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Original Article

Non-invasive evaluation of steatosis and fibrosis in the liver in adults patients living with cystic fibrosis

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ABSTRACT

Background & aims: Cystic fibrosis hepatobiliary involvement is a heterogeneous and systemic entity. The primary objective was to determine the prevalence of steatosis, by magnetic resonance-proton density fat fraction (MR-PDFF), and liver fibrosis, by magnetic resonance elastography (MRE), in a cohort of adults with cystic fibrosis. The secondary objective was to determine the diagnostic yield of widely available non-invasive liver markers for steatosis and fibrosis, and vibration controlled transitional elastography (VCTE) releasing Control Attenuation Parameter (CAP) (dB/m) and stiffness (kPa), with the aim of proposing a diagnostic algorithm.

Methods: We conducted a cross-sectional study including 101 adult patients with cystic fibrosis seen in a multidisciplinary unit. The study encompassed a clinical evaluation, morpho-functional assessment, VCTE, non-invasive liver markers and MR-PDFF and MRE. Diagnostic accuracy was assessed using ROC curves and 2 × 2 tables.

Results: MR-PDFF detected hepatic steatosis in 18 of 101 (17.8 %) patients, while MRE detected significant liver fibrosis in 15 of 101 (14.9 %). The VCTE cut-off with the best diagnostic yield, determined by the Youden index, was 222 dB/m for the presence of steatosis (AUC 0.864 (95 % CI 0.768–0.961; $p < 0.001$) and the VCTE cut-off was 6.65 kPa for liver fibrosis (AUC 0.951(95 % CI 0.81–1; $p = 0.053$). A screening algorithm for hepatic steatosis was developed using the fatty liver index (FLI) and CAP, with a negative predictive value of 83.3 %. For liver fibrosis, it was outperformed by the Hepamet Fibrosis Score (HFS) and VCTE, with a negative predictive value of 100 %.

Conclusions: The prevalence of hepatic steatosis and liver fibrosis was 17.8 % and 14.9 %, respectively. VCTE alone or in combination with FLI for steatosis or HFS for fibrosis demonstrated high diagnostic accuracy. This approach effectively allows for the exclusion of steatosis and fibrosis, thereby reducing the need for MR-PDFF and MRE studies.

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator, hepatology and nutrition; NASPGHAN, North American society for paediatric gastroenterology, hepatology & nutrition; MR-PDFF, magnetic resonance quantification of liver proton density fat fraction; MRE, magnetic resonance elastography; AGA, American gastroenterological association; AASLD, American association for the study of liver diseases; SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CFRD, cystic fibrosis related diabetes; CFRPD, cystic fibrosis related prediabetes; CFRIG, cystic fibrosis related indeterminate glycemia; SGA, subjective global assessment; GLIM, global leadership initiative on malnutrition; HSI, hepatic steatosis index; FIB-4, fibrosis-4 index for liver fibrosis; NFS, NAFLD fibrosis score; APRI, AST to platelet ratio index; HFS, HepaMet fibrosis score; FLI, fatty liver index; CPRM, cholangiopancreatography; AAR, AST-to-ALT ratio; SPSS, statistical package for social science; OR, odds ratio; CI, confidence interval; VTCE-CAP, vibration-controlled transient elastography controlled attenuation parameter; PPV, predictive positive value; NPV, negative predictive value.

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1. Introduction

Cystic fibrosis (CF) is a rare autosomal recessive disease caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene, which encodes a cAMP-activated chloride channel that regulates exocrine mucus secretion in ductal systems such as those present in the tracheobronchial tree, pancreas, sweat glands, intestinal tract, intrahepatic bile ducts and reproductive organs [1,2,3]. More than 2000 associated mutations have been documented in CFTR2.org [4], the most frequent being the ΔF508 mutation. These mutations are divided into six classes according to the defect produced by the mutation [1]. In addition, there are other non-CFTR genetic components (gene modifiers) that contribute to variation in phenotype [5].

An inflammatory status, which is partly independent of infection [6,7], is a hallmark in this disease. Pulmonary involvement accounts for 90 % of mortality [8] and consists of chronic inflammatory pneumopathy, infection, atelectasis, hemoptysis and pneumothorax together with nasosinusal involvement. Other notable gastrointestinal complications include exocrine and endocrine pancreatic insufficiency. These can lead to malnutrition, which has been reported in 25–40 % of cases and is predictive of disease progression and survival [9]. As survival increases, new complications or changes in the presentation of known complications appear. One example is CF hepatobiliary involvement (CFHBI), which is currently well characterized in children but not in adults [10,11]. The current prevalence of liver disease in adults living with CF remains elusive and seems to be highly variable [10,12].

CFTR is located in the apical region of the biliary cell membrane. When its function is altered, there is a modification in biliary composition and excretion, which produces retention of toxins and consequent cell damage and inflammation. This can eventually lead to liver fibrosis and biliary cirrhosis [13–15]. Fibrosis progression seems to be associated with an increase in activated hepatic stellate cells [14] together with impaired enterohepatic circulation and ileal absorption of fatty acids [16]. However, the mechanisms of progression of the disease remain controversial beyond the interaction among biliary dysfunction, inflammation, and fibrosis. Indeed, fibrosis has been demonstrated in some liver explants, but in the absence of inflammation, dilated bile ducts or thickened bile [17].

The clinical spectrum of CFHBI is very wide. This has meant that until recently there have been no clear diagnostic criteria, which has hindered CFHBI research. In 2023, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) established standardized criteria for the classification of hepatobiliary manifestations in CF [18]. Prior to this, criteria proposed by Debray et al. [19] and Koh et al. [10] relied on a combination of physical, biochemical and radiological parameters [10,11,19]. However, the prevalence obtained with these methods varies.

