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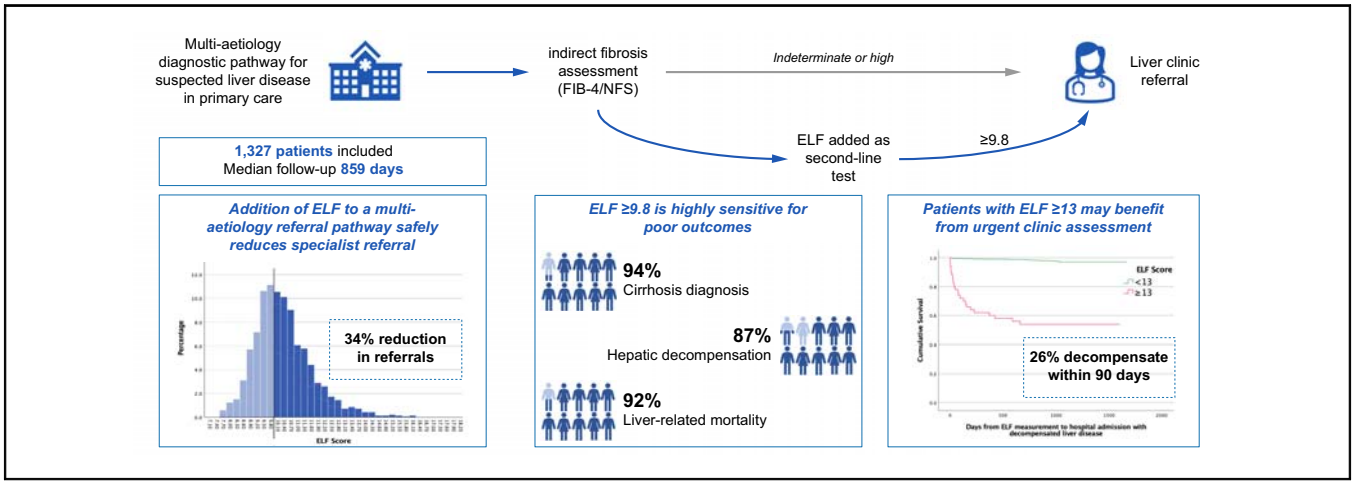
Graphical abstract



Highlights

- Improved diagnosis of liver disease increases demand for fibrosis assessment.
- ELF testing can be combined with indirect fibrosis scores.
- The addition of ELF testing reduced referral rates by 34% in a multi-aetiology pathway.
- ELF scores <9.8 have a high negative predictive value (>95%) for hepatic events.
- ELF scores ≥13 are associated with rapid decompensation and warrant urgent referral.

Impact and implications

Primary care pathways for suspected liver disease are increasingly common and often lead to increased specialist hepatology referrals for fibrosis assessment. This study, using clinical follow-up for liver-related outcomes, provides further evidence supporting ELF testing to safely reduce referrals in a two-step approach when combined with other simple fibrosis markers. Additionally, ELF scores predict liver-related morbidity and mortality, with ELF scores ≥13 indicating particularly high-risk patients. This study may help inform the implementation of diagnostic pathways for early detection of liver disease and highlights the need for urgent review of individuals with very high ELF scores.

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Research article

JHEP|Reports

Enhanced liver fibrosis (ELF) score predicts hepatic decompensation and mortality

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Background & Aims: In community pathways for detection of liver disease the most common reason for referral is fibrosis assessment. We investigated the impact of adding the Enhanced Liver Fibrosis (ELF) score as a second-line test (subsequent to an indeterminate or high Fibrosis-4 index [FIB-4] and/or non-alcoholic fatty liver disease fibrosis score) to guide referral and prognostication in our multi-aetiology pathway.
Methods: Patients with ELF results from the intelligent Liver Function Testing (iLFT) pathway were recruited. Case note review was undertaken to compare ELF with endpoints of cirrhosis, hepatic decompensation, and mortality (liver-related and all-cause death).
Results: In total, 1,327 individuals were included with a median follow-up of 859 days and median ELF score of 10.2. Overall sensitivity for cirrhosis at the 9.8 threshold was 94% (100% for metabolic-associated steatotic liver disease, 89% for alcohol-related liver disease). Determination of the ELF score as a second-line test reduced the referral rate by 34%. ELF scores predicted hepatic outcomes; each unit change was associated with increased decompensation (adjusted Hazard Ratio [aHR] 2.215, 95% CI: 1.934–2.537) and liver-related mortality (aHR 2.024, 95% CI: 1.674–2.446). ELF outperformed FIB-4 for risk of liver-related mortality, particularly in the short-term (area under the curve [AUC] 94.3% *vs.* 82.8% at six months). Where FIB-4 was indeterminate, ELF had higher AUC for all outcomes within at least 2 years. ELF ≥13 was associated with particularly high rates of decompensation (26% within 90 days) and all-cause mortality (38% at 1 year).
Conclusions: The addition of ELF reduced the number of individuals referred for fibrosis assessment following iLFT pathway testing and provided useful prognostic information. Individuals with ELF scores ≥13 were considered at high-risk of negative outcomes warranting urgent clinical assessment.
Impact and implications: Primary care pathways for suspected liver disease are increasingly common and often lead to increased specialist hepatology referrals for fibrosis assessment. This study, using clinical follow-up for liver-related outcomes, provides further evidence supporting ELF testing to safely reduce referrals in a two-step approach when combined with other simple fibrosis markers. Additionally, ELF scores predict liver-related morbidity and mortality, with ELF scores ≥13 indicating particularly high-risk patients. This study may help inform the implementation of diagnostic pathways for early detection of liver disease and highlights the need for urgent review of individuals with very high ELF scores.

