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Liver Disease in Patients with Cystic Fibrosis

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Abstract

Purpose of review—To aim of this study was to provide an overview of the current understanding of the pathophysiology, diagnosis, and management of cystic fibrosis-liver disease (CFLD).

Recent findings—CFLD has a variety of manifestations. Previously, it was thought that patients progressed from mild cholestatic disease to cirrhosis to decompensated cirrhosis with portal hypertension. Newer evidence suggests that some patients may develop cirrhosis while others develop non-cirrhotic portal hypertension. Advances in our understanding of the pathophysiology of disease necessitate modifications to the current diagnostic criteria. Both fibroscan and non-invasive biomarkers can be used to identify patients with cirrhosis and portal hypertension. Ursodeoxycholic acid remains the mainstay of therapy despite a paucity of rigorous studies supporting its use. Novel therapeutic agents such as CF transmembrane conductance regulator (CFTR) modulators and potentiators are encouraging but need to be evaluated specifically in CFLD.

Summary—A better understanding of the pathophysiology of disease is critical to developing more disease specific diagnostics and therapeutics.

Keywords

Cystic fibrosis liver disease; Ursodeoxycholic acid; transient elastography; biomarkers; non-cirrhotic portal hypertension

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INTRODUCTION

Cystic fibrosis (CF) is the most common, autosomal recessive, systemic disease of newborns in the United States(1, 2). It is the result of mutations in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR is located on the apical surface of cholangiocytes but is not found on hepatocytes(3). Defects in the CFTR protein lead to a wide spectrum of hepatobiliary conditions collectively referred to as cystic fibrosis liver disease (CFLD). CFLD is now the third leading cause of mortality in cystic fibrosis (4). Early identification and management of patients with CFLD continues to be clinically challenging. This review will explore the pathophysiology of CFLD, evaluate the evidence supporting the use of non-invasive diagnostic tools, as well as describe both traditional and emerging therapies.

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY

CFLD is an umbrella term that encompasses a wide spectrum of liver disease that result from having cystic fibrosis. These include elevated liver enzymes, hepatic steatosis, neonatal cholestasis, focal biliary cirrhosis, multilobular cirrhosis, and cholangiopathy (4). In 2007, the North American Cystic Fibrosis Foundation classified CFLD into three categories: pre-clinical disease, CFLD without cirrhosis and portal hypertension (PH), and CFLD with cirrhosis and PH. The most clinically relevant forms of CFLD are biliary cirrhosis and PH because of their associated mortality risk. More recent studies have reported an increasing identification of non-cirrhotic portal hypertension in patients with CF (5, 6).

Cirrhosis

Cirrhosis in CFLD is likely due to multiple pathways that are a result of defects in the CFTR gene. Cirrhosis typically occurs in patients with severe mutations (class I-III) (7). These mutations lead to changes in the CFTR that affect its ability to control water and solute movement. This results in increasingly viscous bile and decreased bile flow, which causes biliary plugging (Figure 1a), hepatocyte damage, inflammation, and fibrosis (7). A recent study has also reported that the CFTR regulates TLR-4-dependent inflammatory responses by inhibiting Rous sarcoma oncogene cellular homologue (Src) activity (9). When CFTR is defective, Src self-activates leading to an increased production of inflammatory cytokines and a loss of epithelial barrier function (8)]. Decreased barrier function allows for translocation of bacteria into the portal circulation. This in turn activates pathways of hepatic inflammation and fibrosis (9). Focal biliary cirrhosis (Figure 1b) is the most well-known manifestation of CFLD but only about 5–10% of these patients progress to multilobular cirrhosis within the first decade of life (10).

