Journal of Cystic Fibrosis 18 (2019) 280–285

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Controlled attenuation parameter: A measure of hepatic steatosis in patients with cystic fibrosis

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ARTICLE INFO

Article history:
Received 3 August 2018
Revised 21 October 2018
Accepted 12 November 2018
Available online 1 December 2018

Keywords:
Cystic Fibrosis
Children
Adolescents
Transient elastography
Controlled attenuation parameter
Hepatic steatosis

ABSTRACT

Background: Hepatic steatosis is a common manifestation of CF-related liver disease(CFLD). Controlled attenuation parameter(CAP) measurement during transient elastography(TE) semiquantifies liver steatosis. We examined the relationship between CAP and CFLD severity, clinical factors and liver stiffness measurements(LSM).
Methods: This is a cross-sectional study of CF patients seen for outpatient care between January 2013–March 2014. CFLD severity was categorized as no CFLD, CFLD without portal hypertension(PHTN) and CFLD with PHTN, based on published criteria.
Results: 129 patients (median 18.4y; 57% male) had valid CAP. 70(54%) had no CFLD, 44(34%) CFLD without PHTN, and 15(12%) CFLD with PHTN. The median CAP was 210 dB/m (IQR 181–239). Steatosis(CAP ≥230 dB/m) was seen in 27% of subjects without CFLD, 48% in CFLD but no PHTN, and 20% in with CFLD and PHTN($P = .04$). CAP was higher for subjects with CFLD without PHTN ($P < .05$). There was no CAP difference between subjects with no CFLD and those with CFLD and PHTN ($P \geq .65$). LSM was not different between no CFLD and CFLD without PHTN ($P = .07$), but each of these groups had lower LSM compared to subjects with CFLD and PHTN($P < .001$ for each). Except for direct bilirubin, CAP was not associated with clinical markers of liver disease.
Conclusion: CAP was normal in 86(67%) of patients with CF and was not associated with standard clinical markers of liver disease. CAP was higher in patients with liver disease, which could possibly reflect the loss of steatosis observed with progression to cirrhosis and portal hypertension.
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1. Introduction

The health outcomes of patients with cystic fibrosis (CF) have greatly improved over the last 20 years due to advances in diagnosis and therapy of chronic lung disease and malnutrition. However, liver disease associated with CF has emerged over this time as a significant contributor to long-term morbidity and mortality. Liver disease is most often diagnosed late in its course, when cirrhosis and portal hypertension are well established.

The prevalence of hepatic steatosis in patients with CF has been described as 20–60% and can present at any age [1]. The degree of steatosis can range from mild changes in echogenicity on ultrasound to extensive fatty infiltration [2]. Focal fat deposition in centrilobular and periportal regions can also occur [3]. The pathogenesis of steatosis remains obscure; it does not seem to be related to a CF Transmembrane Conductance Regulator secretory defect, but rather to selective nutritional deficiencies and altered phospholipid metabolism [4,5]. Whether simple steatosis is a risk factor for the development of steatohepatitis and progression to cirrhosis in CF patients remains unclear [1].

Ultrasound (US) is a low-cost, safe and widely accessible imaging technique. US is accurate in detecting steatosis if it involves at least 20–30% of hepatocytes [6]. However, it lacks sensitivity and the ability to consistently detect and quantify hepatic steatosis, and it is operator dependent. Other modalities like magnetic resonance imaging and magnetic resonance spectroscopy are more accurate for the detection of hepatic steatosis but are not widely used due to expense, practicality and limited clinical availability [7].

A noninvasive method called the controlled attenuation parameter (CAP) has been developed to assess hepatic steatosis. CAP is based on the radiofrequency ultrasound signal acquired by the transient elastography device (Fibroscan®, Echosens, Paris, France). CAP is an estimate of the ultrasonic attenuation coefficient at 3.5 MHz. These measures are reproducible, as well as operator and machine independent. CAP has been shown to correlate with hepatic steatosis in adults [8] independent of the degree of fibrosis and etiology of liver disease. Depending on the applied cut-off value and the estimated prevalence in the population of interest, CAP can provide semi-quantitative assessment of liver steatosis in adults [8–11] and children [12]. To our

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https://doi.org/10.1016/j.jcf.2018.11.004
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knowledge, there are very few data on the use of CAP in children and adults with cystic fibrosis.

