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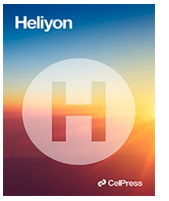

Improving detection of cystic fibrosis related liver disease using liver fibrosis assessment tools☆

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ABSTRACT

Background & aims: Cystic Fibrosis related liver disease (CFLD) is the 3rd largest cause of death in Cystic Fibrosis (CF). As advances in pulmonary therapies have increased life-expectancy, CFLD has become more prevalent. Current guidelines may underdiagnose liver fibrosis, particularly in its early stages. Newer modalities for the assessment of fibrosis may provide a more accurate assessment. FibroScan is validated in assessing fibrosis for several aetiologies including alcohol and fatty liver, the CFLD cohort have an entirely different phenotype so the cut off values are not transferrable. We appraised fibrosis assessment tools to improve diagnosis of CFLD.
Methods: A prospective cohort (n = 114) of patients from the Manchester Adult Cystic Fibrosis Centre, UK were identified at annual assessment. Demographic data including co-morbidity, *CFTR* genotyping, biochemistry and imaging were used alongside current guidelines to group into CFLD and CF without evidence of liver disease. All patients underwent liver stiffness measurement (LSM) and assessment of serum-based fibrosis biomarker panels. A new diagnostic criterion was created and validated in a second, independent cohort.
Results: 12 of 114 patient classified as CFLD according to the European Cystic Fibrosis Society best practice guidelines. No specific risk factors for development of CFLD were identified. Liver enzymes were elevated in patients with CFLD. Serum biomarker panels did not improve diagnostic criteria. LSM accurately predicted CFLD. A new diagnostic criterion was proposed and validated in a separate cohort, accurately predicating CFLD in 10 of 32 patients (31 %).
Conclusion: We present a cohort of patients with CF assessed for the presence of liver fibrosis using blood biomarkers and LSM based platforms. We propose a new, simplified diagnostic criteria, capable of accurately predicting liver disease in patients with CF.
Clinical trials number: NCT04277819

☆ All participants in this study gave informed consent. Ethical approval was granted from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) as well as the North West – Greater Manchester West Research Ethics Committee (reference 18/NW/0827).

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1. Introduction

Advances in nutritional and respiratory management of Cystic Fibrosis (CF) have improved survival in successive generations of people with CF (PwCF). However, there has been a lack of similar improvements for patients with cystic fibrosis related liver disease (CFLD), which is becoming more prevalent [1].

CFLD is the 3rd leading cause of death accounting for 2.5–5% of overall CF mortality [2,3]. Historical post-mortem studies highlighted the propensity of CF to affect the liver with more than 70 % of PwCF showing evidence of focal biliary cirrhosis [4]. CFLD is most likely a complex, multi-faceted disease with multiple causative pathologies, including biliary fibrosis, obliterative portal venopathy and nodular regenerative hyperplasia [5,6]. These can be simultaneously active but their contribution to disease may vary between individuals and over time in the same person.

Conventionally, CFLD is believed to develop during childhood. However, recent studies demonstrate that incidence of CFLD continues linearly, at least into early adulthood, highlighting the need for continued screening for CFLD in PwCF [1,7]. Over 30 % of PwCF demonstrated presence of CFLD by the age of 25 years [1]. Contrary to other complications of CF, the incidence of cirrhosis is increasing [8].

Current guidelines for diagnosis of CFLD may not be reliable for early disease [9,10]. Liver function tests (LFTs) fluctuate and correlate poorly with histology [9]. Whilst ultrasound (USS) is helpful for detecting steatosis and portal hypertension (PHT), sensitivity for detection of fibrosis is poor [11,12]. The diagnostic gold-standard for the majority of liver diseases is liver biopsy. However this invasive procedure has poor diagnostic reliability in CFLD due to the focal nature of disease [13]. Dual-pass liver biopsy may improve reliability, but validation is limited as relatively small number of patients undergo biopsy [13,14].

Non-invasive tests offer the potential to predict presence of disease. Fibrosis tests aspartate aminotransferase (AST)-to-platelet-ratio-index (APRI), Fibrosis-4 (FIB4) and Gamma-GT (GGT)-to-platelet-ratio (GPR) and may assist the diagnosis of fibrosis and PHT in CFLD [15–19]. However, they require further validation. Liver stiffness measurement (LSM) is increasingly used as a surrogate for liver fibrosis. The commonest modalities being FibroScan Transient Elastography (TE) and Acoustic Radiation Force Impulse (ARFI). However, PwCF are a different phenotype, they are often younger and have a lower BMI than alcohol related or fatty liver disease that TE is validated in. Therefore, current diagnostic values cannot be applied to the CFLD cohort. Utility of LSM for detection of CFLD has been the subject of several studies [16,17,20,21]. Promisingly, LSM by TE in CFLD, has been shown to correlate with biochemical and USS evidence of CFLD [15,20,22,23]. However, there has been no consensus agreement on a diagnostic value in PwCF [24].

