

Original Article

Transient Elastography in the Evaluation of Cystic Fibrosis–Associated Liver Disease: Systematic Review and Meta-analysis

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Abstract

Background and aims: Complications of cystic fibrosis–associated liver disease (CFLD) are a leading nonpulmonary cause of death. Transient elastography (TE) has recently been investigated to detect CFLD. This study reviews the current literature for TE in the detection CFLD. A meta-analysis was performed to determine the ideal liver stiffness measurement (LSM) cutoff.

Methods: PubMed, Medline, EMBASE and Web of Science were searched from inception until April 2016 for publications involving the detection of CFLD with TE. Data were extracted using a fixed protocol (a priori design) including study design, population characteristics, probe size and AST Platelet Ratio Index (APRI).

Results: Diagnostic properties were summarized from six studies of 605 patients. Cutoff for LSM was determined using pooled data submitted by authors. The cutoff for LSM and APRI were ≥ 5.95 kPa and ≥ 0.329 respectively, yielding a sensitivity, specificity and area under receiver operator characteristic of 55%, 87%, 0.76, 52%, 93% and 0.84 for LSM and APRI, respectively. When LSM ≥ 5.95 kPa and APRI ≥ 0.329 , the sensitivity, specificity, positive predictive value and negative predictive value were 43%, 99%, 92% and 87% with a diagnostic odds ratio of 74.9. A bivariate metaregression model showed that pediatric specific cutoffs for liver stiffness and APRI may not be necessary.

Conclusion: Individually, LSM and APRI have poor sensitivity but good specificity for detecting CFLD. They are most useful when combined. We propose that patients with LSM ≥ 5.95 kPa and APRI ≥ 0.329 be investigated thoroughly for the presence of cystic fibrosis–associated liver disease.

Abbreviations:

CF, cystic fibrosis;
CFLD, cystic fibrosis–associated liver disease;
CT, computed tomography;
MRI, magnetic resonance imaging;
TE, transient elastography;
LSM, liver stiffness measurement;
APRI, AST platelet ratio index;
HSROC, hierarchical summary ROC;

AUROC, area under receiver operator characteristic;
ROC, receiver operator characteristic;
ALT, alanine aminotransferase;
AST, aspartate aminotransferase;
GGT, gamma-glutamyl transferase;
IQR, interquartile range;
PPV, positive predictive value;
NPV, negative predictive value;
DOR, diagnostic odds ratio

Keywords: *Cystic fibrosis; Liver disease; Meta-analysis*

Cystic fibrosis (CF) is a common autosomal recessive disease. Although pulmonary disease is the main cause of morbidity and mortality, cystic fibrosis-associated liver disease (CFLD) and its complications are increasingly recognized as a leading nonpulmonary cause of death (1). Up to one-third of individuals with CF will develop CFLD, with about 5% of those with CFLD progressing to chronic liver failure (2). Current methods of detecting CFLD include monitoring of liver enzymes, ultrasonography, abdominal computed tomography (CT) and abdominal magnetic resonance imaging (MRI) (3). Although the gold standard for diagnosis is hepatic biopsy, this procedure is invasive, not without morbidity, prone to sampling error and impractical for population screening. Abdominal ultrasound is the most widely used imaging technique due to widespread accessibility and noninvasive nature. However, the utility of ultrasonographic assessment is limited by inter-observer variability and low sensitivity and specificity (3). Currently, the most widely accepted diagnostic criteria for CFLD are the EuroCare CFLD criteria, which includes ≥ 2 of the following: persistent abnormal liver biochemistry over 12 months, hepatomegaly and/or splenomegaly, or ultrasound abnormalities (3). Transient elastography (TE) is a novel technique used for liver stiffness measurement (LSM) as a surrogate of liver fibrosis. It has been validated for use in various forms of chronic liver disease in adults including hepatitis B and C, primary biliary cirrhosis, and nonalcoholic fatty liver disease (4). Liver stiffness measurements may be useful in the clinical setting for detecting and monitoring CFLD because it is a noninvasive, relatively inexpensive, fast, and less resource-intensive technique with less inter-observer variability compared with ultrasonography (3). Few studies have evaluated the role of TE in the detection of CFLD (5–11), with limited studies specifically evaluating pediatric patients (5, 6, 11). The purpose of this study is to perform a systematic review to determine the diagnostic properties of TE in the detection of CFLD in adult and pediatric populations compared with currently accepted international CFLD diagnostic criteria. A single indicator of test performance, the diagnostic odds ratio (DOR), was also reported (12). Our secondary objective was to perform a meta-analysis to determine the most appropriate LSM cutoff for the detection of CFLD using data submitted by original authors from included studies. In addition, cutoffs for AST platelet ratio index (APRI), when available, were calculated to determine if this could augment the diagnostic properties of LSM.