The aims of this study were: 1) to determine the prevalence of hepatic steatosis, as determined by CAP, in a cross-sectional sample of pediatric patients with CF, 2) to examine the association of CAP measurements with the presence and severity of CF-related liver disease (CFLD) and 3) to examine the association of CAP measurements with biochemical and clinical parameters including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), platelet count, body mass index (BMI), pancreatic insufficiency, use of feeding tube, presence of CF-related diabetes and liver stiffness measurements (LSM).

2. Material and methods

2.1. Study design

This was a cross-sectional observation study of children and young adults with cystic fibrosis (age 6–25 years) who underwent transient elastography measurements during routine non-emergent care at Boston Children's Hospital (BCH) between January 2013 and March 2014. CAP measurements were obtained during transient elastography done for another study of CFLD [13]. Exclusion criteria were known liver disease other than CFLD, liver transplant and pregnancy. Reported here are CAP/LSM studies performed at each patient's first visit.

Clinical and biochemical data were obtained from the medical records, including age, sex, weight, height, presence or absence of splenomegaly as determined by physical examination or ultrasound, pulmonary function test results, and prescription for ursodeoxycholic acid at the time of CAP measurement. Biochemical parameters closest to the CAP measurement date were recorded. Findings from the most recent abdominal ultrasound and/or GI endoscopy, if performed, were recorded. Body mass index *Z*-scores (BMI*Z*) were calculated for subjects age 6–20 years according to CDC reference charts.

This study was approved by the BCH Institutional Review Board. Written informed consent was obtained from parents, guardians, and subjects ≥18y. Assent was obtained from children 7–17 years.

2.2. Transient elastography

Steatosis as determined by CAP and fibrosis as determined by LSM were measured by transient elastography (TE) by trained research investigators during annual routine care visits using the FibroScan ® device (Echosens, Paris, France). CAP and LSM were obtained by placing an ultrasonic transducer in a right intercostal space to transmit a vibration which induces an elastic shear wave through the right lobe of the liver. Elastography measures the liver stiffness in kiloPascals (kPa). The velocity of propagation is directly related to tissue stiffness: the harder the tissue (as in hepatic fibrosis), the faster the shear wave propagates. The TE probe uses ultrasound to track the wave and subsequently CAP is calculated as a measure of the ultrasound attenuation, which corresponds to the decrease in amplitude of ultrasound waves as they propagate through the liver, expressed as decibel per meter (dB/m). CAP is calculated automatically by the device, and only if the liver stiffness measurement is valid.

CAP was measured with the M probe at 3.5 MHz, at depths between 25 and 65 mm, since all subjects had a thoracic perimeter 75–110 cm. In each subject, 10 valid measurements (as recommended by the manufacturer) were obtained in rapid succession. The adequacy of the measurement was assessed by the FibroScan© device. If the measurement was invalid, owing to either patient characteristics or operator error, then neither LSM nor CAP measurement was given. The test typically was completed in 5–10 minutes. CAP measurements were obtained by technicians who were blinded to clinical data.

2.3. CFLD Categories

Patients were categorized into three groups according to clinical, biochemical, sonographic, and endoscopic parameters. The groupings from published guidelines on CFLD were reviewed and modified based on accepted clinical parameters at our institution [14,15]. Subjects were classified as having no CFLD when all the following criteria were met:

1. Most recent ALT <1.3 × ULN (upper limit of normal; 30 IU/mL at BCH).
2. Not prescribed ursodeoxycholic acid.
3. Normal ultrasound (if done).

Subjects were classified as CFLD without portal hypertension (PHTN) when at least one of the following criteria were met:

1. Most recent ALT >1.3 × ULN.
2. Prescribed ursodeoxycholic acid.
3. Abnormal liver echogenicity without evidence of PHTN.

Subjects were classified as having CFLD with PHTN when at least one of the following were met:

1. Splenomegaly on physical exam defined as spleen below costal margin.
2. Presence of esophageal varices by traditional or video capsule endoscopy.
3. Platelet count <100,000/mm^3.
4. Evidence of PHTN on ultrasound (ascites, reversed portal flow, varices, and/or splenomegaly). Splenomegaly by ultrasound was defined as spleen length-for-age above 90% of upper confidence limit [16].