The search for a reliable diagnostic test is limited by the poor usefulness of liver biopsy, the results of which have been shown to be inconsistent in CF due to sampling error and heterogeneous pathophysiology [11,20,21]. In this context, the role of liver proton density fat fraction (MR-PDFF) quantification and magnetic resonance elastography (MRE) as a diagnostic tool stands out, as they are considered by both the American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD) as the non-invasive gold standard technique for the diagnosis of steatosis and fibrosis in patients with steatotic liver disease (SLD) [22–24]. Historically, hepatic steatosis has been considered a benign finding related to malnutrition in children with CF and no longer relevant [20]. In recent studies, it has been associated more with elevated BMI and improved FEV1 parameters due to current therapies rather than malnutrition [25,26]. Metabolic dysfunction-associated steatotic liver disease (MASLD) in people with metabolic syndrome progresses to cirrhosis and even hepatocellular carcinoma, even from early stages. Given the above, some authors have called for reconsideration of hepatic steatosis as a benign finding [11], although further studies are needed to determine whether it may have the same evolution in CF as in metabolic syndrome.

The main objective of our study was to determine the prevalence of hepatic steatosis and liver fibrosis in a cohort of adults living with CF. The secondary objectives were to determine the diagnostic yield of non-invasive serum and imaging biomarkers of steatosis and fibrosis using magnetic resonance as the gold standard, and also, to elucidate factors related to a higher prevalence of steatosis and liver fibrosis.

2. Methods

2.1. Study design

A cross-sectional study was carried out involving 101 patients diagnosed with CF (mean age 33 (IQR 25–40.5), 43.6 % female) who met the following inclusion criteria: older than 18 years, CF diagnosed by genetic testing, active clinical follow-up, and ability to understand and sign the study protocol and informed consent. Patients were excluded if there were any circumstances that, in the opinion of the research team, interfered with the study protocol. This study was approved by the local Ethics Committee.

2.2. Study variables and complementary tests performed

- Clinical evaluation (age, presence of comorbidities, treatments, alcohol, drugs, and drug abuse screening).
- Evaluation of exocrine and endocrine pancreatic function: presence of exocrine pancreatic insufficiency (based on the use of lipase, significant steatorrhea or decreased faecal elastase levels, all assessed by a Digestive System specialist who is included in the multidisciplinary CF unit); and/or endocrine pancreatic insufficiency (basal glucose, glycated hemoglobin (HbA1c) and classification of patients into CF-related diabetes mellitus (CFRD), CF-related prediabetes (CFRPD) and CF-related indeterminate glycemia (CFRIG) (according to the Cystic Fibrosis-Related Diabetes Clinical Care Guidelines [27]. In addition to this classification, patients with CFRD, CFRPD or CFRIG were considered to have endocrine pancreatic insufficiency overall.
- Morpho-functional assessment: weight, height, waist circumference, brachial and tricipital circumference (the 10th percentiles (p10) for patients between 30 and 39 years of age were used as a reference). Subjective Global Assessment (SGA), Global Leadership Initiative on Malnutrition (GLIM) criteria [28], phase angle measurement, manual dynamometry (p10 of patients under 45 years of age was used as a reference), muscle ultrasound (performed on the anterior rectus femoris, in which the muscle area (cm^2) was assessed) and ultrasound of the abdominal adipose tissue (the preperitoneal adipose tissue was assessed). The GLIM criteria were used as a reference for the diagnosis of malnutrition. According to the GLIM criteria, a diagnosis of malnutrition requires meeting two conditions: one phenotypic and one etiological. The phenotypic criteria include (1) weight loss >5 % in the last 6 months or >10 % in more than 6 months, (2) BMI < 20 for individuals under 70 years and <22 for those over 70 years, and/or (3) reduced muscle mass as assessed by body composition measurement. The etiological criteria involve the presence of inflammation or reduced food intake or assimilation.
- Biochemical and serological parameters: blood count, visceral proteins (albumin, prealbumin, retinol-binding protein), renal function, ionogram (sodium, potassium, magnesium, phosphorus, plasma calcium), liver function (AST, ALT, GGT, alkaline phosphatase, LDH, total bilirubin), viral hepatitis serology, iron metabolism, C-reactive protein, vitamin profile (Vitamins A, E, D, B12).
- Evaluation of liver disease included determining the following predictive scores: hepatic steatosis index (HSI), fibrosis-4 index for liver fibrosis (FIB-4), NAFLD fibrosis score (NFS), AST to Platelet Ratio Index (APRI), Hepamet Fibrosis Score (HFS), fatty liver index (FLI).

In addition, for liver fibrosis, the results of the non-invasive markers (HFS, NFS and FIB-4) were combined according to whether the result was low, moderate or high risk. Determination of the AGA clinical care pathway [23]; transient elastography (FibroScan®, Echosens, France) (TE) (cut-off points used in liver assessment were CAP > 248 dB/m for steatosis and CAP > 280 dB/m for severe steatosis; and TE > 8 kPa for significant fibrosis and TE > 10 kPa for advanced fibrosis); and MRI by HepatoBilioPancreatic MRI with 3 complementary techniques: (Dixonquant® as PDFF measurement, cholangiopancreatography -CPRM-) and MRE. The cut-off points used in the MR were PDFF > 5 % for hepatic steatosis and in MRE < 2.65 kPa for excluding liver fibrosis, kPa = 2.65–3.14 for F1 (mild fibrosis), kPa = 3.14–3.53 for F2 (significant fibrosis), kPa = 3.53–4.45 kpa for F3 (advanced fibrosis) and kPa > 4.45 for F4 (cirrhosis) [29]. Advanced fibrosis was considered to be stages F3 and F4. Patients were also assessed for a diagnosis of CFHBI according to the Koh criteria. A diagnosis of CFHBI is confirmed if a patient has a pathological liver biopsy or evidence of cirrhosis or diffuse liver disease on imaging or has 2 or more of the following features: elevated transaminases on at least 2 occasions; imaging evidence of hepatomegaly, splenomegaly or portal hypertension; transient elastography abnormality; or persistent elevation of FIB-4, APRI or AST-to-ALT ratio (AAR).