Improved diagnostic tools are needed to detect CLFD. In this study we assess the diagnostic ability of current diagnostic guidelines and identify potential risk factors for developing CFLD. We evaluate the role of LSM and liver fibrosis panels, establishing potential diagnostic values and criteria in CFLD.

2. Patients and methods

2.1. Patients

A cohort of adult patients with genetically confirmed CF, were recruited from the Manchester Adult Cystic Fibrosis Centre (MACFC), between September 2018 and March 2020. A second, cohort from the Edinburgh Cystic Fibrosis Unit was used for validation. The study was approved by the UK Health Research Authority (HRA) after Research Ethics Committee (REC) review (study identifier: 18/NW/0827) and listed on clinicaltrials.gov.

Clinically stable patients were identified and recruited at their out-patient annual review. Sequential recruitment avoided bias by genotype/phenotype, bacterial colonisation or acute illness. Demographic data collected included: age, genotype, gender, body mass index (BMI), lung function by FEV_1 (forced expiratory volume in the first second). CF related co-morbidities were recorded, including: previous history of meconium ileus, exocrine pancreatic insufficiency, previous or current enteral feed, diabetes mellitus (including impaired oral glucose tolerance test) and organ transplantation.

2.2. CFLD definition

Data was analysed and compared to best practice guidelines (hereafter called “Current Criteria”) [9]. Briefly, at least two of; abnormal physical exam, LFTs, USS or liver biopsy are required for a diagnosis of CFLD.

2.3. Markers of liver fibrosis

Normal values for LFTs were based on assay cut-offs defined by Manchester University NHS Foundation Trust hospital’s laboratory. Non-invasive fibrosis scores were calculated including: APRI, FIB4, GPR and AST-to-ALT ratio (AAR) in all patients. Additionally, we compared alkaline phosphatase (ALP) and LSM measured with FibroScan™ (Echosens, Paris, France).

2.4. Liver stiffness measurement

All patients underwent a standard abdominal examination and LSM, done by a single certified operator to avoid any intra-operator discrepancy. Readings were taken with the patient supine and right arm behind their head, from a position in an intercostal space, on

the mid-axillary line around the level of the xiphisternum. For a scan to be valid, ten readings were required, with an IQR/Med (Interquartile range/median value) less than 30 % to ensure accuracy. Laboratory tests, BMI and FEV_1 were taken at enrolment. As not all patients undergo annual ultrasound scan, the most recent result was used (within 6 months).

2.5. Statistical analysis

Statistical analysis was done using GraphPad Prism version 8. Baseline demographic data is presented as median and IQR. To compare categorical data, two-sided Fishers-Exact test and Mann-Whitney test were used. Comparison of blood test results and serum markers of fibrosis to LSM was performed via Spearman's correlation co-efficient and Mann-Whitney test. Comparison of transient elastography was performed using *t*-test with Welch correction. Area under the ROC curve (AUROC) was analysed from LSMs. Statistical significance was considered if $p < 0.05$.

3. Results

3.1. Study population

119 PwCF were sequentially enrolled from MACFC. 114 (96 %) patients successfully underwent LSM. 4 (3 %) patients declined FibroScan and 1 test failed.

Patient characteristics are summarised in Table 1. Over the course of this study, 6 patients died at a mean age of 36 years (range 22–58 years). There were no significant characteristic differences between groups for risk factors for CFLD or severity of CF (Table 1).

3.2. Current diagnostic criteria

Using Current Criteria for CFLD 12 (11 %) patients were diagnosed with CFLD (Table 1). There was no significant difference in age, gender or CF genotype between groups. Similarly, there was no difference in co-morbidities, BMI, FEV_1 or previous organ transplantation. 2 of the 6 patients that died during the study period had CFLD, as defined by Current Criteria.

Pairwise comparison of blood results from those diagnosed with and without CFLD based on Current Criteria is summarised in Table 1. The median ALP for patients defined as CFLD was higher (145 U/L (127–222) vs 113 (89–133) U/L $p = 0.0032$). Greater than a third (34.5 %) had an ALP above the upper limit of normal (ULN). Furthermore, patients with CFLD defined by Current Criteria had higher levels of ALT, AST and GGT (Table 1). ALP and GGT above laboratory normal reference range successfully identified all patients with Current Criteria defined CFLD. Abnormal AST and ALT offered no additional diagnostic utility.