2.4. Statistical analyses

Categorical data are described with frequency counts and percentages and compared across outcome categories by Fisher's exact test. Continuous data are described with median (interquartile range; IQR) and compared by Wilcoxon rank-sum test or Kruskal-Wallis test according to whether two or three categories are compared, respectively. The Wilcoxon rank-sum test compares sums of ranks between two groups and not the medians, such that the medians can be equal even when the test returns a significant *P* value. Since this occurred for direct bilirubin (DB), an additional comparison for DB = 0.1 mg/dL and DB > 0.1 mg/dL is presented in Table 3 for added clarity, which was also significant at $P = .01$ by Fisher's exact test. All tests of significance were two-sided, with $P < .05$ deemed statistically significant. Analysis was performed with SAS® v9.4 (Cary, NC).

3. Results

A total of 348 patients with CF were seen for routine care during the study period, representing 76% of all CF patients under 26 years in the BCH CF Patient Registry. Of these, 219 were excluded due to failure to meet inclusion criteria, refusal to participate, patient not approached due to being unavailable for enrollment, small (S) probe used (which is unable to calculate CAP), and invalid TE measurement. A total of 129 subjects with thoracic parameters >75 cm and valid medium (M)-probe CAP measurements and determinable liver disease status comprised the sample for this study. Derivation of the study population is shown in Fig. 1.

Subjects were 18.4 (15.8, 23.1) years of age, with 2% <12y, 42% 12–17y, and 56% ≥18y. CF was diagnosed by either sweat test or genetic test, with 57 (46%) homozygous and 55 (45%) heterozygous for the Δ F508 CFTR mutation. Eleven (9%) subjects had no Δ F508 mutations; genotype results were unknown for 6 subjects. Among 75 subjects who underwent abdominal ultrasound, abnormalities were found in 32

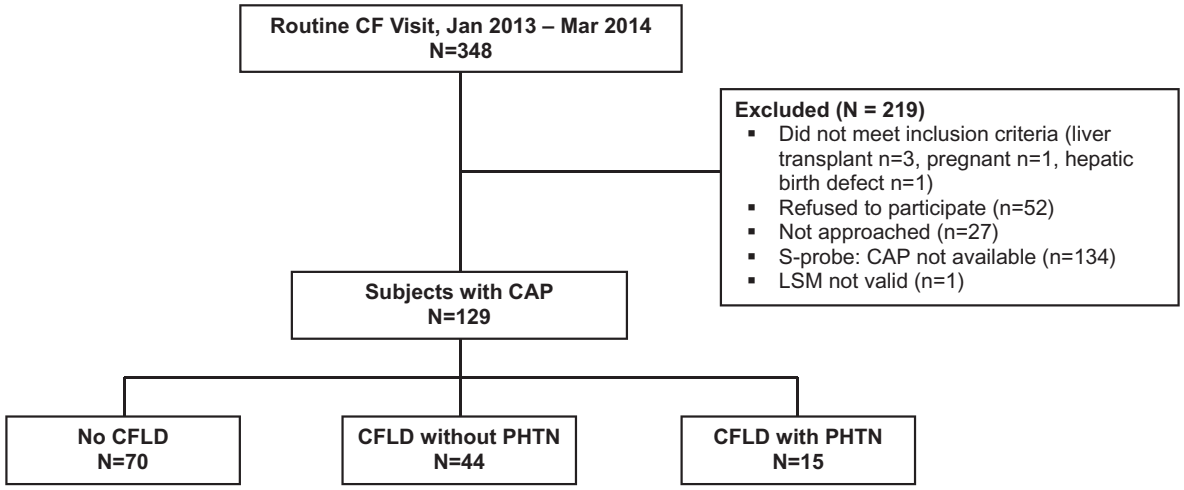

Fig. 1. Patient flowchart.