Introduction

In contrast to other major diseases, deaths attributable to chronic liver disease (CLD) in the UK are rising; there has been a fourfold increase in the death rate since 1970. CLD is currently the leading cause of death in individuals aged 35–49 years, and is the third most common cause of premature death in the UK.[1] Symptoms of liver disease may take up to two decades to emerge following liver insult,[2] when the damage may be challenging to reverse. The majority of individuals are diagnosed following presentation to secondary care with end-stage liver disease when management options are limited.[1] As over 90% of patients with CLD can be attributed to potentially reversible causes (excess alcohol consumption, obesity, and viral hepatitis),[1] early diagnosis provides a crucial opportunity to intervene and prevent—or even reverse—disease progression and subsequent complications. Liver function tests (LFTs) undertaken as primary care screening frequently show abnormalities[3] but are often underinvestigated, resulting in a lost opportunity to detect liver disease at an early, treatable stage.[4] To combat this, various early liver disease screening pathways have been developed across the UK.[5] Locally, the intelligent Liver Function Testing (iLFT) pathway, designed by the University of Dundee and National Health Service (NHS) Tayside, demonstrated

Keywords: Enhanced Liver Fibrosis testing; Liver fibrosis; Referral pathway; Multi-aetiology; Non-invasive tests; Stratification; Prognostication.
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a 43% increase in the diagnosis of liver disease in the pilot trial.[6] However, increased identification of liver disease can lead to increased demand on Secondary Care liver clinics, which often receive requests for fibrosis assessment. Many pathways therefore utilise a two-step process to stratify individuals by risk of fibrosis, using blood tests and/or imaging studies.[5]

The iLFT pathway has previously been described in detail.[6–8] In brief, iLFT is available only to primary care clinicians and is recommended for use in patients in whom liver dysfunction is suspected. An iLFT request starts with a standard LFT panel (albumin, bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), and gamma-glutamyltransferase [GGT]). The ALT threshold used in the iLFT is lower than that of standard LFT panels (30 U/L rather than 55 U/L) as many individuals with advanced fibrosis and cirrhosis have levels within the standard reference range,[9–11] as opposed to the true 'normal' range. Patient demographics (age, sex) and selected clinical details (alcohol intake, body mass index [BMI], and presence of diabetes mellitus/metabolic syndrome) are incorporated from the electronic ordering system. If an abnormality in the initial LFT panel is identified, a cascade of further testing is automatically initiated to determine the likely cause and severity of liver disease. This is reported back to the requestor electronically with a plan for further investigation or management and a referral recommendation. To help determine whether an individual requires specialist consultation, two indirect fibrosis scores (the Fibrosis-4 [FIB-4] index and the non-alcoholic fatty liver disease [NAFLD] Fibrosis Score [NFS]) are calculated. However, many individuals score in the 'indeterminate' range resulting in significant numbers of patients requiring liver clinic review for fibrosis assessment. To address this, we investigated the impact of adding the Enhanced Liver Fibrosis (ELF) score as a second line 'rule-out' test for all individuals with indeterminate indirect fibrosis scores.

The ELF score is calculated from an algorithm based on the measurement of three serum biomarkers: hyaluronic acid (HA), procollagen III N-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1).[12] These components are all directly related to extracellular matrix turnover, and thus the ELF score is a Class I, or 'direct', fibrosis marker.[13] The ELF score has been shown to have excellent diagnostic performance in detecting advanced fibrosis across a range of CLD aetiologies,[14] and is recommended by the National Institute for Health and Care Excellence (NICE) for the assessment of fibrosis in individuals diagnosed with NAFLD (now termed metabolic-associated steatotic liver disease [MASLD], although the guideline has not yet been updated to reflect this).[15] Additionally, the ELF score is one of only two serum biomarkers designed for use in all aetiologies[16]: it has been validated for use in hepatitis B, hepatitis C, alcohol-related liver disease (ARLD), and mixed pictures of liver disease.[17–20] The ELF score is also useful as a prognostic tool, outperforming liver biopsy,[16] with a one unit increase in ELF corresponding to a doubling of the risk of liver-related outcomes.[21]

The aims of this study were: 1) to investigate whether the addition of the ELF score to the iLFT pathway can contribute to the safe stratification of individuals with indeterminate fibrosis score estimates, enabling a reduction in referrals; and 2) to assess the use of the ELF score as a prognostic marker for CLD within the primary care assessment, as part of real-world clinical practice.

Patients and methods

Patient samples and definitions

Initially, a pilot study (2019) and waiting list initiative (early 2020) were performed on samples from individuals with indeterminate fibrosis scores (NFS or FIB-4 index). Subsequently, the ELF test was added into the iLFT pathway algorithm in July 2020 and is now routinely performed on all individuals with high or indeterminate fibrosis score estimates. Within NHS Tayside, fibrosis estimates were classed as indeterminate based on the following age-specific ranges: FIB-4 index (for any iLFT outcome) – indeterminate range ≥1.45 and ≤3.25 if 65 years or under, or ≥2.00 and ≤3.25 if over 65 years; NFS (for presumed MASLD only) – indeterminate range ≥-1.455 and 0.675 if 65 years or under, or ≥0.12 and ≤0.675 if over 65 years. MASLD was defined in the iLFT algorithm as elevated ALT and/or GGT, alcohol intake <14 units/week, presence of at least one feature of the metabolic syndrome, and negative tests for the other causes of CLD (for example, viral hepatitis). ARLD was defined as elevated ALT and/or GGT, alcohol intake ≥14 units/week, absence of metabolic syndrome, and negative tests for other aetiologies. Combined metabolic-alcohol related liver disease (Met-ALD) was defined as an elevated ALT and/or GGT, alcohol intake ≥14 units/week, presence of metabolic syndrome, and negative tests for other aetiologies.

Study inclusion and exclusion criteria

All patients with an ELF measurement as part of the iLFT pathway were included in the study. This included individuals who had ELF measured retrospectively as part of the initial pilot study or from a subsequent waiting list initiative, and those who had ELF measured in real-time between July 2020 and May 2021. Following the pilot, a Delphi approach was used to decide the optimal ELF cut-off value for the iLFT pathway. A 'higher risk' threshold of ≥9.8 was chosen in line with the manufacturer's guidelines and based on previous studies.[22–24] As such, the iLFT algorithm recommended referral for all individuals with an ELF score ≥9.8, or with a high fibrosis estimate (irrespective of their ELF score). For individuals who were evaluated by the iLFT pathway multiple times, the earliest ELF measurement was used. Individuals were excluded from the study if the iLFT request and/or results were incomplete or if the ELF was added for a reason other than indeterminate FIB-4/NFS (such as patients referred to clinic despite low FIB-4/NFS, or platelet disorders which affect the utility of FIB-4). For the pilot study, ethical approval was granted by the East of Scotland Research Ethics Committee (19/ES/0002) and the Tayside Biorepository Tissue Access Committee (TR000529). Caldicott Guardian approval for use of patient identifiable information was granted by NHS Tayside for all included patients.