METHODS

Search Strategy

Medline (Pubmed), Medline (OvidSP), EMBASE, Web of Science, Cochrane Database of Systematic Reviews and Google Scholar were searched from database inception to present, using combinations of the following key terms: cystic fibrosis, liver disease, cystic fibrosis associated liver disease, hepatic disease, transient elastography, Fibroscan, and elasticity imaging techniques. The literature search was performed on April 22, 2016 (Appendix 1).

Manual searches of reference list from primary studies were performed to locate any missing studies from initial electronic search strategies. Abstracts and proceedings from the American Association for the Study of the Liver, European Association for the Study of the Liver and Digestive Disease Week annual meetings were also reviewed from 2011 to 2016. This time period was chosen because the currently used criteria for the diagnosis of CLFD was published in 2011. Prior to this, diagnosis of CFLD was not well defined.

Selection of Studies

Inclusion Criteria.

Studies were considered if they included the current EuroCare criteria defining CFLD or similar parameters. Liver stiffness measurement was measured via transient elastography and data available to construct a 2×2 table of test performance for analysis. Articles assessing LSM in multiple forms of chronic liver disease were included if CFLD-specific data could be extracted. Studies with adult and pediatric data were also included.

Case definition of CFLD was based on the EuroCare CFLD criteria (≥ 2 of the following: persistent abnormal liver biochemistry over 12 months, hepatomegaly or splenomegaly, or ultrasound abnormalities).

Exclusion Criteria.

Non-English articles, letters, editorials, comments, review articles or case report formats were excluded.

Data Extraction Protocol

Two independent reviewers (SL, JD) reviewed the titles and abstracts of all search results. Relevant articles were independently reviewed for inclusion and exclusion criteria. Any disagreement was resolved through consensus between the reviewers. Data extracted included first author, country of first author, year of publication, study design, number of patients,

patient characteristics (pediatric, adult or mixed and number of patients with CFLD), median LSM with interquartile ranges (IQR) (if available), optimal cutoff value to detect CFLD, area under receiver operator characteristic (AUROC), sensitivity and specificity. Where available, aspartate APRI information was also extracted. Corresponding authors of included studies were contacted to request data from their study. This included age, sex, presence of CFLD (as classified by submitting authors), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), platelet count, pancreatic sufficiency, ultrasound findings and LSM. The upper limits of normal for liver enzymes and platelet counts from respective laboratories were also requested.

Quality Assessment

The quality of the diagnostic studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). This tool has been validated to assess the internal and external validity of diagnostic accuracy studies included in systematic reviews (13, 14).

Statistical Analysis

Meta-analysis.

The eligible studies were summarized with sensitivity and specificity described. A hierarchical summary receiver operator curve (HSROC) curve was calculated using a bivariate random effects model accounting for study-specific sensitivity and specificity using STATA 13.1 (STATA Corp LP, College Station, TX, USA) and Revman 5.2 (The Cochrane Collaboration, Copenhagen, Denmark). The technique models the true positives and true negatives as a bivariate response with random effects for accounting for heterogeneity. Based on the same hierarchical model, a meta-regression was used to investigate the effect of pediatric and adult groups on the estimation.

To estimate the diagnostic value of TE for the diagnosis of CFLD, a weighted summary DOR, as a single indicator of test performance, was determined using STATA. I^2 and the forest plot were generated with R v3.4.0 (R Core Team, Vienna, Austria).

Pooled analysis.

The author SL contacted corresponding authors of eligible studies to request their original data. Individual patient data were normalized to the current EuroCare CFLD criteria to facilitate a pooled analysis. Only patients with valid ($\geq 60\%$ successful measurements) and reliable (IQR/median ≤ 0.30) LSMs were included. Age, liver enzymes, platelets, LSM and APRI were compared between groups using the Wilcoxon-Rank sum test using STATA 13.1 (STATA Corp LP, College Station, TX, USA).

Sex and pancreatic sufficiency between groups were compared using Chi-squared and Fisher Exact methods,

respectively. Optimal cutoffs for LSM and APRI were assessed by the receiver operating characteristic (ROC) (STATA 13.1). This was calculated as sensitivity versus 1-specificity (Microsoft Excel 2016). The optimal cutoff was determined by the point yielding the maximum sum of sensitivity and specificity. The AUROC was expressed. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for these cutoffs. Diagnostic odds ratio was also calculated for selected cutoffs to evaluate test performance.

Stratified analysis of children (<18 years) and adults (≥ 18 years) was also performed.

RESULTS

Search Results

The online search revealed 116 published articles (Figure 1). After removal of duplicates, 69 abstracts were manually reviewed. Subsequently, 36 abstracts were excluded due to the following reasons: 16 were unrelated to TE, eight were unrelated to CFLD and 12 were review articles. The remaining 33 abstracts were reviewed as full text published articles. Subsequently, 27 studies were excluded, 13 did not use the current EuroCare CFLD criteria, nine articles and conference abstracts did not contain sufficient information to extract required data, three conference abstracts were subsequently published into a study which was included in analysis (i.e., duplicate), and two were letters to editor. Six studies were included in the final analysis. Of note, a Google scholar search, up to page 10, did not reveal additional relevant articles not already found by our described search method.