(43%), in the form of abnormal liver echogenicity in 19 (25%) and signs of PHTN in 13 (17%). ALT and AST were > 1.3 times the ULN in 19 (15%) and 8 (6%) of all subjects, respectively. Using the criteria described above, 70 (54%) subjects were classified as no CFLD, 44 (34%) as CFLD without PHTN, and 15 (12%) as CFLD with PHTN (Table 1).

TE measurements by liver disease severity are shown in Table 2. Steatosis was defined as CAP ≥230 dB/m. The median CAP measurement for the entire sample was 210 dB/m (IQR 181–239) and 43 (33%) had steatosis. Steatosis was seen in 27% of subjects without CFLD, 48% of those with CFLD but no PHTN, and 20% of those with CFLD and PHTN ($P = .04$). CAP measurement (and steatosis prevalence) was statistically higher for subjects categorized as CFLD without PHTN than either of the other two categories ($P < .05$), while there was no difference between subjects categorized as no CFLD and those with CFLD and PHTN ($P \geq .65$).. Liver stiffness measurements (LSM) were not statistically different between subjects with no CFLD and those categorized

Table 1
Subject characteristics ($n = 129$). Shown are median (IQR) or n (%).

Characteristic	Overall	By disease severity			
		No CFLD	CFLD without PHTN	CFLD with PHTN	
	(n = 129)	($n = 70$)	($n = 44$)	($n = 15$)	P *
Demographics					
Male sex	73 (57%)	39 (56%)	24 (55%)	10 (67%)	0.77
Age at LSM (y)	18.4 (15.8, 23.1)	18.2 (14.9, 22.2)	18.5 (16.7, 23.3)	22.2 (17.1, 23.8)	0.09
3–6	1 (1%)	1 (1%)	0 (0%)	0 (0%)	
7–11	2 (1%)	1 (1%)	1 (2%)	0 (0%)	
12–17	54 (42%)	32 (46%)	18 (41%)	4 (27%)	
18–25	72 (56%)	36 (51%)	25 (57%)	11 (73%)	
Homozygous delta F508	57 (46%)	28 (42%)	25 (58%)	4 (29%)	0.10
Heterozygous delta F508	55 (45%)	29 (44%)	18 (42%)	8 (57%)	0.59
Growth and nutrition					
BMIZ ($n = 76$ age ≤ 20y)	−0.07 (−0.70, 0.60)	0.13 (−0.57, 0.75)	−0.36 (−0.88, 0.46)	−0.64 (−1.15, −0.43)	0.16
BMI ($n = 53$ age > 20y)	22.1 (20.6, 24.3)	22.1 (20.4, 24.1)	22.1 (21.1, 24.4)	21.4 (20.3, 26.3)	0.66
Gastrostomy tube	17 (13%)	7 (10%)	7 (16%)	3 (20%)	0.39
Labs					
GGT (u/L), n = 76	16 (11, 27)	13 (11, 17)	18 (13, 31)	26 (18, 47)	
ALT (u/L)	22 (16, 30)	20 (16, 25)	25 (17, 47)	26 (14, 30)	
AST (u/L)	25 (20, 30)	23 (19, 29)	27 (20, 37)	26 (23, 33)	
ALT >1.3 × ULN	19 (15%)	0 (0%)	16 (36%)	3 (20%)	
AST > 1.3 × ULN	8 (6%)	0 (0%)	6 (14%)	2 (13%)	
INR, $n = 104$	1.01 (0.98, 1.06)	1.01 (0.98, 1.06)	1.01 (0.99, 1.05)	1.05 (0.95, 1.19)	
Albumin (g/dL), $n = 121$	4.3 (4.0, 4.6)	4.3 (4.1, 4.6)	4.3 (3.9, 4.6)	4.3 (3.6, 4.5)	
Direct bilirubin (mg/dL), $n = 96$	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.2)	
PLT (K cells/uL), $n = 127$	269 (239, 335)	280 (254, 330)	262 (241, 342)	147 (73, 309)	
$HgbA_1C$, $n = 87$	5.4 (5.2, 5.8)	5.4 (5.2, 5.7)	5.5 (5.3, 6.1)	5.5 (5.2, 7.6)	
Clinical					
Ascites	1 (1%)	0 (0%)	0 (0%)	1 (7%)	
Meconium ileus, $n = 74$	20 (27%)	11 (28%)	9 (31%)	0 (0%)	
Ursodeoxycholic acid	42 (33%)	0 (0%)	29 (66%)	13 (87%)	
Pancreatic insufficiency	123 (95%)	64 (91%)	44 (100%)	15 (100%)	
Diabetes	24 (19%)	8 (11%)	11 (25%)	5 (33%)	

* P value from Kruskal-Wallis test or Fisher exact test. P value not shown for laboratory and clinical variables since they were used to either define or are known to be related to the CF liver disease severity categories.