Noncirrhotic Portal Hypertension

More recent findings propose an alternative disease course in which PH may present independent of cirrhosis. Histologic evaluation of patients with PH has led to the recognition that cirrhosis is only present in some patients. Pereria et al. have reported that only 27% of patients with PH in CF present with cirrhosis (6, 11). Witters et al., examined histologic specimens from 5 explanted livers and 4 biopsy specimens, none of which were cirrhotic on

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histology (6). These patients had low hepatic venous portal gradient (HPVG) (range 4–9mm Hg) despite having manifestations of PH such as varices, ascites, and splenomegaly. These manifestations were thought to be due to a pre-sinusoidal-type of PH due to obliterative venopathy (Figure 1c) with dense fibrosis within portal vein branches, a finding seen in non-cirrhotic portal hypertension (NCPH) (Figure 1d) (6). Similarly, 8 of the 10 patients in a study by Hillaire et al. showed signs of PH without cirrhosis(5). As patients with cystic fibrosis begin to have longer life spans, more cases of NCPH may be reported.

DIAGNOSIS

CFLD is often difficult to diagnose due to the subclinical nature of disease and the wide spectrum of hepatic manifestations. A single diagnostic test is usually not sufficient to screen for all types of CFLD. Liver biopsy remains the gold standard for diagnosing and staging liver disease in cystic fibrosis even though disease is patchy. Dual pass biopsy specimens have been described to improve the accuracy of diagnosing CFLD, but discordance still occurs in 38% of biopsy pairs (12).

Experts from the joint National Institutes of Health / Cystic Fibrosis Foundation Clinical Research Workshop in 2009 (13), the CF Foundation (14), and Koh et. al (15) have all proposed diagnostic criteria (Table 1). The diagnosis is dependent on multiple parameters including liver function tests, physical exam, imaging, non-invasive biomarkers, transient elastography, and liver biopsy.

Liver function tests

Elevated liver function tests occur frequently in cystic fibrosis and cannot be used alone to diagnose CFLD, however, persistent elevations should raise clinical suspicion for liver involvement. Transient elevations can occur due to malnutrition, concurrent illness, and drug-related injury and are not specific for liver disease. At least one abnormal value of AST or ALT are seen in 53% – 93% (16, 17) and at least one abnormal value of GGT is seen in over one third of cystic fibrosis patients by age 21(17). In a prospective longitudinal study evaluating the relationship between elevated liver tests and CFLD, liver enzymes were frequently found to be persistently elevated (defined as abnormal values more than 6 months apart) with ALT being persistently elevated in 85% of patients (17). In the same study, an elevated AST >1.5 × ULN or GGT >1.5X ULN were the strongest predictor of having clinically significant liver disease (17). Regarding this finding, the authors identify that the confidence intervals were wide and the specificity for liver disease was low. If liver tests are combined with an abnormal ultrasound then the specificity for liver disease is improved, from 41% to 74% (16). Given that only 10% of cystic fibrosis patients will develop cirrhosis, whereas the majority of patients will develop an abnormal liver function test, elevations should only raise clinical concern when persistently elevated or in conjunction with a second abnormal screening test (14).

Non-invasive Biomarkers

Non-invasive fibrosis biomarkers are serologic tests that provide a novel and inexpensive method to screen for fibrosis in CFLD. Non-invasive fibrosis biomarkers such as the AST-to-

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platelet-ratio-index (APRI) [AST/upper limit of normal AST × 100/ Platelet count (10^9/l)] and the fibrosis-4 index (FIB-4) [Age (years) × AST/ Platelets (10^9/l) × ALT] have recently demonstrated clinical utility in CFLD (18). The APRI appears to be superior to the FIB-4 in the assessment of fibrosis (AUROC: 0.75 vs. 0.60; $P = 0.005$) and cirrhosis (AUROC: 0.81 V 0.70, p>0.05) (18). An APRI score > 0.264 had a sensitivity of 73.1% and specificity of 70.2% for predicting CFLD (18). FIB-4, however, performed better when differentiating patients with PH from those without PH, with an AUC of 0.91 and a sensitivity and specificity of 78% and 93% respectively (18). Stonebraker et al. have also shown significantly different FIB-4 and APRI scores among patients with and without varices (19). The integration of biomarkers, such as APRI and FIB-4, into the diagnostic criteria for CFLD has demonstrated to capture more patients with liver involvement at an early stage compared to the Debray criteria and warrants further consideration given their ability to identify patients with both fibrosis and portal hypertension(15).