The included studies are described in Table 1. Studies included authors from Canada, Australia, Germany and Belgium. Three studies had exclusively adult patients (8, 9, 11) and three studies had a mixed population of adults and pediatrics (7, 10, 15). A total of 633 patients, comprising 460 (73%) adult and 173 (27%) pediatric patients, were included in the meta-analysis.

Quality Assessment

When QUADAS-2 criteria were applied, studies had low to unclear risk of bias, except one (16) (Figure 2). The reference standard bias was classified as unclear in all studies because none of the studies explicitly stated that the interpretation of the reference EuroCare criteria was made independently from the LSM data as measured by TE. One study had a high risk of patient selection bias because only patients with liver abnormalities were referred for assessment (9). All studies had low applicability concerns.

Diagnostic Properties of TE in the Detection of CFLD

The diagnostic properties for TE in the detection of CFLD with varying cutoffs are summarized in Table 2. Qualitatively,

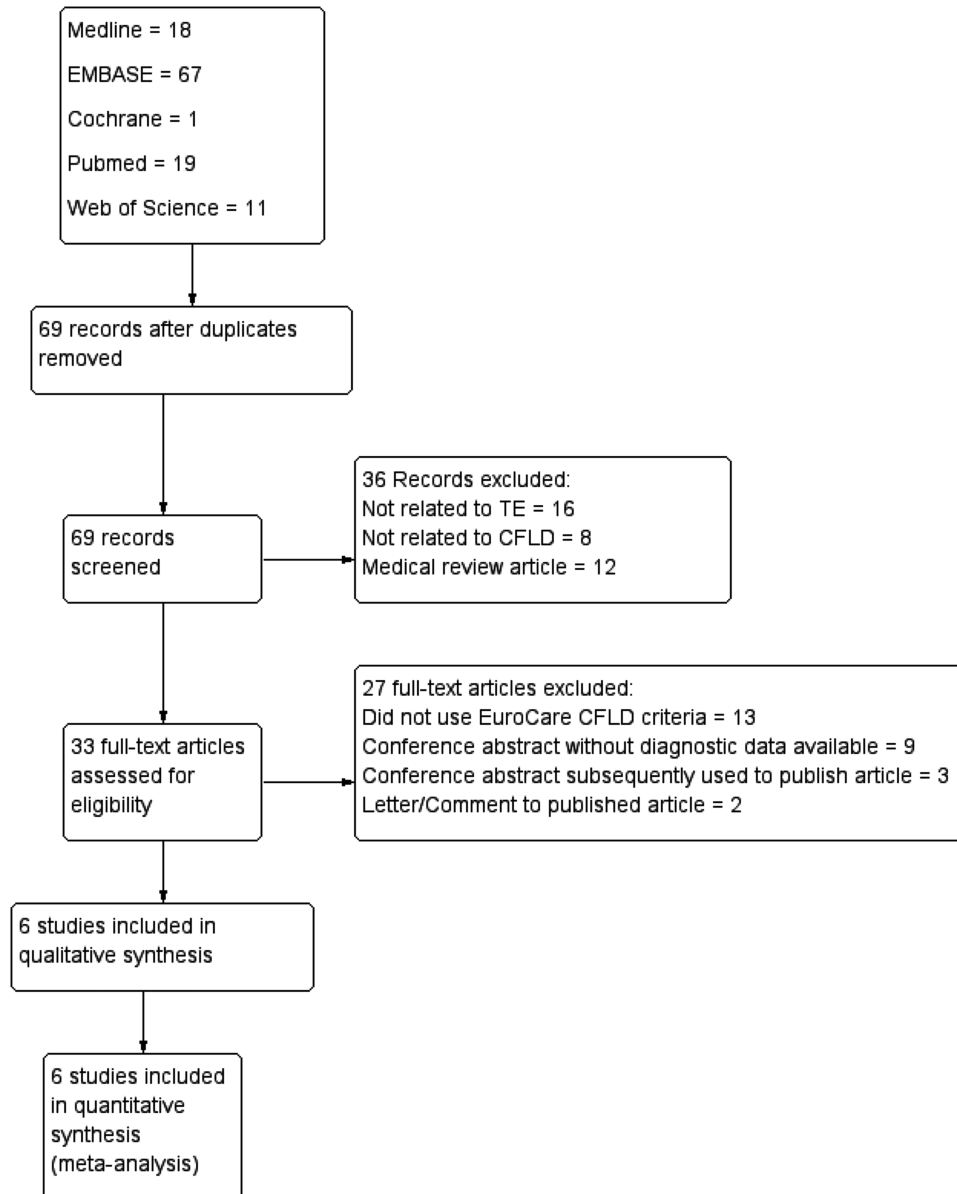


Figure 1. PRISMA search method.