The CFLD group had a lower serum albumin but there was no difference in bilirubin or Prothrombin Time (PT) values to suggest liver synthetic dysfunction (Table 1). CRP was also non-discriminatory to suggest a low albumin secondary to inflammation.

Table 1
Patient characteristics of Manchester experimental cohort using Current Diagnostic Criteria.

Characteristic	All patients (n=114)	CFLD (n=12)	No CFLD (n=102)	*Sig.*
Male	63 (55%)	7 (58%)	56 (55%)	0.99
Age (years)	28 (22-39)	30.5 (24-40.8)	28 (22-39.3)	0.59
Phe508del homozygote	55 (48%)	7 (58%)	48 (47%)	0.99
Phe508del heterozygote	41 (36%)	4 (33%)	37 (36%)	0.99
CF-related diabetes mellitus	58 (51%)	9 (67%)	49 ($8%)	0.13
Exocrine pancreatic insufficiency	96 (84%)	11 (92%)	85 (84%)	0.69
FEV_1 (%)	56 (42.3-71)	55 (35.3-71)	56.5 (43.7-71.4)	0.86
BMI (kg/m^2)	21.7 (19.6-24.9)	23.6 (18-26.8)	21.4 (19.8-24)	0.70
Enteral feeding	16 (14%)	1 (8%)	15 (15%)	0.69
History of meconium ileus	12 (11%)	2 (17%)	10 (10%)	0.62
Previous organ transplantation	5 (4%) (2 lung, 2 liver, 1 kidney)	1 (8%) (lung)	4 (4%) (1 lung, 2 liver and 1 kidney)	0.45
Prescribed Ursodeoxycholic acid	37 (32%)	7 (58%)	30 (29%)	0.055
ALT (iU/L)	24 (16-35)	40.5 (20.8-66.8)	23 (16-32)	0.0185
AST (iU/L)	25 (21-32)	36 (25-43)	24 (20-31)	0.0051
ALP (iU/L)	116 (90-139)	145 (126-310)	113 (88.8-135.3)	0.0032
GGT (iU/L)	18 (13-27)	130 (42-210)	16 (12-24)	<0.0001
Bilirubin (μmol/L)	8 (6-11)	7 (6-10.5)	8 (6-12)	0.6455
Albumin (g/L)	39 (36-41)	35.5 (27-38.5)	39 (36-41)	0.0343
Platelet count (10^9/L)	280 (237-336)	232.5 (164-308)	284 (244-347)	0.0288
Prothrombin time PT (secs)	11.8 (11.1-12.4)	11.8 (11.2-12.1)	11.7 (11.1-12.4)	0.8956
CRP (mg/L)	4.5 (2-11)	4 (1-9)	4 (2-12.5)	0.2880
Abnormal Ultrasound	42 (37%)	12 (100%)	30 (29%)	0.393

3.3. Liver stiffness measurement as a diagnostic tool in CFLD

We analysed the diagnostic ability of LSM against best practice. CFLD group defined by Current Criteria had a higher median LSM compared to no CFLD group (8.5 (6.5–11.0) kPa vs 4.4 (3.8–5.4) kPa, $p = 0.002$) (Fig. 1 A). Amongst the total study population, 12 patients had evidence of portal hypertension (PHT) on their abdominal USS. These patients had significantly higher LSM compared to CF patients without PHT (8.9 kPa vs 4.4 kPa, $p < 0.0001$) (Fig. 1 E and F).

These data suggested LSM has the potential to be a stand-alone diagnostic tool for CFLD and portal hypertension. To assess its utility, an optimal LSM cut-off of 6.85 kPa was defined from our cohort to predict CFLD, using index of union methodology [25].