2.3. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS®) version 29 for Windows (IBM Corporation. New York. USA). Descriptive analysis was performed obtaining the median and quartiles for quantitative variables, expressed as P50 (P25–P75) and frequency for qualitative variables, expressed as *n* (%). To evaluate the specificity and sensitivity of different tests for estimating the presence of liver steatosis and fibrosis, ROC curves and 2 × 2 tables were performed. A *p*-value of less than 0.05 was considered statistically significant. Results of the area under the curve from ROC curves were expressed as odds ratios (OR) with 95 % confidence intervals (CI). A univariate analysis was performed and subsequently a multivariate analysis including those variables with a result of $p < 0.1$ to study the predictive factors of steatosis and fibrosis. Results of the univariate and multivariate analysis were expressed as OR with 95 % CI.

3. Results

A cohort of 101 patients with CF was included in the study. The median age was 33 years (IQR 25–40.5) and 43.6 % were female. They were followed for more than 24 years. Genetic profiles showed that half had residual CFTR function. More than a third ($n = 29$) had a homozygous Δ508 mutation, two thirds ($n = 64$) had exocrine deficiency and nearly a half ($n = 44$) had pancreatic endocrine deficiency. According to the GLIM criteria, half of the cases were classified as malnourished (Table S1), although the SGA revealed a normal nutritional status in 93 (92 %) patients. The median BMI was 23.96 (22.6–25.5) kg/m^2 for men and 22.1 (19.4–23.9) kg/m^2 for women. In terms of treatment, one third (34 cases) were receiving ursodeoxycholic acid, one fifth (21 cases) were receiving insulin therapy, one half (51 cases) were receiving CFTR modulators and one half ($n = 50$ cases) were receiving oral nutritional supplements (Table S2). The proportion of patients with analytical abnormalities is shown in Table S3. Nineteen (18.8 %) patients met the Koh criteria for the diagnosis of CFHBI (Table 1).

3.1. Hepatic steatosis

MR-PDFF showed hepatic steatosis in 18 (17.8 %) patients. The diagnostic accuracy for hepatic steatosis was 0.864 (0.768–0.961) using VCTE-CAP; 0.594 (0.428–0.759) for FLI and 0.539 (0.386–0.692) for HSI (Fig. 1). The VCTE-CAP cut-off with the highest Youden index point was 222 dB/m.

Using the cut-off point of CAP 222 dB/m, hepatic steatosis was detected in 37 (36.6 %) patients. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CAP > 222dB/m value (FibroScan®) were 88.9 %, 74.6 %, 43.2 % and 96.8 %, respectively. The HSI score was 72.2 %, 32 %, 19.6 % and 83.3 %, respectively; and the FLI score was 41.1 %, 85.3 %, 36.8 % and 87.5 %. A two-step algorithm using FLI and CAP showed a sensitivity of 85.7 %, a specificity of 41.6 %, a PPV of 46.1 % and an NPV of 83.3 % (Fig. 2).

A sensitivity analysis was conducted in patients with minimal function mutations ($n = 27$) and in the group with CFRD ($n = 50$). In both subgroups, a two-step algorithm including FLI > 30 and VCTE-CAP > 222 dB/m reached 100 % NPV excluding steatosis. In CFRD, the sensitivity was 66 %, specificity 100 %, PPV 66 % and NPV 100 %. For minimal function mutations, sensitivity and NPV were 100 % and specificity and PPV were 60 %.

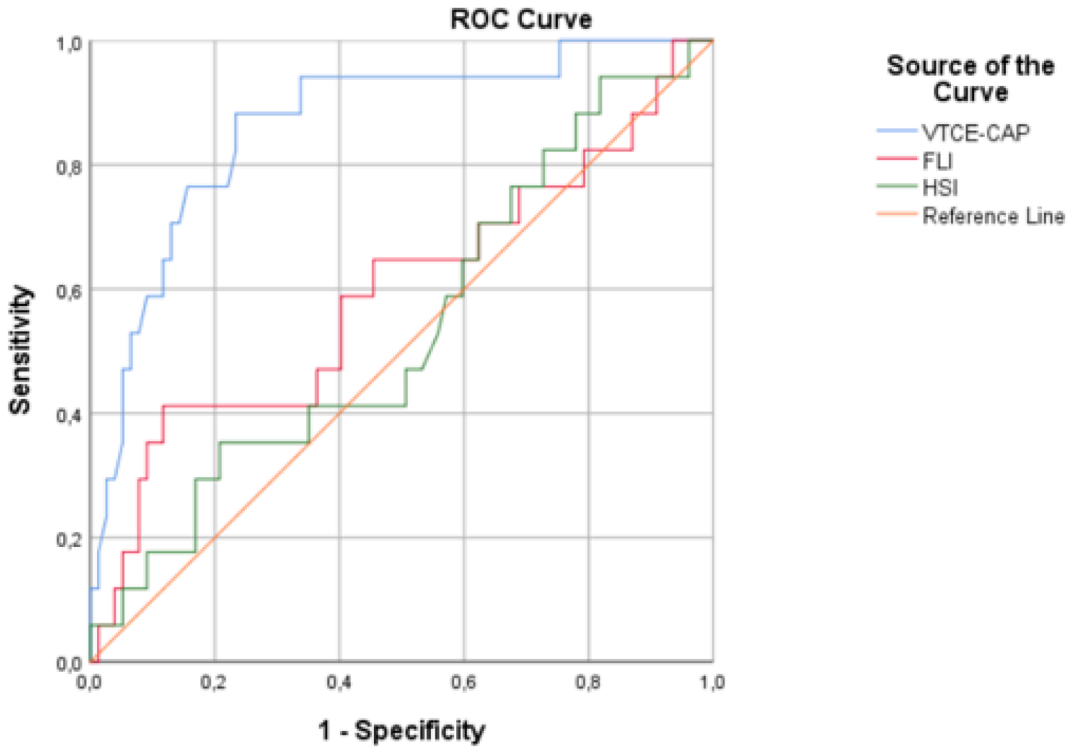
The factors that were associated with hepatic steatosis in univariate and multivariate analysis are shown in Table 2.