ELF analysis

Retrospective ELF score analysis was performed on aliquots of serum which had been stored at −20 °C, as is standard for iLFT immunology samples locally. Samples for ELF analysis remain stable at or below −20 °C for up to 12 months.[24] All ELF analysis was performed as per the manufacturer's recommendations using the Siemens Centaur XP Immunoassay system (until 20 April 2021) and subsequently using the Siemens Atellica IM analyser (both Siemens Healthcare Diagnostics) in the UKAS

accredited Blood Sciences Laboratory, NHS Tayside. The ELF score was calculated from individual HA, PIIINP, and TIMP-1 measurements using the appropriate formula on board the analyser. Standard daily quality control and regular external quality assurance practices were followed.

Follow-up

The unique Community Health Index (CHI) Number was used to undertake case note review for each patient. The aetiology of CLD was recorded from clinic letters where available, otherwise the iLFT-determined aetiology was used. The primary endpoints were diagnosis of cirrhosis (documented by a hepatology specialist based on all available evidence, including signs, symptoms, biochemistry, stiffness measurements and/or imaging), and liver-related morbidity, defined as an admission to hospital with an episode of decompensated liver disease (ascites, variceal bleeding, hepatic encephalopathy), or diagnosis of hepatocellular carcinoma (HCC). Secondary endpoints included liver-related mortality and all-cause mortality. For consistency, deaths were only classified as liver-related if liver disease was listed in Part 1 of the Medical Certificate of the Cause of Death (MCCD).

Statistical analysis

All baseline characteristics had non-normal distribution, with summary statistics presented as median and interquartile range. ELF data was categorised into high (≥9.8) and low/moderate (<9.8) values, as described above, and analysed against patient outcomes using Chi-Square tests. As all baseline characteristics were non-parametric, Mann–Whitney *U* tests were used to compare the continuous demographics data of individuals with a high or low/moderate ELF score, and Chi-square tests were used to compare sex-based differences and clinical characteristics. A p value <0.05 was considered statistically significant. Time-dependent area under the curve (AUC) analysis of ELF for patient outcomes was compared with the FIB-4 scores at 6, 12, 18, 24, and 30 months. Time-dependent AUC analysis also compared the FIB-4 and ELF scores for patient outcomes in the subset of patients with indeterminate FIB-4 scores. DeLong's test was used to compare the AUCs for FIB-4 and ELF at different time points. Time-dependent AUC analysis was not performed for NFS as this score has only been validated for use in patients with MASLD, and therefore only applied to a smaller subset of the study cohort. Very few hepatic events occurred in this group, preventing any meaningful interpretation. Survival analysis was performed using Kaplan–Meier curves. A Cox proportional hazards regression was used to adjust outcome risks for age, sex, and BMI, and stratified by presence of metabolic syndrome (aHR). Proportional hazard assumptions were met. Statistical analysis was performed using R version 4.3.1 (2023).

Results

Data were collected from 1384 individuals presenting iLFT requests between June 2018 and April 2021. Overall, 1327 individuals with ELF results were included for further analysis in the study, of which 609 had ELF analysed retrospectively (102 individuals from the initial pilot study, 507 from a waiting list initiative) and 718 had ELF analysed in real-time following addition to the iLFT pathway (Fig. 1). Overall, the median age of patients was 61 years, 61% were male and the median ELF score was 10.2 (Table 1). High ELF scores (≥9.8) were recorded in 64%,

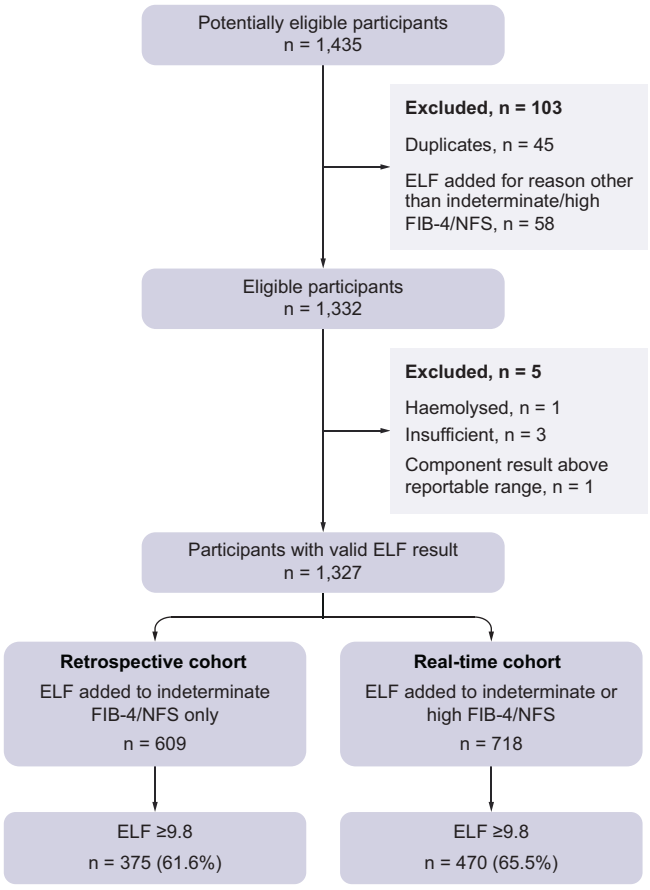

Fig. 1. Participant flow chart. ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4 index; NFS, non-alcoholic fatty liver disease Fibrosis Score.

with this group being older (64 years *vs*. 57 years, p ≤0.001) but with similar BMI values. The median time from ELF measurement to follow-up was 859 days (IQR, 750–1280 days). The use of ELF at a cut-off of 9.8 as a second line rule-out test reduced referrals in the indeterminate group by a further 40.7%, and by 34.4% overall (Fig. 2).

The ELF Score was highly sensitive for cirrhosis; overall 94.4% (n = 152/161) of individuals diagnosed with cirrhosis in the follow-up period had an ELF score ≥9.8 (p <0.001). Of the nine patients with ELF scores <9.8, referral would have been recommended for four because of the high FIB-4 score. The remaining five patients had ARLD (n = 4) and Met-ALD (n = 1). Sensitivities for the common aetiologies of cirrhosis ranged from 88.9% for ARLD to 100% for MASLD. For all rarer aetiologies ELF scores had 100% sensitivity (Fig. 3). At the higher threshold of 11.3 recommended by the manufacturer for ruling-in cirrhosis, sensitivities for the diagnosis of cirrhosis ranged from 61.0% for MASLD to 80.0% for Met-ALD (Fig. 3).