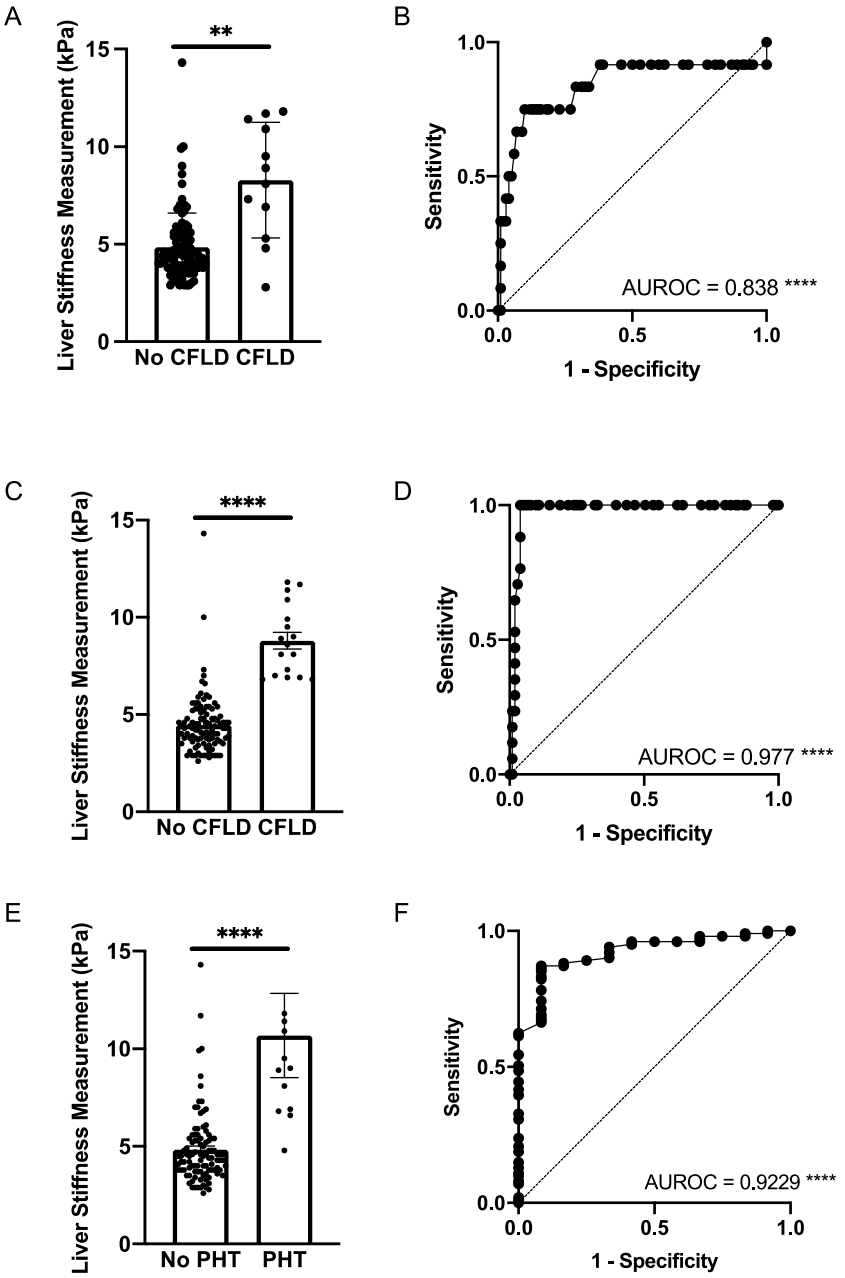

Fig. 1. Liver Stiffness Measurement for the diagnosis of CFLD. (A) Comparison of LSM between those with and without CFLD according to Current Criteria. (B) AUROC curve for FibroScan as a diagnostic tool for CFLD defined by Current Criteria. (C) Comparison of LSM between those with and without CFLD according to Proposed Criteria. (D) AUROC curve for LSM as a diagnostic tool for CFLD defined by Proposed Criteria. (E) LSM between those with and without PHT on USS. F) AUROC Curve for LSM of 7.15 kPa as a diagnostic tool for portal hypertension secondary to CFLD. Significance determined by two-tailed student's t-test with Welch correction; **P < 0.01.

Reassuringly, this was consistent with previous studies [23]. In practice (FibroScan hardware used gives values to 1 decimal point), therefore LSM ≥6.9 kPa suggested CFLD. Applying this diagnostic value to the total study cohort enabled diagnosis of CFLD with an AUROC of 0.838 (95 % CI 0.67–0.99; sensitivity 75 % and specificity 90 %) using Current Criteria as the gold standard (Fig. 1 A and B).

LSM can be used as a surrogate for PHT in patients with cirrhosis [26]. A cut-off of 6.85 kPa had a sensitivity of 77 % and specificity