3.2. Liver fibrosis

Significant liver fibrosis was detected by MRE in 15 out of 101 (14.9 %) patients and advanced fibrosis in four (4 %). Four patients with liver fibrosis also had hepatic steatosis. The age of the patients with advanced

Table 1
Factors associated with the presence of hepatic steatosis in univariate and multivariate analysis in a cohort of adults with CF.

	Univariant analysis		Multivariant analysis	
Variable	OR (CI 95 %)	*p*	OR (CI 95 %)	*p*
Sex	0.30 (0.09–1.011)	0.052	0.36 (0.09–1.36)	0.135
Age	1.008 (0.95–1.06)	0.75	1.03 (0.97–1.09)	0.314
Alkaline phosphatase	1.01 (1.005–1.03)	0.006	1.01 (1.002–1.03)	**0.027**
HOMA index	1.66(1.09–2.52)	0.017	1.47(0.94–2.3)	0.086
BMI	1.056 (0.904–1.23)	0.495		
Waist circumference	1.041 (0.933–1.091)	0.096		
Preperitoneal adipose tissue	3.4(1.15–10.05)	0.026		
GLIM positive	0.512 (0.181–1.45)	0.208		
GSA negative	0.256 (0.052–1.265)	0.095		
Minimal function mutation	2.36 (0.812–6.91)	0.115		
CFTR modulators	1.243 (0.448–3.44)	0.676		
Exocrine pancreatic insufficiency	2.31 (0.966–7.63)	0.17		
Cystic fibrosis related diabetes	1.87 (0.645–5.47)	0.248		
Lymphocites	1.51 (0.934–2.441)	0.093		
Platelets	1.001 (0.995–1.007)	0.678		
AST	0.994 (0.969–1.01)	0.615		
ALT	0.996 (0.979–1.01)	0.684		
Transferrin	1.013(1–1.027)	0.058		
Albumin	1.151 (0.247–5.36)	0.858		
FEV1	0.998 (0.974–1.02)	0.836		
HSI	1.056 (0.936–1.191)	0.374		
FLI	1.019 (0.995–1.044)	0.119		



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.	Asymptotic 95% Confidencie Interval	
				Lower Bound	Upper Bound
FLI	,594	,085	,229	,428	,759
HSI	,539	,078	,616	,386	,692
VTCE-CAP	,864	,049	,000	,768	,961

Fig. 1. Comparative diagnostic accuracy by under curve area of hepatic steatosis using VCTE-CAP and noninvasive markers HIS, FLI using MR-PDFF as gold standard in a cohort of 101 adults living with cystic fibrosis.

fibrosis was 26 (17–33) years. The ROC curves obtained when evaluating the diagnostic accuracy of VCTE and the different non-invasive markers used in relation to MR elastography are shown in Fig. 3. The area under the kPa curve was 0.901 (0.788–1) for VCTE, 0.579 (0.399–0.759) for APRI, 0.773 (0.649–0.898) for NFS, 0.577 (0.388–0.766) for FIB-4, 0.702 (0.523–0.881) for HFS and 0.614 (0.435–0.793) for the combined markers. The cut-off point for the diagnosis of fibrosis using the Youden index was 6.65 kPa (Table 3).

Using the VCTE cut-off point of 6.65 kPa, sensitivity was 80 %, specificity 95.2 %, negative predictive value 96.3 %, and positive predictive value 75 %. These results improved when a two-step diagnostic algorithm for liver fibrosis combining HFS (with a cut-off point of 0.035 obtained using the Youden index) and VCTE was implemented (Fig. 4). In a patient with an HFS > 0.0.035 and VCTE > 6.65 kPa sensitivity of 100 %, specificity of 100 %, PPV of 100 % and NPV of 100 % were achieved.

The usefulness of this algorithm was also tested in patients with CFRD and in patients with minimal function mutations, achieving 100 % diagnostic accuracy.

Multivariate analysis of variables associated with liver fibrosis included CFRD (OR 17.36 (95 % CI 2.93–102.76); $p = 0.002$), and platelets (OR 0.97 (95 % CI 0.96–0.99); $p = 0.002$).

Regarding the factors associated with advanced liver fibrosis in the multivariate analysis, only platelet count was statistically significant as an independent factor related to advanced liver fibrosis (OR 0.97 (95 % CI 0.94–0.99); $p = 0.009$).