Table 1. Summary of included studies

Author	Year	Country	Study Design	Population	Number of Patients	Number of CFLD
Friedrich- Rust et al.	2013	Germany	Prospective	Mixed	106	24
Karlas et al.	2012	Germany	Prospective	Adult	55	14
Kitson et al.	2013	Australia	Prospective	Adult	50	25
Rath et al.	2012	Germany	Prospective	Mixed	145	68
Sadler et al.	2015	Canada	Prospective	Adult	127	18
Van Biervliet et al.	2016	Belgium	Prospective	Mixed	150	20
Total					633	169

the range of sensitivities and specificities for using TE to detect CFLD were 46% to 100% and 76% to 92%, respectively. The calculated summary DOR as a single indicator

of test performance was 14.9 (95% CI, 6.06–36.5; $Q=5.01$, $P=0.414$), with a low degree of heterogeneity between studies (Figure 3).

In order to determine the effect of being a child or adult on the diagnostics of LSM for individual study cutoffs, we conducted a meta-regression adjusting for the covariate ‘adult/pediatric’. In the studies that had both pediatric and adult patients, categorization into pediatric or adult did not have any effect on sensitivity ($P=0.83$) nor false positive rates ($P=0.53$).

The effect of being or adult on the diagnostic properties of APRI could not be analyzed as APRI cutoffs were only reported in adult studies.

Pooled Analysis

Data for 644 patients were submitted by collaborating authors for pooled analysis. Author SV submitted eight more patients than her initial cohort of 150 (15). Author ER submitted three more than the initial 145 patients (10). After normalizing the data between studies, 39 patients were excluded from analysis, 24 had unreliable measurements, and 15 had failed LSM measurement. By standardizing all data to current CFLD criteria, one patient was recategorized into the CFLD group. The pooled analysis of 605 patients meeting eligibility criteria is summarized in Table 3.

The median age was 24 years old, with 293 females (48%), and 171 patients (28%) had CFLD. The patients with CFLD had higher median LSM (6.3 kPa versus 4.4 kPa) ($P<0.005$) and a lower platelet count ($258 \times 10^9/L$ versus $307 \times 10^9/L$) ($P<0.005$). As expected, the ALT, AST and GGT were all higher in the CFLD group compared with the non-CFLD group: 30 U/L, 30 U/L 27 U/L versus 19 U/L versus 24U/L, 14 U/L ($P<0.005$), respectively. The APRI was calculated for 379 patients. The median APRI value was higher in patients with CFLD compared with non-CFLD: 0.330 versus 0.151 ($P<0.005$).

The diagnostic properties of calculated cutoff values from the pooled analysis were summarized in Table 4. The optimal LSM cutoff was ≥ 5.95 kPa yielding a sensitivity, specificity, PPV, NPV, AUROC and accuracy of 55%, 87%, 65%, 83%, 0.76 and 78%, respectively (Figure 4A). The optimal APRI cutoff was ≥ 0.329 , yielding sensitivity, specificity PPV, NPV, AUROC and accuracy of 52%, 93%, 66%, 88%, 0.78 and 84% (Figure 4B). A meta-regression showed no effect on the sensitivity ($P=0.47$) nor false positive rate ($P=0.37$) based on being an adult or child with the pooled LSM cutoffs.

Similarly, the meta-regression did not show an effect for the calculated APRI cutoff sensitivity ($P=0.79$) and false positive rate ($P=0.11$).

Combining LSM and APRI

When both LSM and APRI values were available for analysis, if the LSM is ≥ 5.95 kPa and APRI ≥ 0.329 , then the sensitivity, specificity, PPV, NPV and accuracy were 43%, 99%, 92%, 87% and 0.87, respectively.

Pediatric subgroup analysis.

In the subgroup analysis of 167 pediatric patients, 45 (27%) had CFLD. The median age was 10 years. Eighty-four patients were female (50%). The median LSM for pediatrics with CFLD was higher, 6.4 kPa versus 4.4 kPa ($P<0.005$). Similarly, the ALT, AST and GGT were all significantly elevated in CFLD patients compared with non-CFLD patients. Platelets were also decreased in the pediatric CFLD patients compared with

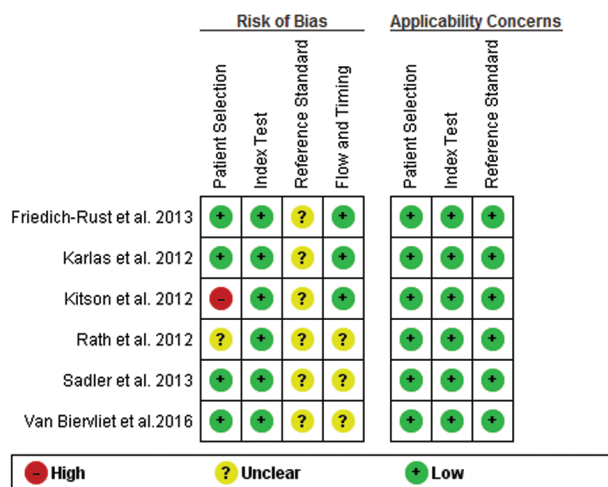


Figure 2. QUADAS 2 summary of methodological quality.