A few studies have also investigated the use of miRNAs for the detection of liver disease in children, though currently these tests are not approved for use in any liver disease. Analysis of miRNA signature in children with CFLD and cystic fibrosis without liver disease has revealed elevated levels of circulating miR-122 in CFLD and elevated levels of MiR-21 and MiR-25 in cystic fibrosis patients without liver disease(20). Based on these results, the combination of miR-122, MiR-21, and MiR-25 could be used for the diagnosis of CFLD in the future (21).

Transient elastography

Vibration controlled transient elastography (VCTE) appears to be a useful tool for identifying and monitoring patients with signs of CFLD. It has been previously validated in viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease. In a cross-sectional observational study, children and young adults were pre-categorized into having no CFLD, CFLD without PH, and CFLD with PH. VCTE showed significantly different liver stiffness measurements for each group (22). The median liver stiffness values were notably higher in patients with CFLD with PH (14.1 kPA) as compared to those with CFLD without PH (5.1 kPA) (22). The same study also compared liver stiffness to the APRI score and demonstrated that the area under the ROC was greater for VCTE (AUC: 0.91) compared to the APRI score (AUC: 0.78). Combining these tests did not improve their ability to identify those with CFLD (22). Similar results were seen in a study aimed to identify patients with early fibrosis that used VCTE to differentiate patients with CFLD (8.2kPA) and those without CFLD (4.5kPA) with an AUC of 0.91(23). They found a mean increase in VCTE scores of >0.38kPA per year identified those most at risk for developing CFLD(23). Taken together, VCTE may be a useful tool for diagnosing and monitoring fibrosis in CFLD.

MANAGEMENT

The current recommendation is for patients with cystic fibrosis to be screened for CFLD with yearly physical exam, liver function tests, and abdominal imaging due to the challenges with early detection of liver disease(13). Once CFLD is identified, the mainstay of therapy is to mitigate the complications of PH and cirrhosis. Unfortunately, evidence- based guidelines

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for the management of CFLD are lacking. A recent Cochrane review set out to determine the best strategies for preventing and managing advanced liver disease in cystic fibrosis by comparing different treatments but did not identify any well-designed trials and so could not make any specific recommendations (24).

Portal Hypertension

Patients with CFLD should be screened for signs of PH given the high risk of mortality associated with this condition. Yearly follow up of patients with CFLD for signs of PH has been recommended (13). Once PH is identified, guidelines regarding management are lacking. Current practice has been to screen at risk children with endoscopy (25). Cystic fibrosis patients are screened at lower rates than patients with biliary atresia or portal cavernoma likely because of the increased risks anesthesia poses to children with poor pulmonary function (25). Esophageal variceal band ligation has been described as a preferred method of primary prophylaxis in CFLD patients when indicated (25). This is likely due to the possibility of bronchoconstriction from non-specific beta-blockade.

Portosystemic shunts and liver transplantation are options for the management of refractory portal hypertension. They can be used as primary therapy or as a bridge to liver transplantation. Liver transplantation is indicated in patients with decompensated cirrhosis as a last resort (4). A query of the United Network for Organ sharing revealed that patients transplanted for cystic fibrosis had worse mortality outcomes compared to patients transplanted for other reasons, unrelated to graft function (26). Regardless, cases of successful transplantation in cystic fibrosis exist. One such case report describes success of liver transplantation in a 10-year-old boy with CFLD complicated by PH using only an epidural for post-operative pain control (27). This case report provides a mechanism to limit the post-operative complications seen with transplantation in this population (27).