Four (3.9 %) patients had both hepatic steatosis and liver fibrosis at the same time. In total, 27 (26.7 %) patients in our cohort had hepatic steatosis and/or liver fibrosis. According to Koh's criteria, 15 (14.9 %) patients had CFHBI. Of the 27 patients with liver impairment on MRI, 10 met Koh's criteria, while 17 did not: 4 had liver fibrosis on MRI, 12 had hepatic steatosis and one patient had both. In addition, there were 5 patients who met Koh's criteria but did not have steatosis or liver fibrosis. Among them, two had splenomegaly and persistently elevated APRI. Another patient had portal hypertension. Another had persistently elevated transaminases and alterations in TE. The last one had splenomegaly and alterations in TE.

4. Discussion

Our study assesses the prevalence of hepatic steatosis and liver fibrosis in a cohort of adults with CF. For this purpose, we used the MRE as the gold-standard. A key contribution of this research is the development of diagnostic screening algorithms using non-invasive liver markers and transient elastography. These algorithms demonstrate strong negative predictive values and can be used across various clinical

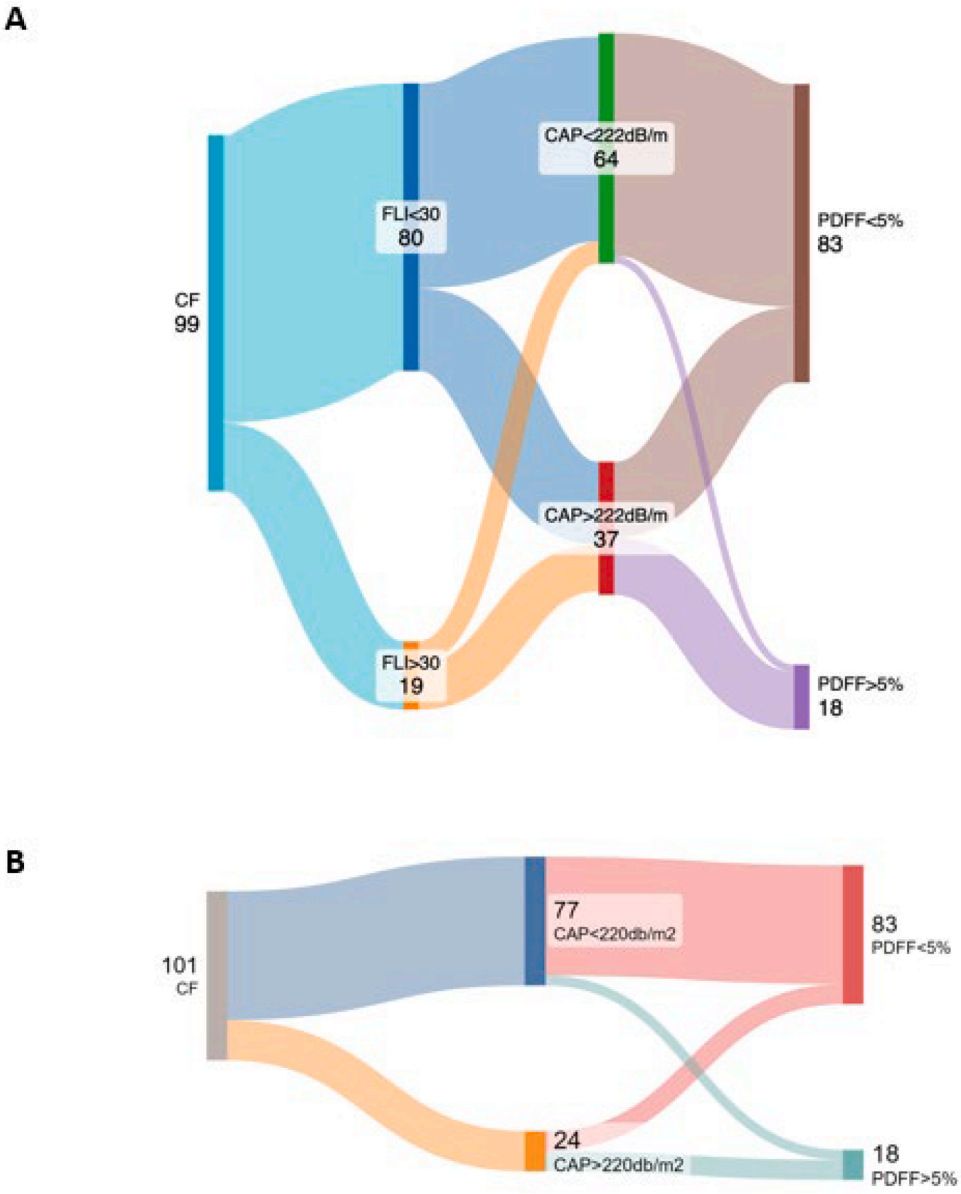


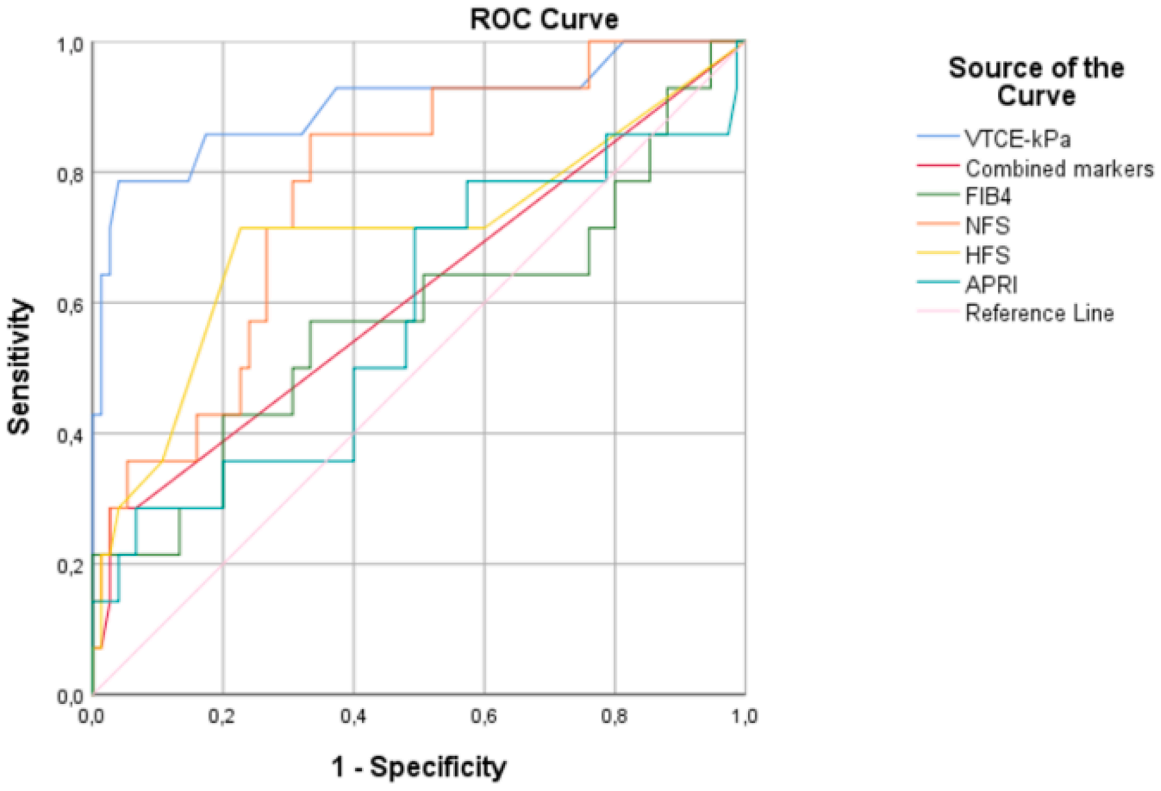
Fig. 2. Two-step screening algorithm for hepatic steatosis in CF with FLI and VTCE (A) and one step with VTCE only (B).

Table 2
Sensitivity, specificity, positive and negative predictive values kPa (FibroScan®) and FIB-4, NFS and APRI for the diagnosis of liver fibrosis.

		Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
kPa (VCTE)	*F2*	80 %	95.2 %	75 %	96.3 %	0.95(0.817–1)
	Advanced fibrosis	100 %	87.3 %	25 %	100 %	0.962(0.91–1)
FIB-4	*F2*	21.4 %	93.9 %	37.5 %	87.6 %	0.577(0.388–0.766)
	Advanced fibrosis	*25 %*	*100 %*	*100 %*	*96.8 %*	0.768(0.447–1)
NFS	*F2*	20 %	97.5 %	60 %	87 %	0.773(0.649–0.989)
	Advanced fibrosis	0 %	100 %	0 %	95.9 %	0.903(0.781–1)
APRI	*F2*	33.3 %	72.6 %	17.8 %	85.9 %	0.579(0.399–0.759)
		0 %	*100 %*	*0 %*	*95.9 %*	
	Advanced fibrosis	0 %	100 %	0 %	95.9 %	0.724(0.445–1)
HFS	*F2*	20 %	97.3 %	60 %	86 %	0.702(0.523–0.881)