Table 2. Summary of diagnostic properties of included studies

Study	LSM Cutoff (≥kPa)	TP	FP	FN	TN	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)
Friedrich-Rust et al. 2013(7)	7.1	11	7	13	71	46 (26–67)	91 (82–96)	8.5 (2.8–26.2)
Karlas et al. 2012(11)	5.9	6	1	8	34	43 (18–71)	97 (85–100)	25.5 (2.7–242.6)
Kitson et al. 2013(16)	5.5	19	2	6	23	76 (55–91)	92 (74–99)	36.4 (6.6–201.7)
Rath et al. 2012(10)	5.5	35	14	32	61	52 (40–65)	81 (71–89)	4.8 (2.2–10.1)
Sadler et al. 2015(8)	5.3	12	19	6	90	67 (41–87)	83 (74–89)	9.5 (3.2–28.4)
Van Biervliet et al. 2016(15)	6.8	18	11	2	119	90 (68–99)	92 (85–96)	97.4 (19.9–475.6)

TP: True Positive, FP: False Positive; FN: False Negative; TN: True Negative

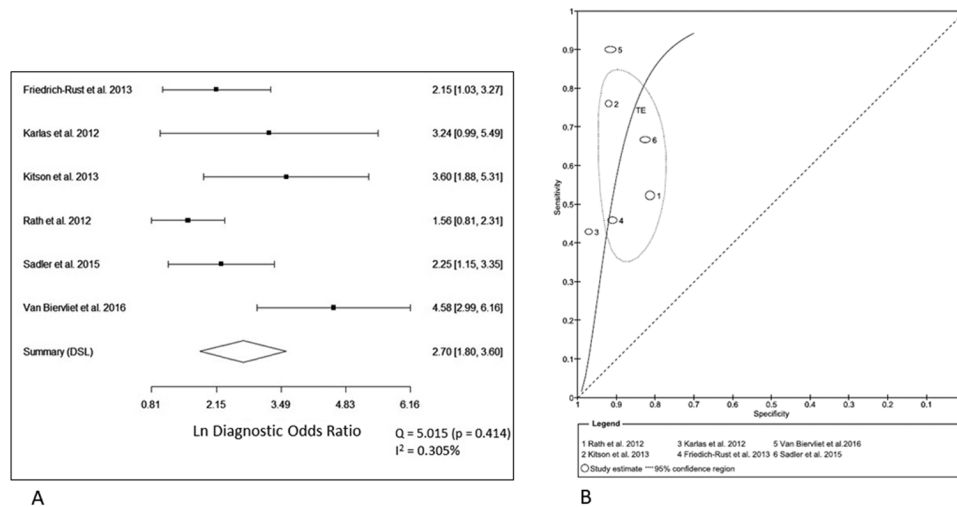


Figure 3. Summary figures of 6 pools studies with 633 pediatric and adult patients with cystic fibrosis. A) Forest plot of diagnostic odds ratios of included studies. B) Hierarchical summary receiver operator characteristic of included studies.

non-CFLD patients $283 \times 10^9/L$ versus $343 \times 10^9/L$ ($P=0.007$). The APRI for 82 pediatric patients showed a higher median APRI in CFLD patients compared with non-CFLD patients, 0.436 versus 0.130 ($P<0.005$).

A significantly lower proportion of CFLD patients were pancreatic insufficient compared with non-CFLD patients: 49% versus 69% ($P=0.019$).

Adult sub-group analysis.

In the subgroup analysis of 442 adult patients including 128 (30%) CFLD patients, the median age was 28 years. There were 209 females (47%). The median LSM for adults with CFLD was higher, 6.2 kPa versus 4.3 kPa ($P<0.005$). Similarly, the ALT, AST and GGT were all significantly elevated in CFLD patients compared with non-CFLD patients. Platelets were also decreased in CFLD patients compared with non-CFLD patients: $246 \times 10^9/L$ versus $292 \times 10^9/L$ ($P<0.005$). The APRI for 297 adults showed a higher median APRI in CFLD patients compared with non-CFLD patients, 0.330 versus 0.169 ($P<0.005$).

In contrast to the pediatric group, a significantly higher proportion of CFLD patients were pancreatic insufficient compared with non-CFLD patients: 79% versus 63% ($P<0.005$).