Using a threshold score of 9.8, the ELF score demonstrated negative predictive values (NPV) of ≥95.6% for all clinical endpoints including cirrhosis, liver-related admission, or mortality (Table 2). At this cut-off specificity ranged from 36.9% to 40.6%.

All-cause mortality within the follow-up period was 11.1%, of which 85.7% (n = 126/147) of patients had an ELF score ≥9.8 (p <0.001) (Table 3). The median time to death was 401 days (IQR 164–673 days). Liver-related mortality (metastatic HCC and sequelae of hepatic decompensation with resultant multi-organ

Table 1. Baseline characteristics by ELF score.

	Total group N = 1,327	ELF score ≥9.8 n = 845	ELF score <9.8 n = 482	*p* value
General				
Sex, n (%)				
Male	816 (61.5)	508 (60.1)	337 (69.9)	0.173
Female	511 (38.5)	337 (39.9)	174 (36.1)	
Age (years), median (IQR)	61 (54–69)	64 (57–73)	57 (51–62)	<0.001
Body mass index, median (IQR)	31 (27–35)	31 (27–35)	31 (27–35)	0.968
Biochemical				
AST, median (IQR)	44 (30–75)	51 (33–80)	37 (27–57)	<0.001
ALT, median (IQR)	65 (45–95)	66 (44–99)	64 (47 –88)	0.648
FIB-4 index, median (IQR)	1.72 (1.13–2.55)	2.06 (1.47–2.84)	1.23 (0.85–1.83)	<0.001
NAFLD fibrosis score, median (IQR)	−0.37 (−1.04 to 0.37)	−0.06 (−0.83 to 0.63)	-0.76 (−1.18 to 0.20)	<0.001
Clinical				
Metabolic syndrome present, n (%)	752 (56.7)	452 (53.5)	301 (62.4)	0.002
Alcohol intake >14 units weekly, n (%)	398 (30.0)	235 (27.8)	163 (33.8)	0.022
Hepatitis C				
Active infection, n (%)	10 (0.8)	9 (1.1)	1 (0.2)	0.084
Past infection, n (%)	7 (0.5)	3 (0.4)	4 (0.8)	0.196
Hepatitis B				
Active infection, n (%)	1 (0.1)	1 (0.1)	0 (0.0)	0.471

Groups were compared by the Mann–Whitney *U* test or Chi-square test, as appropriate. IQR, interquartile range. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4 index; NAFLD, non-alcoholic fatty liver disease.

failure) occurred in 1.9% of all individuals, of which 92.0% (n = 23/25) patients had a high ELF score ($p = 0.003$). The two individuals with ELF scores <9.8 both had high FIB-4 scores and thus referral would still have been recommended. The median time to death secondary to underlying liver disease was 271 days (IQR 100–622 days).

Fifty-two individuals (3.9%) were admitted to hospital because of an episode of liver disease decompensation, 86.5% (n = 45) of whom had a high ELF score (p <0.001). The seven individuals with a previous ELF score <9.8 who decompensated during the follow-up period all had ARLD (n = 6) or Met-ALD (n = 1). Referral would still have been recommended in three of these individuals owing to the high FIB-4 scores. Only one individual for whom referral was not recommended decompensated within 1 year. The median time to decompensation necessitating hospital admission was 198 days (IQR 35–661 days), and 15% (n = 8) of individuals died within 2 weeks of their initial episode of decompensation.

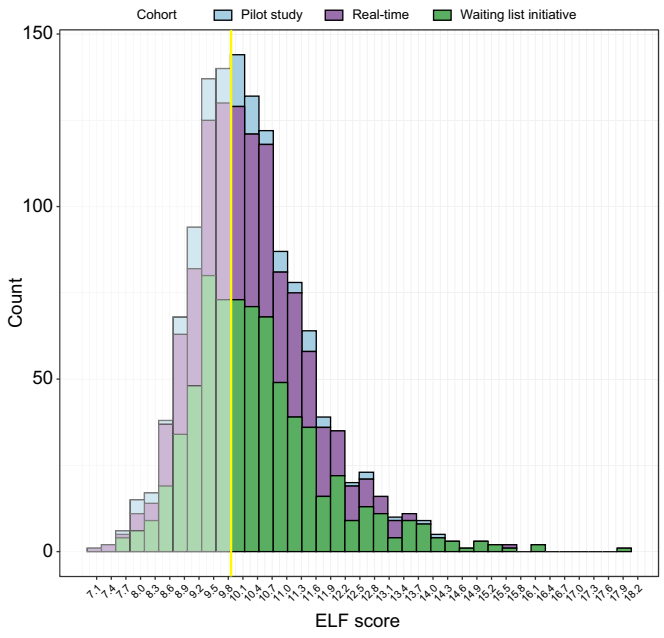

Fig. 2. ELF Score by cohort. ELF scores of patients stratified by cohort. The yellow line highlights the 9.8 cut-off value used in the iLFT pathway. Referral to secondary care is not recommended to all individuals with indeterminate fibrosis scores to the left of this line. ELF, Enhanced Liver Fibrosis.

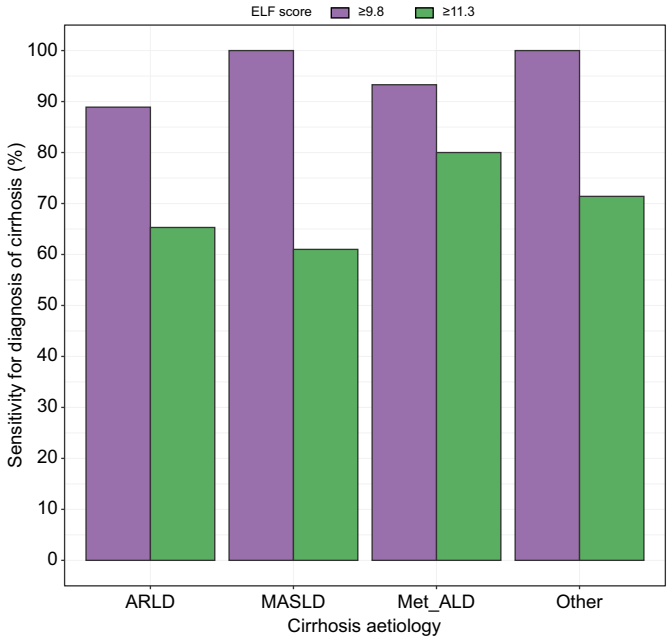

Fig. 3. Sensitivity of the ELF score for cirrhosis with different thresholds. Percentage of individuals with ELF scores ≥9.8 and ≥11.3 for different aetiologies of cirrhosis. Other includes: hepatitis C (n = 4), cryptogenic (n = 4), drug induced (n = 2), cardiac backpressure (n = 2), primary biliary cholangitis (n = 1) and hemochromatosis (n = 1). ARLD, alcohol-related liver disease; ELF, Enhanced Liver Fibrosis; MASLD, metabolic dysfunction associated steatotic liver disease; Met-ALD, combined metabolic-alcohol related liver disease.

