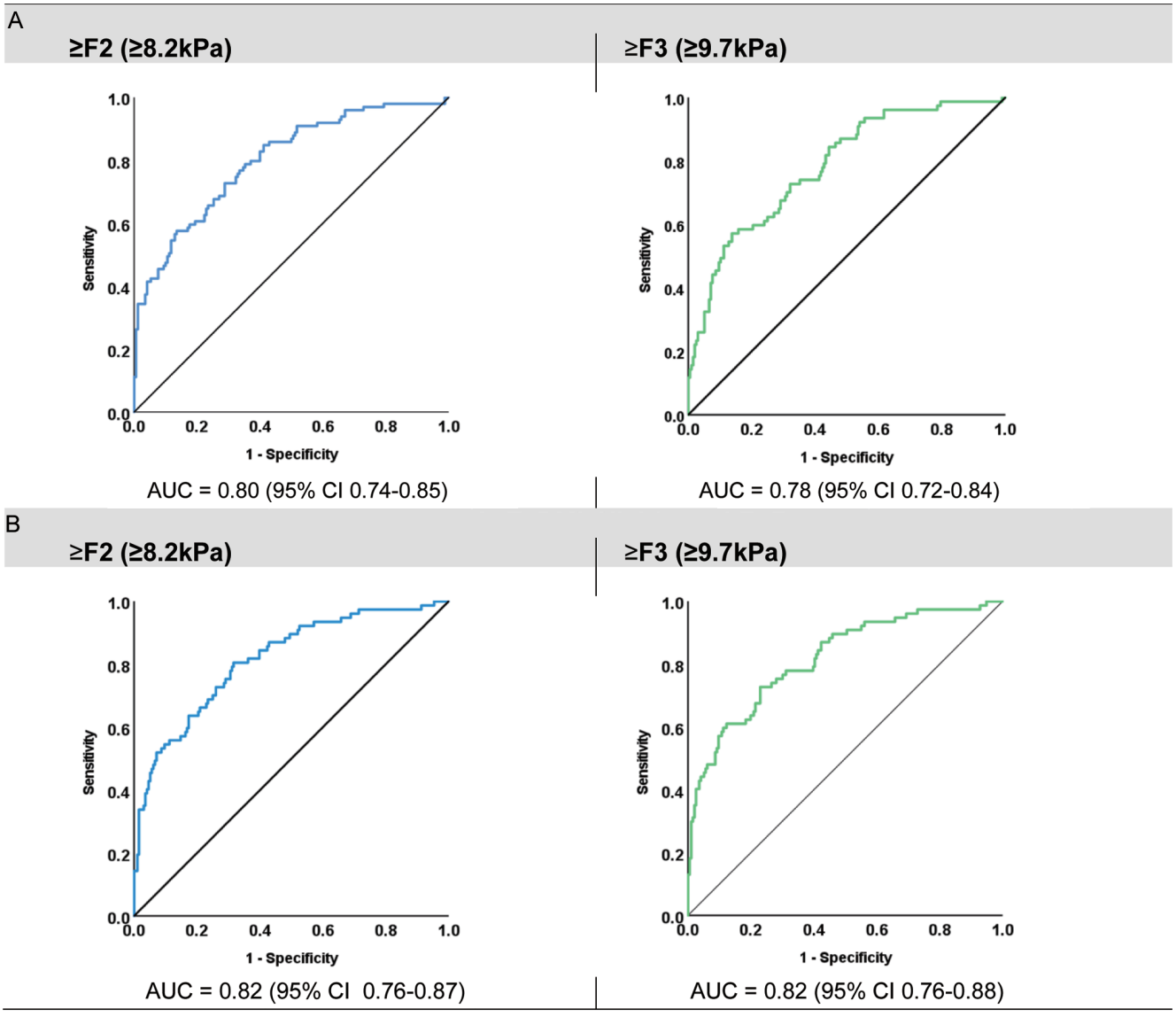

Fig. 3. Area under the curve (AUC) receiver operating characteristics (ROC) for the prediction of significant (≥F2/≥8.2 kPa) and advanced fibrosis (≥F3/≥9.7 kPa) using (A) ALT, BMI, and HbA1c and (B) ALT, BMI, HbA1c, and ELF. ALT, Alanine transaminase; BMI, Body mass index; ELF, Enhanced liver fibrosis test; HbA1c, Glycated hemoglobin; CI, confidence interval; F2, moderate fibrosis; F3, severe fibrosis.

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 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 to assess whether a patient is at risk of ≥F2.

Strengths and limitations

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

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 represented a more realistic prevalence of fibrosis in a community setting. We did not have measurements of AST available, so we could not calculate other liver fibrosis scores such as the Fibrosis-4[14] score for comparison with ELF or ALBA. Finally, VCTE assessment is a validated noninvasive 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 to monitor patients for any length of time post liver-biopsy procedure.