DISCUSSION

Optimal screening in the CF population for CFLD continues to be a challenge. Current recommendations include routine bloodwork and abdominal ultrasound, which have limited sensitivity and specificity (3). Although these methods are noninvasive, they can be anxiety-provoking and time-consuming, especially in the pediatric population. When there is diagnostic uncertainty, a liver biopsy is required, which can lead to morbidity and mortality. In pediatrics, a liver biopsy typically

requires a general anesthetic, which may be further complicated by a patient's respiratory status. Liver stiffness measurement measured by TE offers a quick, noninvasive alternative to the traditional methods of detecting CFLD. This tool may add further diagnostic clarity to avoid the need for biopsy. Several small studies have attempted to address the optimal cutoff and diagnostic properties of LSM to detect CFLD.

In this systematic review and meta-analysis, we have summarized the diagnostic properties of LSM as measured by TE for the detection of CFLD. To our knowledge, this is the first review of the literature and the largest pool of raw data from independent cohort studies. By evaluating this data submitted by contributing authors, standardization to current EuroCare CFLD criteria could be applied to all patients. Our primary outcome was to determine the usefulness of TE in the detection of CFLD. As described in the HSROC, LSM has high specificity. The summary DOR for TE in the detection of CFLD was robust at 14.9 (95% CI, 6.06–36.5). This is in a similar range to a previous meta-analysis assessing TE and detecting fibrosis in hepatitis C patients, showing that TE had a DOR of 7.6 to 10.2 for detecting F2–F4 fibrosis (17).

Our secondary outcome was to determine the optimal cutoff for the detection of CFLD by pooling data from all eligible studies. Our cutoff of ≥ 5.95 kPa was within the lower range for the detection of F2 fibrosis in the published literature for various other liver diseases (18). This comparison should be interpreted with caution because the cutoff for CFLD was intended to detect disease and not to stage degree of fibrosis. Recent literature also suggests that different diseases may require different cutoffs (19). This may be especially relevant as steatosis is a manifestation of CFLD. Steatosis can decrease the velocity of the acoustic wave, thus decreasing the LSM value.

Our pooled cutoff had a specificity of 87% (95% CI, 83–89%) which was within the expected range as

Table 3. Summary of compiled patient characteristics submitted by authors

All patients				
	All (n=605)	Non CFLD (n=434)	CFLD (n=171)	P value
Age (years)	24 (16–33)	24 (16–33)	25 (17–33)	0.97
Female	291 (48%)	210 (48%)	83 (48%)	1.00
LSM (kPa) (n=605)	4.6 (3.7–5.9)	4.4 (3.6–5.2)	6.3 (4.4–10.6)	<0.005
ALT (U/L) (n=598)	21 (16–30)	19 (15–26)	30 (20–47)	<0.005
AST (U/L) (n=455)	25 (20–31)	24 (19–29)	30 (24–40)	<0.005
GGT (U/L) (n=495)	16 (11–28)	14 (10–21)	27 (16–60)	<0.005
PLT (x 10 ⁹ /L) (n=523)	298 (243–366)	307 (257–371)	258 (184–346)	<0.005
Pancreatic Insufficient (n=555)	368 (66%)	264 (65%)	104 (70%)	0.26
APRI (n=379)	0.173 (0.116–0.260)	0.151 (0.107–0.220)	0.330 (0.195–0.637)	<0.005
Pediatric Subgroup				
	All (n=167)	Non CFLD (n=122)	CFLD (n=45)	P value
Age (years)	10 (7–13)	10 (7–14)	10 (8–13)	0.89
Female	84 (50%)	59 (48%)	25 (56%)	0.49
LSM (kPa) (n=167)	4.6 (3.8–5.7)	4.4 (3.7–5.2)	6.4 (5.1–15.4)	<0.005
ALT (U/L) (n=162)	21 (15–30)	19 (14–24)	31 (20–52)	<0.005
AST (U/L) (n=94)	28 (24–32)	27 (23–31)	33 (27–47)	0.007
GGT (U/L) (n=144)	13 (10–20)	11 (9–15)	20 (15–35)	<0.005
PLT (x 10 ⁹ /L) (n=155)	331 (269–395)	343 (283–398)	283 (220–387)	0.007
Pancreatic Insufficient (n=165)	105 (66%)	83 (69%)	22 (49%)	0.019
APRI (n=82)	0.135 (0.107–0.188)	0.130 (0.106–0.161)	0.436 (0.197–0.687)	<0.005
Adult Subgroup				
	All (n=438)	Non CFLD (n=314)	CFLD (n=128)	P value
Age (years)	28 (22–37)	28 (22–37)	28 (23–36)	0.89
Female	207 (47%)	151 (48%)	58 (45%)	0.60
LSM (kPa) (n=438)	4.5 (3.7–6.0)	4.3 (3.5–5.2)	6.2 (4.35–9.5)	<0.005
ALT (U/L) (n=436)	21 (16–32)	20 (15–27)	28 (20–43)	<0.005
AST (U/L) (n=361)	24 (19–30)	23 (19–28)	28 (23–39)	<0.005
GGT (U/L) (n=350)	18 (12–32)	16 (10–24)	31 (18–63)	<0.005
PLT (x 10 ⁹ /L) (n=368)	284 (232–349)	292 (251–356)	246 (171–333)	<0.005
Pancreatic Insufficient (390)	263 (67%)	181 (63%)	82 (79%)	<0.005
APRI (n=297)	0.185 (0.118–0.278)	0.169 (0.111–0.235)	0.330 (0.195–0.603)	<0.005