	Advanced fibrosis	25 %	97.7 %	33.3 %	96.5 %	0.734(0.411–1)

PPV, Positive predictive value; NPV, Negative predictive value.

setting as they are widely available, inexpensive and relatively simple to perform and interpret. For hepatic steatosis, the diagnostic yield was higher with one-step screening, i.e., directly performing transient elastography on patients. Elastography also appears to be an accurate method to address fibrosis in this population because of the lack of obesity. Currently, the Cystic Fibrosis Foundation recommends baseline liver assessment in adults and annual monitoring of liver fibrosis markers and elastography in patients with CFHBI [30]. Following these



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
VTCE-kPa	,901	,058	,000	,788	1,000
Combined markers	,614	,091	,178	,435	,793
FIB4	,577	,096	,361	,388	,766
NFS	,773	,064	,001	,649	,898
HFS	,702	,091	,017	,523	,881
APRI	,579	,092	,353	,399	,759

Fig. 3. Comparative diagnostic accuracy of liver fibrosis using ROC curves of FibroScan® and noninvasive markers used in relation to MRE in a cohort of 101 adults living with cystic fibrosis.

recommendations, we believe that our algorithm for liver fibrosis can improve the cost-effectiveness of screening by combining both results. In patients without abnormalities, the Cystic Fibrosis Foundation has not yet established a consensus on the frequency of monitoring. Finally, it should be noted that we also propose new cut-off for CAP.

The prevalence of chronic liver disease in patients with CF was around one in six patients when assessed by MRI-PDFF and MRE. Currently, and given the low prevalence of CF, there are few studies that evaluate CFHBI, and these are mainly based on the use of ultrasound and transient elastography including heterogeneous populations and children. As previously reported in alpha-1 antitrypsin deficiency, the threshold to define significant fibrosis (6.65 kPa) is lower in CF than in the general population with MASLD (8 kPa). Further validation studies should confirm our findings. We also propose a new cut-off point for interpreting transient elastography to rule out hepatic steatosis.