Table 2
Fibroscan measurements (n = 129). Shown are median (IQR) or n (%).

Characteristic	Overall	By disease severity			
		No CFLD	CFLD without PHTN	CFLD with PHTN	
	(n = 129)	(n = 70)	(n = 44)	(n = 15)	P *
CAP (dB/m), median (IQR)	210 (181, 239)	204 (175, 232)	227 (194, 274)	196 (183, 222)	0.02
Steatosis (CAP≥230)	43 (33%)	19 (27%)	21 (48%)	3 (20%)	0.04
LSM (kPa), median (IQR)	5.3 (4.3, 6.4)	4.9 (4.2, 5.7)	5.4 (4.5, 6.5)	11.8 (6.4, 24.8)	<0.0001

* *P* value from Kruskal-Wallis test or Fisher exact test.

as CFLD without PHTN ($P = .07$), but each of these groups had statistically lower LSM compared to subjects with CFLD and PHTN ($P < .001$ for each), as previously reported [13].

Association of steatosis, as defined by CAP score ≥ 230 dB/m, with patient and clinical factors is shown in Table 3. With the exception of direct bilirubin (DB), CAP measurements were not associated with clinical and biochemical markers of liver disease. Median DB was 0.1 (range 0.1–1.4) mg/dL in subjects without steatosis compared to 0.1 (range 0.1–0.2) mg/dL in subjects with steatosis ($P = .01$). Notably, neither group had elevated direct bilirubin levels.

The association of CAP with liver disease severity and the association of CAP with ultrasound measurement exhibited similar trends to one another (Fig. 2). In both cases, CAP for the least-extreme (no CFLD; normal ultrasound) and most-extreme (CFLD with PHTN) groups were not statistically different from one another ($P = .65$ and $P = .29$, respectively), while the least- and most-extreme groups were each statistically different from the group between these extremes (CFLD without PHTN; abnormal echogenicity; $P < .05$ for each).

4. Discussion

To our knowledge, this is the first study evaluating CAP for the assessment of steatosis in CF patients. CAP appears to be a promising tool for the non-invasive detection and quantification of steatosis in patients with CFLD. CAP measurements can be evaluated simultaneously with LSM to assess hepatic fibrosis. Desai et al. demonstrated a difference in CAP between no steatosis and steatosis, and between grades of steatosis in children [12]. Aqul et al. showed a correlation between liver stiffness measurement (LSM) with presence and severity of liver disease in children and young adults with CF [13]. An optimal CAP threshold for steatosis of 232 dB/m was demonstrated in a meta-analysis in chronic liver disease and 225 dB/m in pediatric patients [12,17]. In our study, we used 230 dB/m as the threshold value. More data and studies are needed to predict accurate thresholds that are disease specific, according to age and BMI.

Identifying patients who are at risk for CFLD and potential hepatic complications is an ongoing challenge. Long-term follow-up of different cohorts of CF patients carefully monitored for hepatic involvement indicates a cumulative incidence of liver disease ranging between 27% and 35%, without incident cases after the age of 18 years. The prevalence of hepatic steatosis has been described to be as high as 20%–60% in patients with CF and can present at any age. Approximately 5 to 10% of all CF patients will develop multi-lobular cirrhosis during the first decade of life. Most of these will present with related complications during the second decade, rarely in the pediatric age group.

In our study, 67% of subjects had CAP measurement in the normal range (<230 dB/m) and curiously CAP was not associated with clinical

Table 3
Unadjusted association of baseline CAP measurements with patient and clinical factors. Shown are median (IQR) or n (%).