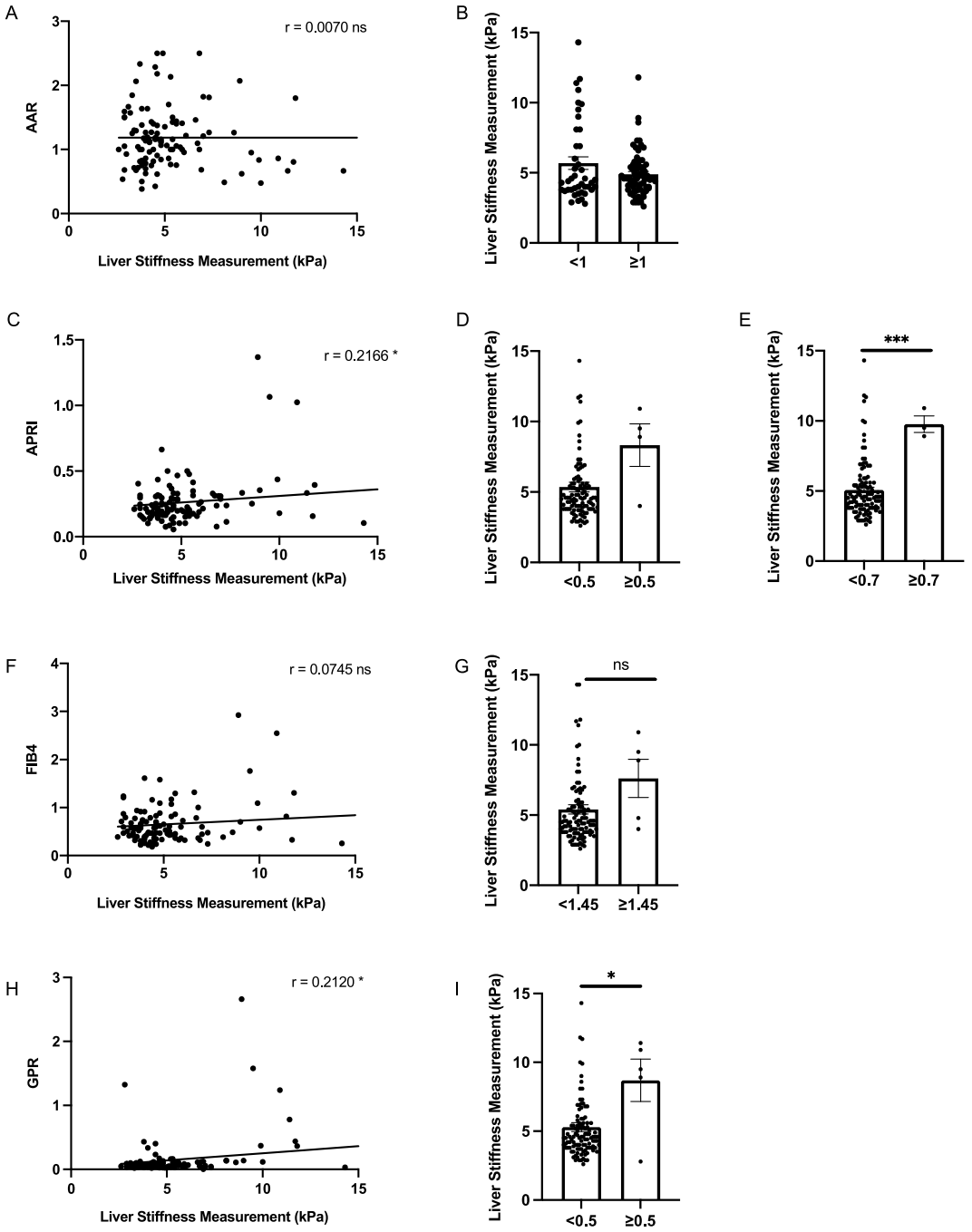

Fig. 2. Fibrosis scores compared to elastography in all study participants. Comparison of FibroScan results with fibrosis scores calculated from blood test result to identify underlying fibrosis in all study participants, including: (A–B) AAR: simple linear regression and comparison of elastography with AAR, cut off value of >1 (predicts presence of cirrhosis). (C–E) APRI: simple linear regression and comparison of elastography with APRI cut off values of <0.5 (absence of fibrosis) and >0.7 (presence of significant fibrosis). (F–G) FIB4: simple linear regression and comparison of elastography with FIB4, cut off value of <1.45 (exclude significant fibrosis). (H–I) GPR: simple linear regression and comparison of elastography with GPR, cut off value 0.5 (predicts significant fibrosis). r = Spearman's rank correlation coefficient. Significance determined by two-tailed student's; ns (non-significant). *p < 0.05, ***p < 0.005, ns = non-significant.

of 89 % for diagnosing PHT in CFLD (Fig. 3 A). However, a proportion of CF patients will have PHT without cirrhosis (non-cirrhotic PHT) [2]. They categorise as CFLD using Current Criteria, but do not necessarily have underlying liver disease and their management differs from patients with CFLD. USS cannot easily distinguish between these two groups. Identifying patients with PHT on imaging but an LSM <6.85 kPa was used to exclude 3 patients with non-cirrhotic PHT. Adjusting for these patients, an LSM value of 7.15 kPa was defined as predictive of PHT secondary to CFLD, with an AUROC of 0.923 (sensitivity 90 %, specificity 94 %) (Fig. 1F).