Median (IQR)

Table 4. Diagnostic properties of cutoffs derived from compiled data

Optimal Cutoff	Sensitivity	Specificity	PPV	NPV	AUROC	Accuracy
≥5.95 kPa	55 (47–62)	87 (83–89)	65 (54–70)	83 (79–86)	0.76 (0.71–0.80)	0.78 (0.75–0.81)
≥0.329	52 (40–63)	93 (90–96)	66 (53–78)	88 (84–91)	0.78 (0.71–0.84)	0.84 (0.80–0.88)
LSM ≥5.95 kPa AND APRI ≥0.329	43 (32–55)	99 (97–100)	92 (78–98)	87 (83–90)	n/a	0.87 (0.84–0.91)

Value (95% CI)

determined by the HSROC. The value in the LSM may be in its specificity and high negative predictive value. As such, if LSM is below the cutoff, it is unlikely that the

patient has CFLD. This is consistent with the role of TE in ruling out advanced disease in other forms of chronic liver disease (20).

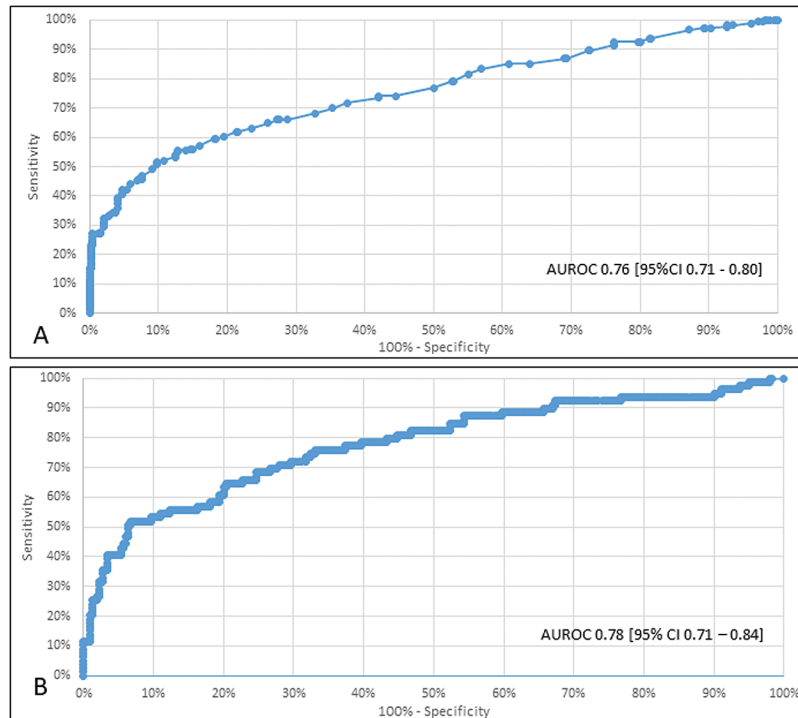


Figure 4. Receiver Operator Curves for pooled data analysis. A) LSM cut-off determined by pooled data from 605 pediatric and adult patients with cystic fibrosis. B) APRI cut-off determined by pooled data from 379 pediatric and adult cystic fibrosis patients.

Another useful parameter may be the APRI. Like LSM, the APRI has good specificity, 93% (95% CI, 90–96%). This may be useful for centers without TE capabilities because components of the APRI can be calculated from standard complete blood counts and liver biochemistry.

Finally, if both LSM and APRI are combined, this may be the most useful for the detection of CFLD. If the LSM was ≥ 5.95 kPa and APRI ≥ 0.329 , then there was a high PPV and NPV. The DOR for combining positive LSM and APRI was 75 (95% CI, 22–253). This is within a comparable range to the DOR of 74.9 (95% CI, 38.7–145.1) when LSM is used in the detection of cirrhosis in patients with chronic hepatitis C (17).

Our analysis has several strengths. First, literature for LSM in detecting pediatric CFLD is limited. At the time of the literature review, there were no studies determining the optimal LSM cutoff for the detecting CFLD exclusively in the pediatric population. By pooling pediatric data from studies with mixed populations, we determined through a meta-regression that pediatric specific cutoff may not be necessary. This notion is supported by a large pediatric study where age was not found to affect LSM (21). A more recent study did reveal age-related LSM differences; however, this group used an M probe for all patients studied, which may not have been appropriate (22).