Characteristic	CAP < 230	CAP ≥ 230	
	(*N* = 86)	(*N* = 43)	*P*
Growth and nutrition			
BMIZ (aged ≤20y) (n = 76)	−0.22 (−0.86, 0.54)	0.33 (−0.57, 0.88)	0.10
BMI (aged >20y) (n = 53)	22.1 (20.4, 23.7)	22.1 (21.1, 24.4)	0.47
BMI (all subjects)	20.9 (19.2, 22.9)	21.5 (19.9, 24.3)	0.19
Gastrostomy tube	10 (11.6%)	7 (16.3%)	0.58
Labs			
GGT (u/L) (n = 76)	16 (11, 25)	14 (12, 30)	0.99
ALT (u/L)	21 (15, 28)	24 (19, 33)	0.08
AST (u/L)	24 (19, 31)	26 (20, 30)	0.93
INR (n = 104)	1.02 (0.98, 1.07)	1.01 (0.98, 1.04)	0.23
Albumin (g/dL) (n = 121)	4.3 (4.0, 4.6)	4.3 (4.1, 4.6)	0.99
Direct bilirubin (mg/dL) (n = 96)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.01
Direct bilirubin = 0.1 mg/dL	49 (75.4%)	30 (96.8%)	
Direct bilirubin >0.1 mg/dL	16 (24.6%)	1 (3.2%)	
PLT (K cells/uL) (n = 127)	263 (227, 312)	280 (254, 347)	0.10
Creatinine (mg/dL) (*n* = 127)	0.6 (0.5, 0.8)	0.6 (0.5, 0.7)	0.54
Glucose (mg/dL) (*n* = 123)	93 (87, 130)	96 (88, 109)	0.92
$HgbA_1C$ (n = 87)	5.5 (5.3, 6.1)	5.4 (5.2, 5.8)	0.46
Clinical			
UDCA	30 (34.9%)	12 (27.9%)	0.55
Pancreatic insufficiency	80 (93.0%)	43 (100%)	0.18
Diabetes	17 (19.8%)	7 (16.3%)	0.81
Noninvasive scores			
LSM	5.3 (4.3, 6.4)	5.3 (4.3, 6.6)	0.87
AST:ALT (APRI) (n = 127)	0.24 (0.16, 0.32)	0.22 (0.15, 0.29)	0.33

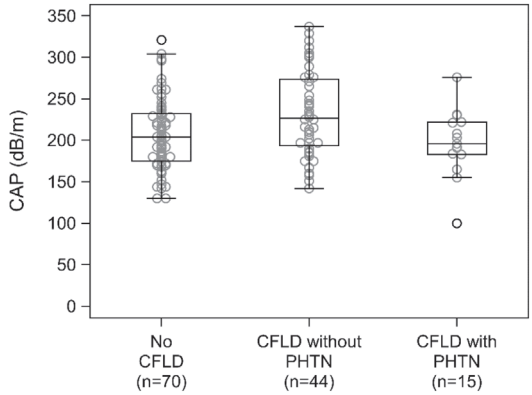

Figure 2a. CAP stratified by disease severity.

	No CFLD	CFLD without PHTN	CFLD with PHTN	*P*
CAP (dB/m)	204 (175, 232)	227 (194, 274)	196 (183, 222)	0.02
	▲	▲		0.02
	▲		▲	0.65
		▲	▲	0.04

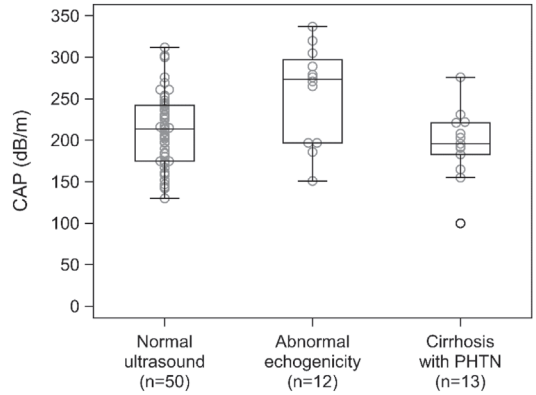

Figure 2b. CAP stratified by ultrasound findings.