3.4. Serum scores of fibrosis for diagnosing CFLD

Non-invasive liver fibrosis panels are increasingly used to predict liver disease from multiple aetiologies. We investigated their potential in our exploratory cohort. Of the total study cohort, 61 % had an AAR >1. There was no difference in AAR between groups defined by Current Criteria (0.906 vs 1.122, $p = 0.15$). No correlation was seen between AAR and LSM (Fig. 2A) and no difference in LSM was seen between patients with an AAR >1 or < 1 (4.90 kPa vs 5.69 kPa, $p = 0.06$) (Fig. 2B).

As liver stiffness increased, APRI score increased (Fig. 2C). Mean APRI scores were higher in patients with CFLD compared to patients without CFLD (0.365 vs 0.212, $p = 0.01$). An APRI score of less than 0.5 could exclude significant liver fibrosis [18]. In our total study cohort, only 4 patients had an APRI score of >0.5 and there was no significant difference in LSM values between groups (8.3 kPa vs 5.3 kPa, $p = 0.09$) (Fig. 2 D). An APRI score greater than 0.7 can predict significant hepatic fibrosis [27]. An APRI of >0.7 was seen in just 3 patients, these had a higher LSM when compared to patients with an APRI of ≤0.7 (9.78 kPa vs 5.07 kPa $p = 0.0002$) (Fig. 2 E).

There was no correlation between LSM and FIB4 score (Fig. 2F). No patients had a FIB4 score >3.25, a previously defined threshold for cirrhosis [28]. A FIB4 score of <1.45 can exclude significant liver fibrosis, this did not correlate with LSM (5.41 kPa vs 7.62 kPa, $p = 0.16$) to exclude significant fibrosis (Fig. 2G).

GPR can potentially discriminate between advanced fibrosis in chronic liver diseases, including CF [19,29]. Here, GPR had similar diagnostic ability as APRI and demonstrated superiority to FIB4 in predicting advanced liver disease compared to LSM (Fig. 2H and I).

3.5. Proposed diagnostic criteria for CFLD

Based on the above findings we developed new diagnostic criteria for CFLD. These could be usefully and easily implemented into clinical practice. The Proposed Criteria require the following to be present to diagnose CFLD:

- Persistently abnormal ALP (above ULN) and/or persistently abnormal GGT (above ULN).
- AND an LSM >6.8 kPa.
- USS evidence of PHT and LSM>7.1 kPa, suggests there is likely to be PHT related to CFLD with liver fibrosis.

Applying the Proposed Criteria to our exploratory cohort (n = 114), 18 (16 %) patients were recognized as having CFLD. Based on Proposed Criteria, there was no difference in demographic data or CF related comorbidities between those diagnosed with and without CFLD. Only GGT and ALP discriminated between those with and without CFLD. 3 of the 6 CF patients that died had CFLD as defined by these Criteria.

Unsurprisingly, applying the Proposed Criteria, a higher LSM was seen in patients with CFLD compared to patients without CFLD (8.8 kPa vs 4.3 kPa, $p < 0.0001$). Patients without CFLD had fewer outlier LSM values (Fig. 1C). LSM accurately differentiated between groups (AUROC 0.98) (Fig. 1 D).

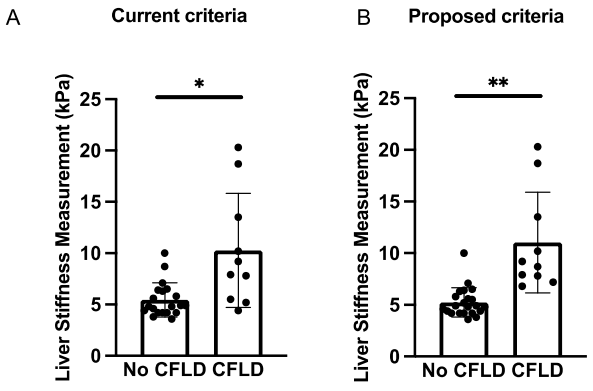

Fig. 3. Liver stiffness measurement in the diagnosis of CFLD in Edinburgh validation cohort. (A) Current and (B) Proposed Criteria. Box plot representing mean with SEM. *$p < 0.05$, **$p < 0.01$.

3.6. Validation of the Proposed Criteria

To validate the criteria, an independent cohort of patients was assessed from the Edinburgh Cystic Fibrosis Unit. Similar to the derivation cohort, all included patients had assessment of liver disease in CF annual review and a concurrent LSM. A total of 32 patients were assessed. Using our Proposed Criteria, 10 (31 %) patients were categorised as CFLD. This was identical to the number categorised as CFLD using Current Criteria, but not all the same individuals were in both groups. This is likely due to the vague current diagnostic criteria increasing the number of patients diagnosed that do not have significant CFLD. However further interpretation is limited due to the small cohort size. There was no difference in patient characteristics between patients with and without CFLD defined by the Proposed Criteria (Table 2).