Comparison with existing literature

Previous studies have focused on patients with established NAFLD or screening for patients with advanced fibrosis/cir-

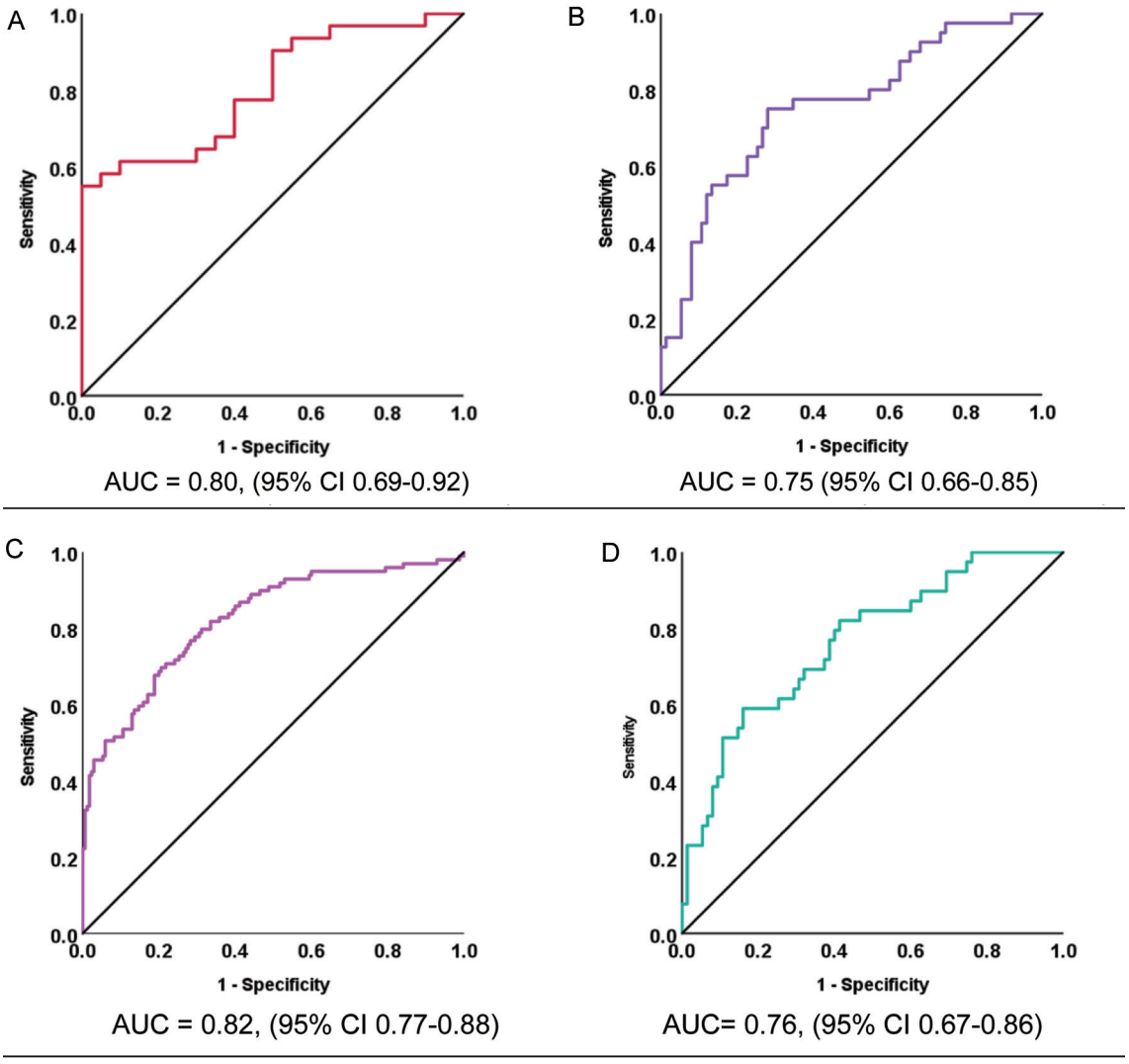

Fig. 4. Area under the curve (AUC) receiver operating characteristic (ROC) for the prediction of significant fibrosis (≥F2/≥8.2 kPa), using the ALBA algorithm on (A) the derivation data and (B) the validation data and using the ALBA algorithm and ELF together to predict significant fibrosis (≥F2/≥8.2 kPa) on (C) the derivation data and (D) the validation data. ALBA, Alanine transaminase, body mass index and alanine transaminase; ELF, enhanced liver fibrosis; kPa, kilopascal; CI, confidence interval, F2, moderate fibrosis.

rhosis.[47,48] However, it is early detection of NAFLD and early stage 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 important risk factor for NAFLD,[37] yet liver function tests are not recommended in the NICE guidelines for diabetes.[52] 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.[53]

Implications for practice

Health care providers considering implementing a liver service should consider 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 cutoff value, referral for VCTE assessment is now set to ELF≥9.5.

Up to 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] 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.[8]

Conclusion

This study has shown that in the absence of access to non-invasive blood tests, the ALBA algorithm can 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≥30 kg/m^2 with liver fibrosis, which lends

further weight to targeting these known high risk groups in screening for liver disease.

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Conflict of interest

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

Author contributions

Study concept and design (TR, MM, JP) acquisition of data (TR), analysis and interpretation of data (TR, DF, CB), drafting of the manuscript (TR, CB), critical revision of the manuscript for important intellectual content (TR, DF, JP, MM, RB, CB) study supervision (CB). All authors have contributed to this study and have approved the final manuscript.

Ethical statement

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 following the guidelines of the Helsinki Declaration.

Data sharing statement

No additional data are available.

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