	Normal ultrasound	Abnormal echogenicity	Cirrhosis with PHTN	*P*
CAP (dB/m)	214 (175, 242)	274 (197, 297)	196 (183, 221)	0.02
	▲	▲		0.02
	▲		▲	0.29
		▲	▲	0.03

Fig. 2. CAP, stratified by CF liver disease severity (Fig. 2a) and ultrasound findings (Fig. 2b). Below each figure is a summary table showing the median (IQR) CAP for each category. The ▲ symbol indicates pairwise comparisons, which are not adjusted for multiple comparisons. CFLD = cystic fibrosis liver disease; PHTN = portal hypertension.

and biochemical markers of liver disease. There are several possible explanations for this. As the pathogenesis of steatosis remains obscure, we might be missing the clinical and biochemical markers that truly correlate with CAP. On the other hand, we may simply need more patients to illustrate an association, or a longitudinal study to investigate whether serial correlation exists with clinical and biochemical markers of liver disease. In addition, we might be observing a sample bias as most of our study sample is relatively healthy.

In the subset of patients with abnormal ultrasound echogenicity, CAP measurements were higher than the CAP measurement for patients with normal ultrasound. This may suggest an association of CAP with steatosis. CAP was significantly lower in patients with evidence of cirrhosis and portal hypertension on ultrasound compared to patients with only increased liver echogenicity (85% vs. 33% normal CAP; $P = .03$). We theorize that this may indicate that as the fibrosis increases and cirrhosis develops, steatosis decreases and fat may be replaced by fibrous tissue. Larger, longitudinal studies are need to investigate the progression of CFLD.

The main limitation of our study is that it is based on a single center with a relatively healthy CF population and a small sample size of patients with CFLD. Furthermore, we lack a gold standard method to evaluate steatosis and compare CAP measurements. Most patients with CFLD do not need clinical liver biopsies and ultrasound is a crude measurement of steatosis. Furthermore, only a subset of our study sample (58%) had ultrasound data available for assessment of association with CAP. This is because routine ultrasound is not the standard of care and are only done if there is a suspicion for liver disease. However, it is possible that with the absence of ultrasound data, this potentially introduces the possibility of misclassification of patients. In addition, ALT >1.3 x ULN was included as part of the classification criteria. We acknowledge that an elevated ALT may not be an exclusively specific marker for CFLD, and thus may add to the risk for misclassification of patients. Further, the use of ursodeoxycholic acid was part of the classification criteria. Since the practice at our institution is to treat patients with CF with persistent elevation of aminotransferases with ursodeoxycholic acid, subjects prescribed ursodeoxycholic acid were categorized as having CFLD even if the most recent ALT was normal. The CFLD categories are broad to be inclusive and to avoid missing subjects with CFLD.

There is a possibility that there is confounding interplay between CAP measurement and liver fibrosis. Although there are no data in CF patients, it has been reported in adults with biopsy proven non-alcoholic fatty liver disease that high CAP values could be associated with overestimation of liver stiffness measurements, particularly in subjects with lower stages of fibrosis [18]. Additional studies are needed to see if this relationship exists in other chronic liver diseases.

This preliminary study is the first to examine CAP and steatosis in patients with cystic fibrosis. CAP measurements were normal in two-thirds of CF patients. CAP measurements were associated with ultrasound findings. Larger studies are needed for more experience using CAP in children with cystic fibrosis. Ultimately, CAP/TE is an important tool which could be used for early detection and surveillance of CFLD.

Conflict of interest statement

Drs. Lee and Jonas have received research support from Echosens® in the form of the transient elastography hardware and software. No other support was provided.

Acknowledgments

Echosens (Paris, France) provided the FibroScan® machine, technical support, and training of investigators for the purpose of this study. Echosens had no role in study design, collection/analysis/interpretation of data, writing the manuscript, or the decision to submit the manuscript for publication.

Intramural funding was provided by the Division of Gastroenterology, Hepatology and Nutrition at Boston Children's Hospital. Statistical work was partially funded by National Institute of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant # P30DK34854.

Portions of this study were presented at The Liver Meeting (the annual meeting of the American Association for the Study of Liver Diseases) on November 11, 2016 in Boston, MA.

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