The prevalence of steatosis in our cohort is slightly higher than in the study by Ayoub et al. [25] (17,8 % vs. 14.9 %), who studied a cohort of 114 adults with CF. However, hepatic steatosis detected by standard imaging techniques (CT, US and MRI) may underdiagnose liver fat infiltration. In MASLD, liver ultrasound requires a fat infiltration higher than 12–25 % to be detected. Thus patients with steatosis in this range remained hidden to standard methods but were detected by MRI-PDFF [31]. Moreover, their cohort was younger, had a lower median BMI and a lower percentage of CFRD. Kutney et al. [26], reported a prevalence of 30 % of hepatic steatosis by MRI-PDFF when also including pediatric patients with impaired glucose metabolism and exocrine pancreatic insufficiency. Marinero Martínez-Lazaro et al. [32] included 95 adult patients with CF and reported a prevalence of 16.9 %. Finally, Bader et al. [33] reported a prevalence of steatosis of around 33 %, although 44 % of the patients were under 18 years of age, using a VCTE-CAP cut-off of 230dB/m, which is very similar to the threshold defined in the current study. The optimal cut-off to define hepatic steatosis using VCTE-CAP has been controversial in patients with MASLD [31]. Interestingly, in our study we validated the threshold of 222 dB/m in VCTE-CAP using PDFF as a reference method, supporting that the CAP cut-off is much lower than that reported in the MASLD definition.

BMI and CFRD have been associated with the presence of steatosis in previous studies [25]. However, this was not confirmed in our study. Indeed, the 75th percentile of BMI in our cohort was only 24.6 kg/m^2 and no association with CFRD was seen. Nevertheless, we did find an association with HOMA IR and preperitoneal adipose tissue indicating a metabolic component as in MASLD. Moreover, the presence of a positive screening for malnutrition (performing VSG) appeared to be associated

Table 3
Factors associated with the presence of any liver fibrosis in multivariate analysis in a cohort of adults with CF.

	Univariant analysis		Multivariant analysis	
Variable	OR (CI 95 %)	*p*	OR (CI 95 %)	*p*
Age	0.94(0.88–1.00)	0.059	0.88(0.8–0.96)	**0.008**
Sex (female)	0.4(0.11–1.35)	0.142	0.25(0.04–1.34)	0.107
CFR Diabetes	5.13(1.62–16.24)	0.005	17.36 (2.93–102.76)	**0.002**
Platelets	0.98(0.97–0.99)	0.001	0.97(0.96–0.99)	**0.002**
Adulthood diagnosis	0.154 (0.019–1.233)	0.078		
Minimal function mutation	2.308 (0.726–7.33)	0.156		
CFTR modulators	2(0.653–6.12)	0.225		
Exocrine pancreatic inssuficiency	4.643 (0.985–21.888)	0.052		
GLIM positive	1.38(0.46–4.16)	0.564		
AST	1.015 (1.000–1.031)	0.053		
ALT	1.022 (0.999–1.046)	0.059		
Alkaline phosphatase	1.019 (1.006–1.033)	0.005		
Total bilirubin	6.517 (2.168–19.588)	0.001		
Hemoglobin	1.469 (1.036–2.083)	0.031		
Lymphocites	0.395 (0.143–1.092)	0.073		
Vitamin E	0.998(0.995–1)	0.015		
Vitamin A	0.882 (0.818–0.95)	0.001		
FEV1	0.981 (0.954–1.009)	0.176		
FFMI	0.933 (0.688–1.26)	0.658		
BMI	0.945 (0.795–1.12)	0.522		
FIB-4	3.21(1.18–8.71)	0.022		
APRI	4.33 (0.625–30.03)	0.138		
HFS	946.77 (4.09–218,944)	0.014		
NFS	3.05(1.53–6.1)	0.002		

with hepatic steatosis, which is consistent with available data [20]. This would support the U-shape of the relationship between body weight and hepatic steatosis.

Concerning analytical parameters, in other studies, CF patients with steatosis showed elevated levels of ALT and AST and decreased levels of albumin and total bilirubin [20,25]. In our study, the presence of higher levels of alkaline phosphatase was associated with a higher risk as previously described [26].

No data are available on the prevalence of liver fibrosis in patients with CF using MRE. Fibrosis by VCTE has been reported to range between 17 % [34] and 18.3 % [32]. A strong correlation was found between VCTE and MRE, supporting a role in screening for liver fibrosis. Routinely available non-invasive tests such as FIB-4, APRI or NFS did not achieve sufficient diagnostic accuracy [35]. However, when HFS and VCTE were combined, an optimal predictive value was found.

In the univariate analysis, older age and diagnosis in adulthood were associated with a lower risk of liver fibrosis. This was consistent with the traditional view that CFHBI only occurs in children. However recent evidence indicates that there is a second peak of incidence in adulthood [36].

Regarding analytical parameters that may indicate the presence of liver fibrosis, the study by Koh et al. [10] they reported an association between elevated AST and ALT levels and decreased platelet levels with elevated kPa values on transient elastography. In this study they found no association with bilirubin levels. In our study only low platelet count was associated in the multivariate analysis, which is not a causative factor of fibrosis but a consequence of fibrosis due to hypersplenism.

Notably, the prevalence of CFHBI detected with MRE in our study is higher than that obtained using the Koh criteria. Most patients with MRE-diagnosed disease who did not meet the Koh criteria had hepatic steatosis. This could be explained by the Koh criteria's focus on more advanced liver disease, under the assumption that hepatic steatosis is not part of CFHBI.