Table 2. Characteristics of the ELF Test at a cut-off score of 9.8 for assessing different outcomes.

Outcome	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)
Cirrhosis diagnosis	94.4	40.6	98.1	18.0
Mortality	85.7	39.1	95.6	14.9
Liver-related mortality	92.0	36.9	99.6	2.7
Hospital admission for decompensated liver disease	86.5	37.3	98.5	5.3

ELF, Enhanced Liver Fibrosis.

Across the full cohort, time-dependent receiver operating characteristic (ROC) curve analysis demonstrated high AUC for ELF scores across all outcomes. The ELF score had a higher AUC than the FIB-4 in the short-term; ELF demonstrated higher AUC at 6 months for liver-related mortality (94.3% *vs.* 82.8%, $p = 0.008$) and all-cause mortality (88.1% *vs.* 80.1%, $p = 0.021$) (Fig. 4A, Table S1). By 12 months, the difference was still evident but no longer statistically significant ($p > 0.05$). Of note, FIB-4 had similar AUCs for admission because of hepatic decompensation until 18 months, where it started to outperform the ELF score.

For individuals with indeterminate FIB-4 scores, the secondary care referral decision is generally based on the ELF score result. Another time-dependent ROC curve analysis was performed on this subgroup of individuals (n = 629) using their paired FIB-4 and ELF results. Higher AUCs were observed for the ELF score compared to FIB-4 for all outcomes up to 2 years, although this observation was significant at only a few timepoints for all-cause mortality given the low overall numbers of events (all-cause mortality n = 66, liver-related mortality n = 7, hospital admission for decompensation n = 17) (Fig. 4B, Table S1).

With every unit increase in ELF score the risk of negative outcomes increased. A Cox proportional regression analysis was performed and adjusted for age, sex, and BMI, and stratified by presence of metabolic syndrome. Each unit change in the ELF score was associated with increased decompensated liver disease (aHR 2.215, 95% confidence interval [CI]: 1.934–2.537), liver-related mortality (aHR 2.024, 95% CI: 1.674–2.446) and all-cause mortality (aHR 1.862, 95% CI: 1.674–2.073).

Kaplan–Meier survival plots showed that the elevated risk for hepatic outcomes was driven by individuals with ELF scores of ≥13 (log rank test [Mantel-Cox] $p < 0.001$) (Fig. 5A and B). Survival plots for all-cause mortality by ELF score showed a graded relationship, whereby an increase in the ELF score correlated with increased mortality (Fig. 5C).

Fifty (3.8%) individuals had very elevated ELF scores of ≥13; of these, 80.0% (n = 40) received a clinical diagnosis of cirrhosis. Of the remaining 10 individuals, seven had died prior to being assessed in clinic (three had advanced malignancy, one was suspected cirrhosis and/or heart failure, three of unknown cause). Additionally, one individual was diagnosed with autoimmune hepatitis but fibrosis was absent on liver biopsy, one individual had significant heart failure with pulmonary hypertension and hepatic congestion, and one individual had hepatitis C with significant fibrosis (13 kPa on transient elastography). An ELF measurement ≥13 demonstrated 99.2% specificity and 25.5% specificity for clinical diagnosis of cirrhosis (NPV 91.2%, PPV 80.0%).

Within 90 days of ELF measurement, 26.0% (n = 13) of individuals with an ELF score ≥13 had required hospital admission for decompensation of their liver disease, all of whom were diagnosed with ARLD. Twelve of these individuals presented acutely jaundiced, consistent with alcoholic hepatitis, whilst the remaining individual presented with severe encephalopathy and melaena. Throughout the follow-up period, 23 individuals (46.0%) were admitted for one (or more) episode(s) of decompensation, of whom 22 were diagnosed with ARLD and one with metabolic dysfunction-associated steatohepatitis. ELF scores ≥13 were highly specific for decompensation (98.0%), with a sensitivity of 43.4%. Of those who experienced an episode of decompensation, 69.6% (n = 16) subsequently died, with a median time from hospital admission to death of 66 days (IQR 34–196 days).

Overall, 29/50 (58.0%) individuals with an ELF score ≥13 died within the follow-up period, with 12 of these deaths recorded as being directly related to liver disease (specificity for liver-related mortality 97.2%, sensitivity 48.0%). The 1-year mortality in patients in the ELF score ≥13 group was 38.0% (n = 19) for all-causes, and 16.0% (n = 8) for hepatic causes. Diagnostic accuracy data for ELF ≥13 is presented in Table S2.

Discussion

The decision to integrate the ELF test into iLFT as a second-line rule-out test for advanced fibrosis was made owing to the demand for liver clinic appointments exceeding available capacity. This was exacerbated by the COVID-19 pandemic, when it became essential to reduce the overall number of secondary-care referrals and prioritise high-risk patients.

iLFT aids detection of liver disease by ensuring all patients with abnormal LFTs are investigated in line with national guidelines[25]; it is an automated system which cascades tests using the primary samples (reducing the need for further venepuncture) and does not require intervention from the primary care physician until the diagnostic/management plan is returned to them. We therefore wished to add a second-line test which could easily be incorporated into the existing pathway. There is a myriad of non-invasive tests for fibrosis assessment described in the literature, which are both biomarker- and imaging-based. Many of the biomarker-based tests are intended for use in

Table 3. Negative outcomes stratified by the ELF score.

Outcome	ELF score ≥9.8, % (n)	ELF score <9.8, % (n)	*p* value
Cirrhosis diagnosis	94.4 (152)	5.6 (9)	<0.001
All-cause mortality	85.7 (126)	14.3 (21)	<0.001
Liver-related mortality	92.0 (23)	7.0 (2)	0.002
Hospital admission for decompensated liver disease*	86.5 (45)	13.5 (7)	<0.001

* Admission reasons included hepatic encephalopathy (n = 11), ascites (n = 26), and upper gastrointestinal bleeding (n = 9). Groups were compared by Chi-Square tests. ELF, enhanced liver fibrosis.