In serum assays, transaminases and ALP were significantly different between groups (Table 2). There were significant differences in LSM between those with and without CFLD using both diagnostic criteria (Fig. 3 A and B). Our Proposed Criteria had a greater LSM difference between groups ($p < 0.01$).

4. Discussion

Liver disease in CF is a progressive phenomenon that continues to develop into adulthood [1,8] contributing significantly to morbidity and mortality in PwCF [23,30]. Identification of patients with liver disease has remained a challenge and a barrier to targeted therapy and specialist care [31]. We have examined the diagnostic ability of biochemical liver fibrosis panels and LSM. Other serum biomarkers of liver fibrosis are not currently used in clinical practice and were therefore unavailable for comparison in this study.

To date, there is no single reliable physical, biochemical or radiological screening tool available for the diagnosis of CFLD and there is no diagnostic gold-standard [32]. In other chronic liver conditions, liver biopsy is often regarded as the gold-standard diagnostic test. Though imperfect, it reproducibly acts as a benchmark against which non-invasive methods, criteria and panels can be compared. The patchy and focal nature of fibrotic disease in CFLD can make liver biopsy an unreliable reference standard [13]. Dual-pass liver biopsy has been used in small numbers in some studies and LSM may corelate with fibrosis stage [13,14]. Only limited conclusions can be drawn; these studies had small numbers and less than 5 individuals had histologically proven advanced fibrosis or cirrhosis. This underlines the difficulty in using this invasive procedure clinically and limits what we can extrapolate from concordance with biopsy. Our Proposed Criteria correlate with known risk factors of advanced disease in CF [8] and potentially improve categorisation of patients with CFLD.

LFTs are a key criterion of Current Criteria. ALT, AST, ALP and GGT are all statistically different between those with and without CFLD (Table 1). However, actual median values between groups demonstrated that ALT and AST, were minimally above laboratory ULN. Moreover, in our cohort, they did not aide discrimination of patients with or without CFLD above ALP and GGT. As such, in our proposed model, aminotransferases were not included, simplifying the criterion without sacrificing accuracy.

ALP is not part of the Current Criteria. Observed ALP levels were higher in those with CFLD when compared to non-CFLD patients (Table 1). On its own, ALP is non-specific, one third of all PwCF had a high ALP. Combining ALP and GGT our Proposed Criteria could identify CFLD in high-risk individuals in both cohorts.

LFTs do not correlate with stage of liver disease in most chronic liver diseases [28,33]. Hence the lack of concordance with LSM and LFTs in PwCF is unsurprising. Overall, LFTs are not reliable on their own to predict extent of liver fibrosis or stage of liver disease in CF.

Fibrosis scores have been developed and studied in liver disease of multiple aetiologies to determine the risk of underlying fibrosis [17,18,34–36]. In our study, APRI and GPR performed best at differentiating between those with and without CFLD, consistent with previous work [18,23]. APRI values correlated to LSM (Fig. 2C). However, previously suggested APRI cut-off values did not

Table 2
Characteristics of Edinburgh validation cohort population using Proposed Diagnostic Criteria.

Characteristic	All patients (n=32)	CFLD (n=10)	No CFLD (n=22)	*Sig.*
Male	23 (72%)	8 (80%)	15 (68%)	0.6808
Age (years)	30.5 (24.8-37)	29.5 (25.3-33.3)	31.5 (23.8-37)	0.7111
Genotype Phe508del Homozygote/heterozygote	26 (81%)	9 (90%)	17 (77%)	0.3855
CF-related diabetes mellitus	14 (44%)	2 (20%)	12 (55%)	0.0448*
Exocrine pancreatic insufficiency	31 (97%)	10 (100%)	21 (95%)	0.999
FEV_1 (%)	65.6 (52.3-73.3)	71.9 (43-77.3)	65 (34.6-71.2)	0.1502
BMI (kg/m^2)	22.5 (20.6-25.7)	23.4 (19.7-29.2)	22.3 (15.9-25.7)	0.5683
Prescribed Ursodeoxycholic acid	31 (97%)	10 (100%)	21 (95%)	0.999
ALT (iU/L)	28.5 (21-50.3)	76.5 (20-148)	24 (8-36.3)	0.0133*
AST (iU/L)	30 (23.8-46)	57.5 (30- 86)	23.5 (22.8-29.3)	<0.0001****
ALP (iU/L)	136 (110-194)	195 (156-267)	128 (101-193)	0.0103*
GGT (iU/L)	29 (19.3-70)	75 (25.3-116)	22 (13-47)	0.0510
Bilirubin (μmol/L)	9 (7-13.5)	10.5 (7.5-18)	8 (6.8-10)	0.1146
Albumin (g/L)	38 (35-39)	38 (35-39.8)	38 (35-39)	>0.999
Platelet count (10^9/L)	202 (159-270)	180 (146-292)	205 (184-260)	0.3610
Prothrombin time PT (secs)	13 (12-14)	13 (12-13)	12 (11.3-13.8)	0.9884
Abnormal Ultrasound	22 (69%)	10 (100%)	12 (56%)	0.905