Another strength to our study is that we calculated LSM cutoffs from individual patient data submitted by authors. Having individual data allowed for the current internationally accepted CFLD criteria to be applied to all patients, thus decreasing heterogeneity. Some studies included patients

with unreliable LSM to be included in their cutoff measurements. With our pooled data, only patients with reliable LSM were analyzed, therefore a more accurate LSM cutoff would be expected.

It has been hypothesized that pancreatic insufficiency may be associated with CFLD (23). Pancreatic insufficiency differed among those with CFLD and without CFLD in the subgroup analysis. Pancreatic insufficiency was more prevalent in the adult CFLD group. In contrast, in the pediatric group, with a median age of 10, CFLD patients were more likely to be pancreatic sufficient. The reason for this is unclear as most patients develop pancreatic insufficiency within the first year of life (24). It was unclear from the data submitted by the authors how pancreatic insufficiency was diagnosed; thus it was a potential confounder. Further studies are needed to further elucidate this new finding.

The prevalence of CFLD within our pooled cohort was 28%, which is in keeping with the current literature (3). Therefore, our proposed LSM and APRI cutoffs can be applied broadly to the CF population and can expect similar positive and negative predictive values.

The quality of included studies was good, but all had an unclear reference standard bias. That is, it is unclear whether the EuroCare CFLD criteria were determined without knowledge of the LSM. Overall, the concern for this is low because it is unlikely that prior knowledge of LSM would affect interpretation of CFLD criteria; therefore, the risk of bias is low.

As expected, the liver enzymes suggestive of liver injury (ALT and AST) were higher in the CFLD group compared with the

non-CFLD group. The elevated LSM in CFLD patients may reflect not only fibrosis but also liver inflammation.

A limitation of our study was the inconsistency of probes used in the studies. Manufacturer recommendation for probe sizes are based on weight and chest circumference. In our analysis, different studies used different probe sizes. For example, one study used a medium probe in all patients (15), which also included pediatric patients, while another used different probes based on patient weight (10). There is emerging literature that different probe sizes may yield statistically significant differences in LSM in the pediatric population (21), although the clinical significance is unknown. In addition, the duration of fasting before the LSM was also unclear from the studies, which may have also affected LSM. As TE is increasingly used, guidelines have been recently published to standardize technique (20).

Another limitation was that genotypic information was not available; therefore, any genotypic correlation with CFLD would not be analyzed.

There was also the risk of misclassification bias due to treatment effects. Ursodoxycholic acid is a frequently used medication to treat CFLD. In our analysis, medication history was not available. Therefore, patients with CFLD who improved on ursodeoxycholic acid may have been misclassified as not having CFLD.

The primary objective of our study was to summarize the diagnostic properties of LSM for the detection of CFLD. Secondly, we sought to determine the optimal LSM cutoff. The APRI information was often available and, therefore, was included in our analysis to determine if this noninvasive index could augment LSM in the detection of CFLD. Our primary literature review did not include APRI as one of the search terms, and therefore, publications reviewing APRI in the detection of CFLD were likely missed. This may be an area of future study. Despite this limitation, we feel that our APRI cutoff based on 379 patients still provides valuable information.

Steatosis is a manifestation of CFLD which may affect LSM; however, ultrasonographic information regarding steatosis was not available to analyze. A future area of investigations would include using controlled attenuation parameter (CAP) in the assessment of CFLD. Using the CAP to quantify the degree of steatosis may improve the diagnostic value of TE in the detection of CFLD. Furthermore, determining different subtypes of liver manifestations (i.e., steatosis only versus fibrosis only) of CF patients may provide further insight into the progression of CFLD.

Lastly, data was not able to segregate LSM or APRI cutoffs with complications of portal hypertension. Two small studies showed that an LSM of >8.9–12.0 kPa may predict the presence of esophageal varices (6, 9). Aql et al. recently published a large pediatric and young adult cohort using LSM to detect the presence and severity of CFLD (25). They found

an optimal LSM cutoff of >6.2 kPa for detecting CFLD with portal hypertension. However, the criteria used for CFLD in this cohort was very broad and was not consistent with the currently accepted diagnostic criteria. Furthermore, as the authors discussed the limitations of their study, one of the criteria used for portal hypertension was splenomegaly on physical examination, which may not be accurate, as lung hyperinflation in the CF population may cause the spleen to be palpable. To our knowledge, other clinically relevant CFLD end points such as liver-related mortality or time to liver transplantation have not been studied in the context of LSM but would be a valuable area of future studies.

CONCLUSIONS

To our knowledge, this is the largest cohort of CF patients used to calculate the diagnostic properties and optimal cutoffs for LSM and APRI in detecting CFLD. These methods have low sensitivity but good specificity. The strength of these tests is in their NPV; therefore, patients with LSM <5.95 kPa or APRI <0.329 are unlikely to have CFLD, especially if neither are above the cutoff. However, if both LSM is ≥ 5.95 kPa and APRI is ≥ 0.329 , these patients are likely to have CFLD and should be thoroughly investigated.

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