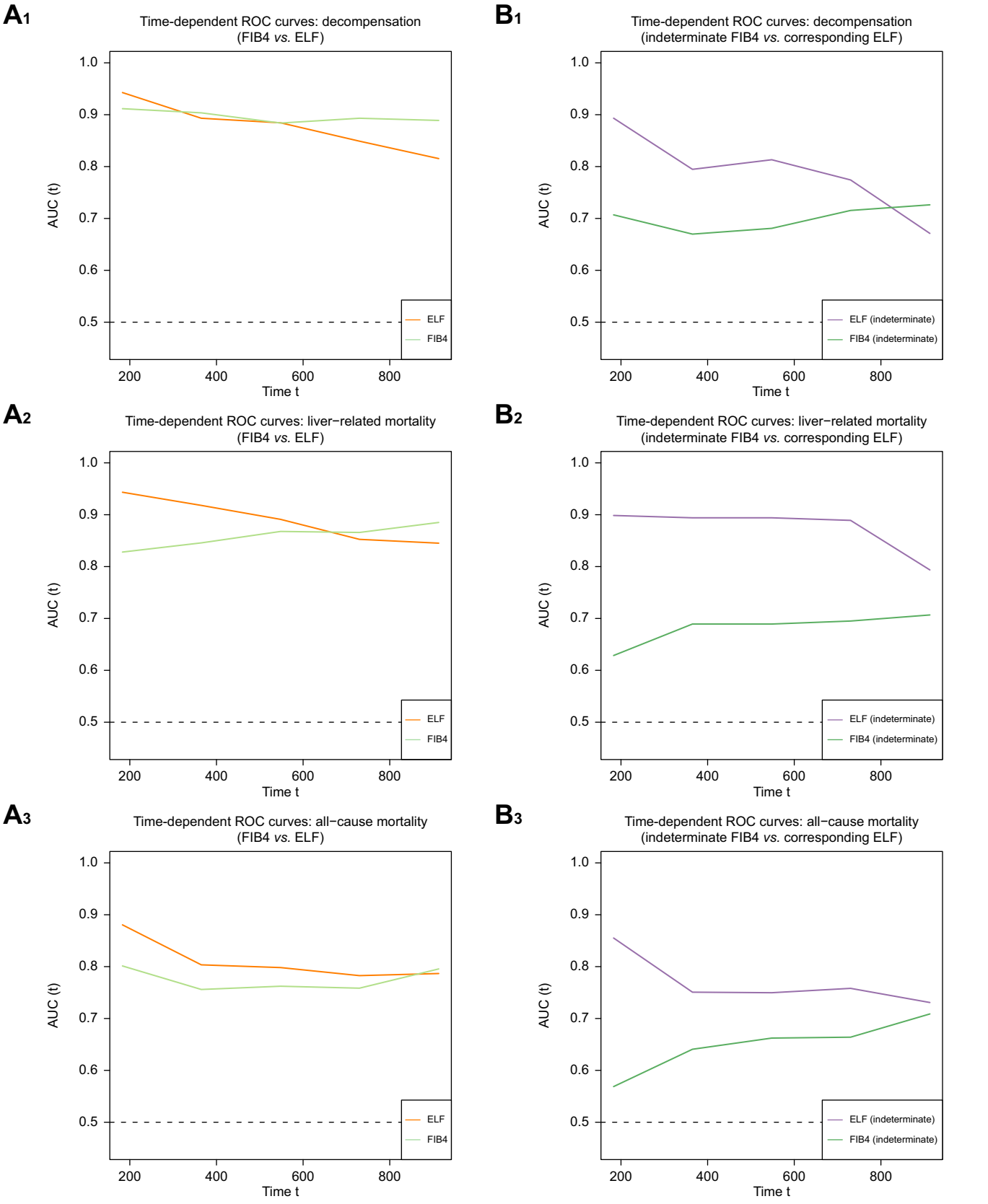

Fig. 4. Time-dependent ROC curves. (A) Time-dependent ROC curves comparing FIB-4 and ELF measurements for the outcomes of hospital admission with decompensated liver disease (A1), liver-related mortality (A2) and all-cause mortality (A3). (B) Time-dependent ROC curves comparing the indeterminate FIB-4 scores with their corresponding ELF scores for the outcomes of hospital admission with decompensated liver disease (B1), liver-related mortality (B2) and all-cause mortality (B3). ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4 index; ROC, receiver operating characteristic.