Following on from the above, it is important to consider the roles of steatosis and liver fibrosis as components of CFHBI. As noted previously, hepatic steatosis was not included in the broad clinical spectrum of CFHBI until the last ESPGHAN/NASPGHAN update of the CFHBI classification in 2023 [18]. However, in our study, we see that it is not uncommon and is associated with components also present in MASLD. Therefore, in the future we will need studies to assess whether patients with cystic fibrosis and hepatic steatosis progress to liver fibrosis. Other studies such as that by Koh et al. [10] suggest that if the presence of fibrosis is taken into account, the prevalence of CFHBI would be higher than that obtained using only the Debray criteria. As Koh combines different criteria before indicating liver involvement, it is an open door that the CFHBI classification will detect more abnormalities as every aspect is rated separately.

The limitations of our study are its cross-sectional nature; the unavailability of a histological reference for comparison, although as previously mentioned this has not been shown to be very useful in patients with CF; the single-center nature of the study (especially given that our cohort is composed of patients with relatively few comorbidities); and that by including only adult patients we may fall into a survival bias that underestimates the prevalence of both steatosis and liver fibrosis.

In conclusion, our study found that the prevalence of steatosis and liver fibrosis was 17.8 % and 14.9 %, respectively, with four (3.9 %) patients presenting both conditions concurrently. It is essential to rule out liver damage in CF patients, as transaminase levels alone are not sufficient for assessment. Combining VCTE and HFS could rule out fibrosis while VTCE with CAP could potentially reduce the need for liver biopsy or MRI-PDFF to confirm steatosis. Using the accepted gold standard for steatosis and fibrosis, this study allowed us to report an algorithm to detect these conditions in patients with CF. Further studies are warranted to validate and confirm these results.

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Author contributions

PPGL, MRG, EQG, FJC, APG, AP and ID contributed to conceptualisation and visualization of the manuscript. PPGL and MRG participated in funding acquisition, methodology, validation and supervision. project administration and resources. FJC adquired and managed software. SGR, MCRC, SG, AJS, IGN, PJRM and APG made the investigation and data curation. APG performed formal analysis and wrote the first draft of the manuscript. APG, PPGL and MRG reviewed and edited manuscript to its final version. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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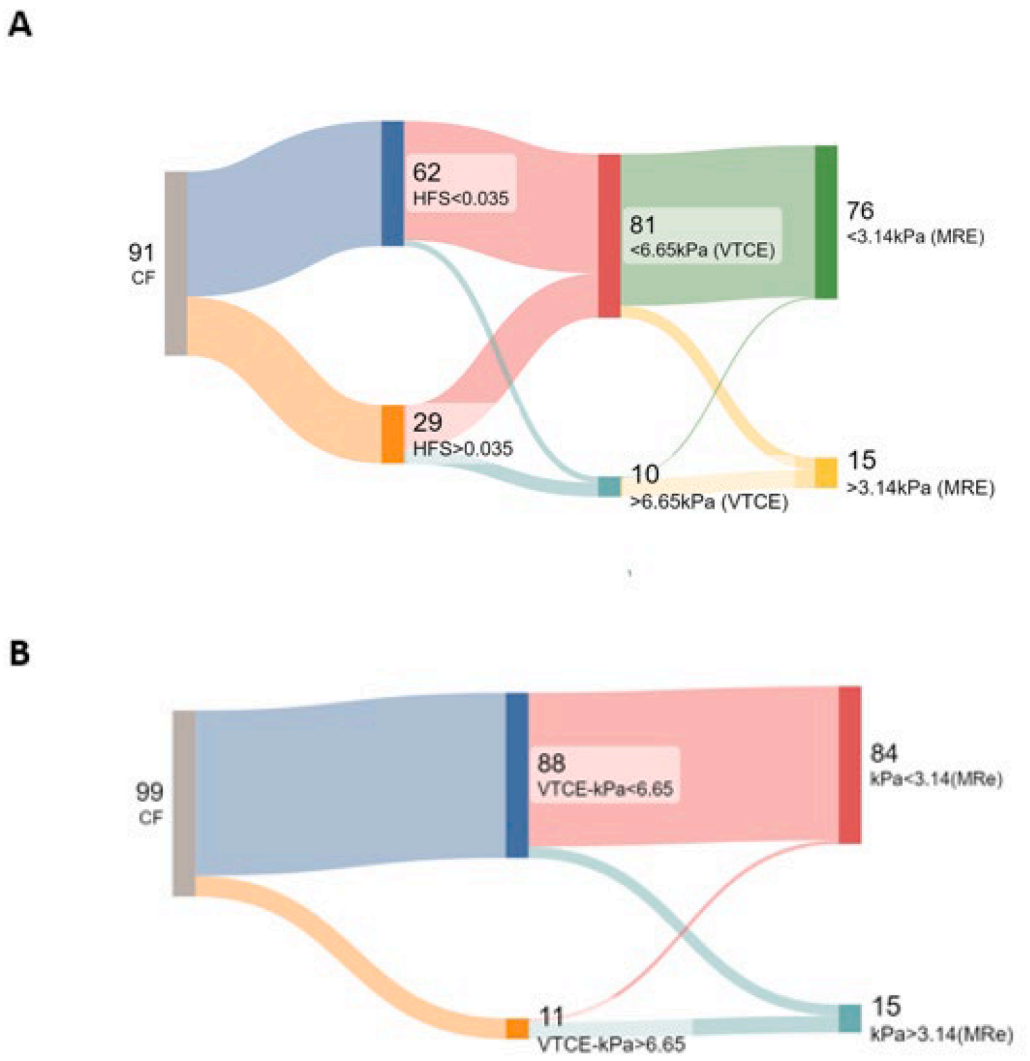

Fig. 4. Two-step screening algorithm for liver fibrosis in CF with HFS and VTCE (A) and one step with VTCE only (B).

there are other authors, they 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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2025.02.007.

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