satisfactorily exclude patients without CFLD (Fig. 2 D). Very few patients were categorised as high risk of advanced fibrosis/cirrhosis (APRI>0.7) making this test unlikely to be sensitive enough to be used independently (Fig. 2 E). GPR may potentially offer better diagnostic utility, especially at excluding significant disease (Fig. 2 I). However, GGT alone had a similar performance and for simplicity was preferred over GPR in our Proposed Criteria.

FIB4 did not correlate with LSM and was unable to predict advanced disease (Fig. 2F–G), unlike previous work in CFLD [23]. An AAR ratio of >1 has previously been used to identify cirrhosis in PBC, NAFLD and Hepatitis C [23,34]. Surprisingly, nearly two thirds of patients in our study had an AAR >1 with poor correlation with LSM (Fig. 2A–B). In summary, none of these fibrosis scores could be advocated as a reliable single diagnostic tool in CFLD.

USS is used commonly in clinical practice and has an important role in confirming presence of PHT, however it lacks diagnostic sensitivity in early liver fibrosis [37]. An abnormal USS as defined by Current Criteria is "evidence of liver involvement" [9]. Consequently, USS liver changes were the most frequently reported abnormality in patients diagnosed with CFLD (42 of 114 (36.8 %)). This imaging criterion is both subjective and operator dependent, it needs to be more specific to be useful in CFLD diagnosis. For example, fatty liver disease in CF may have a different prognosis. Moreover, it does not specify if ultrasonic evidence of PHT should be included or not. Considering these deficiencies, USS was removed from our proposed system, simplifying the criteria and reducing healthcare costs.

In CF, PHT can occur as a result of focal biliary cirrhosis, or non-cirrhotic PHT which is thought to be secondary to vascular endothelial injury [5,32,38]. LSM may be useful at differentiating between cirrhotic and non-cirrhotic PHT [39]. Using our cohort dataset, an LSM of >7.1 kPa is suggestive of the presence of PHT on the background of CFLD (Fig. 1E–F). However, given how close this is to 6.8 kPa, it is not a clinically useful tool to separate CFLD patients with and without PHT. An LSM of 7.1 kPa is low in comparison to values used to diagnose PHT in other causes of liver disease, potentially because CFLD-PHT results from a combination of factors [40].

In our study, LSM performed well for differentiating between patients with CFLD and without CFLD using both the Current and Proposed Criteria (Figs. 1 and 3). While previous studies have shown LSM to be a sensitive and specific tool in CFLD, the cut-off diagnostic values have differed [15,20,22]. In our study, ROC analysis determined a diagnostic cut off value of >6.85 kPa as being indicative of CFLD. This was essentially identical to previous studies [15,23].

Previous work has suggested that CFLD affects between 30 and 70 % of the CF population [1,4,9]. Using Current Criteria, only 11 % of our 114 patients were categorised with CFLD (Table 1). For comparison using our Proposed Criteria 16 % of our total cohort were diagnosed with CFLD. This increased to 31 % in our validation cohort. These figures in keeping with prevalence of CFLD in national datasets [1,8]. This is important as presently patients with CFLD could be missed.

A significant limitation in our study was the small patient cohort size, particularly in our validation cohort. This is a reflection on the CF population in general as they represent a small percentage of chronic liver disease. However, our sample sizes, including the validation cohort are comparable to those used in previous publications in CFLD.

Current diagnostic tools cannot reliably confirm or exclude CF related liver involvement and are unsatisfactory for both the diagnosis and surveillance of CFLD [10]. LSM is a readily available clinical tool, shown to have good diagnostic ability. Here we propose and validate a new, simplified criteria to diagnose CFLD, excluding ultrasound. Adapting existing CFLD guidelines using these criteria may improve diagnosis and reduce investigations for patients with CF.

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Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Jennifer A. Scott: Conceptualization, Investigation, Writing – original draft, Data curation, Formal analysis, Methodology. **Andrew M. Jones:** Conceptualization, Writing – review & editing. **Elliot Jokl:** Investigation. **Timothy Gordon-Walker:** Data curation. **Peter J. Barry:** Data curation. **Neil A. Hanley:** Conceptualization, Writing – review & editing. **Karen Piper Hanley:** Conceptualization, Writing – review & editing. **Varinder S. Athwal:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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