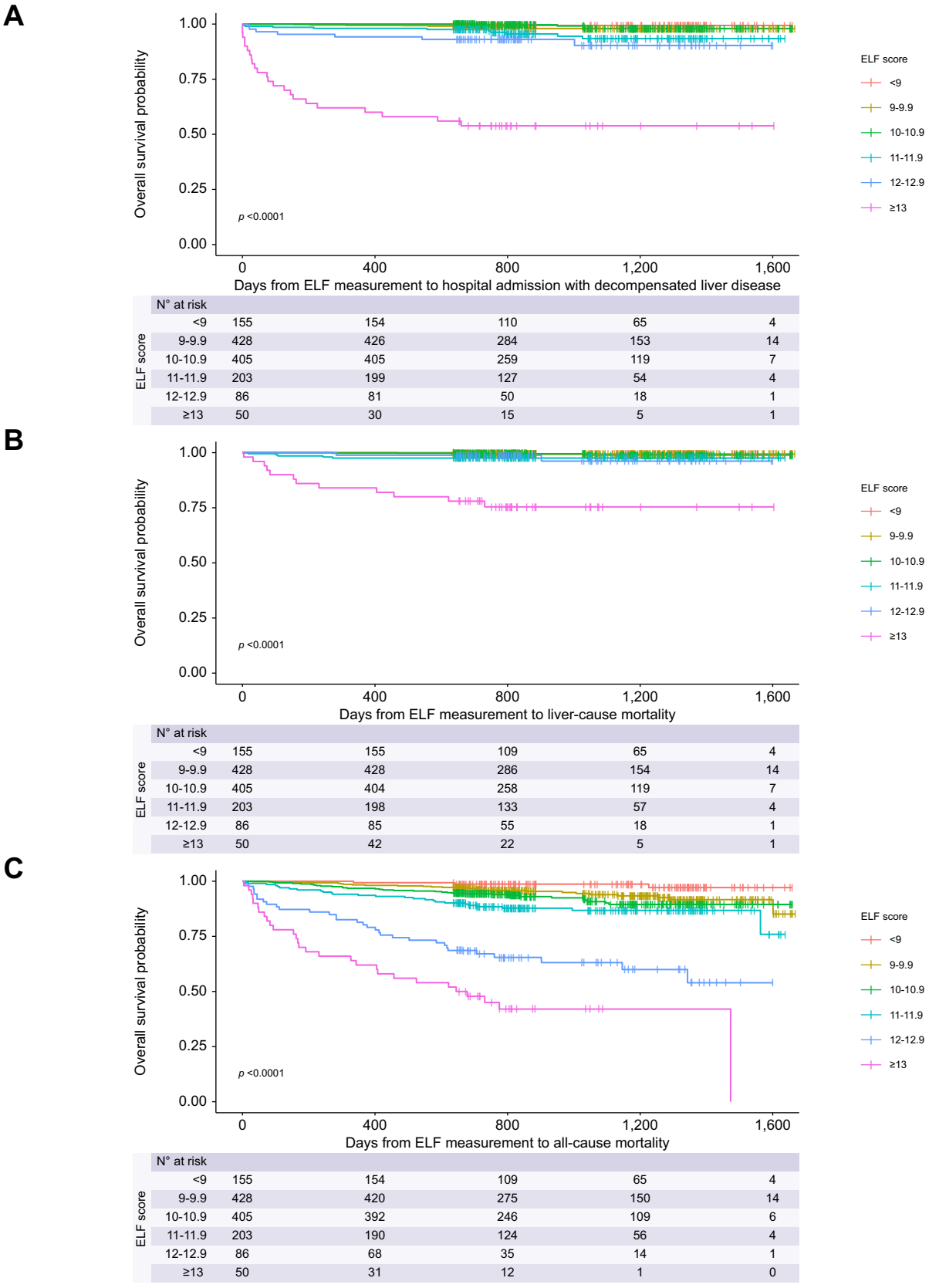

Fig. 5. Survival stratified by ELF scores. (A) Kaplan–Meier plots showing the cumulative incidence of hospital admission with decompensated liver disease from the initial ELF measurement; (B) Kaplan–Meier plots showing the cumulative incidence of liver-related mortality from the initial ELF measurement; (C) Kaplan–Meier graph showing the cumulative mortality from the time of initial ELF measurement. ELF, Enhanced Liver Fibrosis.

MASLD, with fewer tests validated across a range of aetiologies of CLD.[26,27] However, iLFT required a validated blood test which was available on our automated laboratory analysers (to allow for high throughput) and was suitable for use across many major causes of CLD (MASLD, ARLD, hepatitis B and C, autoimmune conditions) and the ELF was the only test which met these criteria. Recently, the LiverRisk score has been developed from a large population-based cohort and has been shown to provide fibrosis assessment and prognostic information. This score uses laboratory tests and clinical information which are mostly already available from the iLFT pathway (aspartate aminotransferase, ALT, GGT, platelet count, age, and sex) along with standard assays for glucose and cholesterol. The LiverRisk score may provide a cost-effective alternative to ELF, which is a proprietary assay, but to our knowledge no such comparison has yet been performed.[28] Another potential non-invasive test is the measurement of von Willebrand Factor levels as a marker for endothelial dysfunction and portal hypertension. Von Willebrand Factor, both alone and in combination with platelet count as the VITRO score, has been shown to predict clinical outcomes such as hepatic decompensation and liver-related mortality.[29–31] ELF and HA, one of its component tests, have been shown to have good discriminating power for the diagnosis of portal hypertension. Simbrunner *et al.* demonstrated a PPV of 98% for clinically-significant portal hypertension when the ELF score is ≥11.1.[32] This may explain the increased risk of liver-related outcomes with very high ELF score observed in our study.

In the iLFT pathway, indirect fibrosis scores, FIB-4 and NFS, reduce the number of recommended referrals from the iLFT pathway by approximately 70%, with the addition of ELF allowing us to reduce the remaining liver clinic referrals by over one-third. For all outcomes, time-dependent AUCs showed that ELF performed better than FIB-4, especially within the first year. Although not statistically significant (likely because of the small number of events), this observation was particularly apparent in the subset of patients for which ELF was introduced to help stratify, namely, those patients with indeterminate indirect fibrosis scores. This confirms the added value that the ELF score brings to the iLFT pathway. In addition to safely reducing liver-clinic referrals, the ELF measurement provides useful short-term prognostic information which is beneficial for prioritisation of higher risk patients.

The decision to use 9.8 as the ELF threshold for severe fibrosis and referral aligns with previous studies[22,23] and the manufacturer's guidelines.[24] The present study has confirmed our prediction that this is a safe and effective approach; an ELF score <9.8 is reassuring, with a NPV for receiving a clinical diagnosis of cirrhosis of 98.1%. This outperforms previously reported figures,[33] although this may be explained by a lower prevalence of disease given the patient cohort of 'suspected' liver disease rather than pre-established disease.[34] Whilst the 94.4% sensitivity seen at the 9.8 cut-off value is high, the 'second-line' nature of the ELF test within the iLFT pathway provides additional safety; all individuals with high FIB-4 fibrosis estimates will also be recommended for referral, regardless of their ELF score. This is particularly important in individuals with underlying ARLD, in whom we found that the ELF test was less sensitive for cirrhosis (89% compared with 94% for all aetiologies) and in whom it was also a poorer prognostic indicator, as discussed later. Additionally, the iLFT guidelines to General Practitioners recommends that fibrosis markers be repeated annually, with ELF repeated at 3 years. This aids assessment of the impact of recommended lifestyle changes and the need for subsequent referral, thereby acting as a further safety net. We showed that liver-related outcomes, including both morbidity and mortality, are more common in individuals with an ELF score ≥9.8 (p <0.01), highlighting the need for these individuals to be referred to specialist liver clinic services.

Although initially developed as a diagnostic tool there is increasing evidence for the use of the ELF test for prognostication.[16,21,35] Indeed, a study by Saarinen *et al.* showed the utility of the ELF test in predicting long-term liver-related outcomes in the general population.[35] Whilst this provides useful information for guiding treatment decisions, it is the short/medium-term risk which is often most immediately relevant in clinical practice and the prioritisation of specialist clinic appointments.

In our cohort, followed up over approximately 2.5 years, 87% of patients subsequently requiring hospital admission for liver disease decompensation (p <0.001) and 92% of the individuals who experienced liver-related mortality (p = 0.002) had an ELF score ≥9.8. Notably the outliers from this relationship were largely found to have underlying ARLD, suggesting that the utility of the ELF test as a prognostic indicator in ARLD is inferior to other aetiologies. Our findings are in contrast to a study by Connoley *et al.*, which found that the ELF test maintained its predictive performance for patients with ARLD.[33] The decompensation rate was high in our study as 3.9% of the cohort were admitted to hospital because of hepatic encephalopathy, ascites, alcoholic hepatitis, or variceal bleeding within the follow-up period, and almost all of these patients had underlying ARLD. One potential explanation for this is that the follow-up period occurred during the COVID-19 pandemic, which was associated with reduced diagnosis and monitoring of CLD, and increased alcohol consumption.[36,37] Additionally, although against the established guidelines, some primary care physicians may have requested iLFT for patients already known to have CLD.

Our study corroborated findings from Parkes *et al.* who showed that the risk of liver-related outcomes double with every unit change in ELF.[21] Furthermore, we showed that the prognostic utility of the ELF test was not limited to hepatic outcomes: over 85% of individuals who died from any cause had an ELF score ≥9.8 and the risk of death increased by 86% per unit change in the ELF score. Whilst the association between ELF score and risk of all-cause mortality has already been recognised,[21] the underlying mechanism for this remains unknown. In the context of the primary care-based iLFT pathway, ELF could provide a helpful indication to the clinician of patients at risk of death from any cause over at least the next year.

Importantly, as highlighted in the survival curves (Fig. 5), the association between a 'high' ELF score and poor outcomes appears to be driven largely by individuals with extremely elevated ELF scores of ≥13. These individuals were at imminent risk as over 25% decompensated within just 90 days of their initial ELF measurement as part of their primary care-based iLFT work-up for suspected liver disease, and almost 50% decompensated within the follow-up time. Post-decompensation the risk escalated further, with 70% deaths occurring at a median of 66 days from hospital admission. Additionally, these individuals have a high baseline risk with 38% 1-year mortality. At present, this study is unique at considering specifically the ELF score ≥13 demographic; the cut-off for a 'high' score is typically much lower.[35] Given the considerable increase in risk that occurs in this group, we recommend the implementation of an urgent referral system for these individuals, aiming for them to be seen

in clinic within 2 weeks of measurement. Whilst many of these individuals will have already progressed to advanced cirrhosis, clinic measures may help to reduce the progression to decompensation. Additionally, this strategy ensures that the individual is known to specialist hepatology services, enabling more coordinated care during any subsequent hospital admissions. In our cohort this 'extremely high risk' group comprised less than 5% of the total measurements, making it practical to implement.

The strengths of our study lie in the substantial sample size and considerable follow-up time of a minimum of 636 days from ELF measurement. Additionally, these were 'real-world' patients, with multi-aetiology disease, allowing for assessment of ELF's utility as a diagnostic and prognostic tool in everyday clinical practice. Fibrosis and cirrhosis are increasingly diagnosed based on composite evidence from signs, symptoms and non-invasive tests (biochemical, stiffness measurement and imaging) rather than liver biopsy.[38] Our cirrhosis outcome was the documented diagnosis obtained by a hepatology specialist based on all the available evidence, which reflects local real-life practice, despite the inherent limitations of this, including lack of standardisation and inter-clinician variability. Although data on interobserver variability was not available all clinicians worked within the same department and routinely discuss complex cases at multidisciplinary team meetings, minimising the impact of variability. Finally, some clinical information (cause of death, in particular) was not available for all individuals and, whilst all individuals were followed-up electronically, some information may have been lost if, for example, they moved out of area.

In conclusion, this study revealed that the ELF test was an important addition to an early diagnosis pathway, providing a safe and effective method to reduce the number of specialist referrals required. Although the ELF test has been validated for use in alcohol-related liver disease, our results have shown that it may be less effective at detecting advanced disease, and subsequent risk of hepatic outcomes, than other liver disease aetiologies. Within the iLFT pathway, its potential inferiority has been mitigated by the additional use of indirect fibrosis scores, but the results of this study highlight the need to consider the entirety of the available results when making patient management decisions. Whilst its utility as a second line rule-out test in the iLFT pathway is clear, our study also showed its added benefit as a prognostic tool, highlighting a previously unrecognised group of 'extremely high risk' individuals, namely, those with ELF scores ≥13. These individuals should be considered at immediate risk of harm and would benefit from expedited secondary care review and management. Further work will be undertaken to assess the effect of early review of these high-risk patients, and to consider the application of the LiverRisk score in the iLFT pathway.

Abbreviations

aHR, adjusted Hazard Ratio; ALT, alanine aminotransferase; ARLD, alcohol-related liver disease; AUC, area under the curve; CHI, Community Health Index; CI, confidence interval; CLD, chronic liver disease; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4 index; GGT, gamma-glutamyltransferase; HA, hyaluronic acid; HCC, hepatocellular carcinoma; iLFT, intelligent Liver Function Testing; LFTs, Liver function tests; MASLD, metabolic-associated steatotic liver disease; MCCD, Medical Certificate of the Cause of Death; Met-ALD, metabolic-alcohol related liver disease; NHS, National Health Service; NPV, negative predictive values; PIIINP, procollagen III N-terminal peptide; TIMP-1, Tissue inhibitor of matrix metalloproteinase-1.

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Conflicts of interest

ED: educational grants and honoraria from Abbott and Siemens. The other authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Acquisition of data: ED, IM, JN, LG, MP. Administrative, technical, or material support: ED, JN. Analysis and interpretation of data: ED, IM, JFD, JN, MP. Critical revision of the manuscript for important intellectual content: ED, JFD, MM. Drafting of the manuscript: ED, IM, JN, LG, MP. Statistical analysis: MP. Study concept and design: ED, IM, JFD, JN, MM, MP. Study supervision: ED, JFD.

Data availability statement

Patient data from this study is confidential and stored in the iLFT database. Whilst it cannot be shared in a publicly-available database, please contact the authors if you would like limited access to the data or any further information.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101062.

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Author names in bold designate shared co-first authorship

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