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is the most commonly used drug for CFLD despite controversy and limited data surrounding its use. UDCA is a hydrophilic secondary bile acid that is thought to be beneficial in CFLD by reducing bile acid viscosity. European guidelines currently recommend UDCA be started when CFLD is first identified, though this recommendation comes with the caveat that no data on long-term outcomes exist (13). A recent observational study, utilized serial VCTE to assess changes in fibrosis in treatment naïve patients and patients treated with UCDA. Non-cirrhotics, who met the Debray-Colombo criteria for initiation of UDCA, had significantly improved VCTE scores compared to patients not treated with UDCA. These results were not seen in cirrhotics. The study found that biochemical parameters (AST, ALT, GGT) significantly improved on UDCA as well (28). These findings suggest that UDCA may be beneficial in some patients with CFLD, however not all CFLD is due to cholestasis. NCPH is increasingly being recognized as a component of CFLD and UCDA may be less effective in this population as it does not target the appropriate mechanism of disease. A recent Cochrane review evaluated the quality of evidence supporting the use of UDCA in CFLD and concluded there is not enough evidence to support its use in CF (29).

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Although clinical practice in CFLD has been to utilize UDCA for treatment, there has been recent controversy surrounding its safety. Primary sclerosing cholangitis patients enrolled in a randomized trial were found to have a 2-fold increase in serious adverse events after being treated with high dose UDCA (28–30mg/kg/day) (30). The increased rate of adverse events was thought to be due to the conversion of UDCA to more toxic acids such as lithocholic acid but a recent study debunked this theory (31). Given the lack of alternate therapies and minimal risks, it is reasonable to prescribe this medication until something superior is identified.

Future Therapeutic Targets

A growing understanding of the pathophysiology of CFLD has led to the development of novel therapeutic agents. Specific CFTR potentiators and modulators have been approved to ameliorate CFTR function in cystic fibrosis patients. Ivacaftor, a CFTR modulator, improves chloride transport through CFTR channels. Lumacaftor, a potentiator, increases membrane expression of the CFTR protein and augments its function. The benefit of these medications have been described in other aspects of cystic fibrosis but their effects on CFLD have not yet been described in human studies (32). Another possible target is the Src tyrosine kinase which activates TLR-4/NF-κB-dependent inflammatory pathway. In vitro, inhibition of Src with kinase inhibitor, PP2, has been shown improve cytoskeletal defects and inflammatory changes. When PP2 is combined with Ivacaftor and Lumacaftor, cholangiocyte fluid secretion is also restored to normal levels (33). Advances in the understanding of the pathophysiology of CFLD have led to exciting emerging therapies.

CONCLUSION

Current diagnostic criteria identify patients with CFLD as a whole, but not all manifestations of disease are equally significant in regard to long-term morbidity and mortality. Clinicians should focus on identifying patients with PH with and without cirrhosis through yearly screening and a combination of diagnostic tools. Transient elastography and non-invasive biomarkers have proved helpful in diagnosing PH and cirrhosis and should be included in future diagnostic algorithms. UDCA remains the mainstay of therapy until more effective medications are developed specifically for CFLD. The advent of CFTR modulators and potentiators looks promising but these medications need to be studied in CFLD.

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Abbreviations:

CF	cystic fibrosis
CFLD	cystic fibrosis liver disease

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UCDA	Ursodeoxycholic acid
CFTR	cystic fibrosis transmembrane conductance regulator
PH	portal hypertension
TLR-4	toll-like receptor 4
Src	Rous sarcoma oncogene cellular homologue
HVPG	hepatic venous pressure gradient
NCPH	non-cirrhotic portal hypertension
ALT	alanine aminotransferase
AST	aspartate aminotransferase
GGT	gammaglutamyltransferase
ULN	upper limit of normal
APRI	ast-to-platelet-ratio-index
FIB-4	fibrosis index based on four factors
AUROC	area under receiver operating characteristic
AUC	area under the curve
miRNA	microRNA
VCTE	vibration controlled transient elastography
ROC	receiver operating characteristic
kPa	kilopascals
NIH	National Institutes of Health

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KEY POINTS

- Current definitions of CFLD should be expanded to include patients with both cirrhosis and non-cirrhotic portal hypertension
- No single diagnostic test can be accurately used to diagnose CFLD
- Current diagnostic criteria may be improved by the addition of serologic biomarkers and transient elastography
- A better understanding of the pathophysiology of CFLD is necessary to develop effective therapies in CFLD

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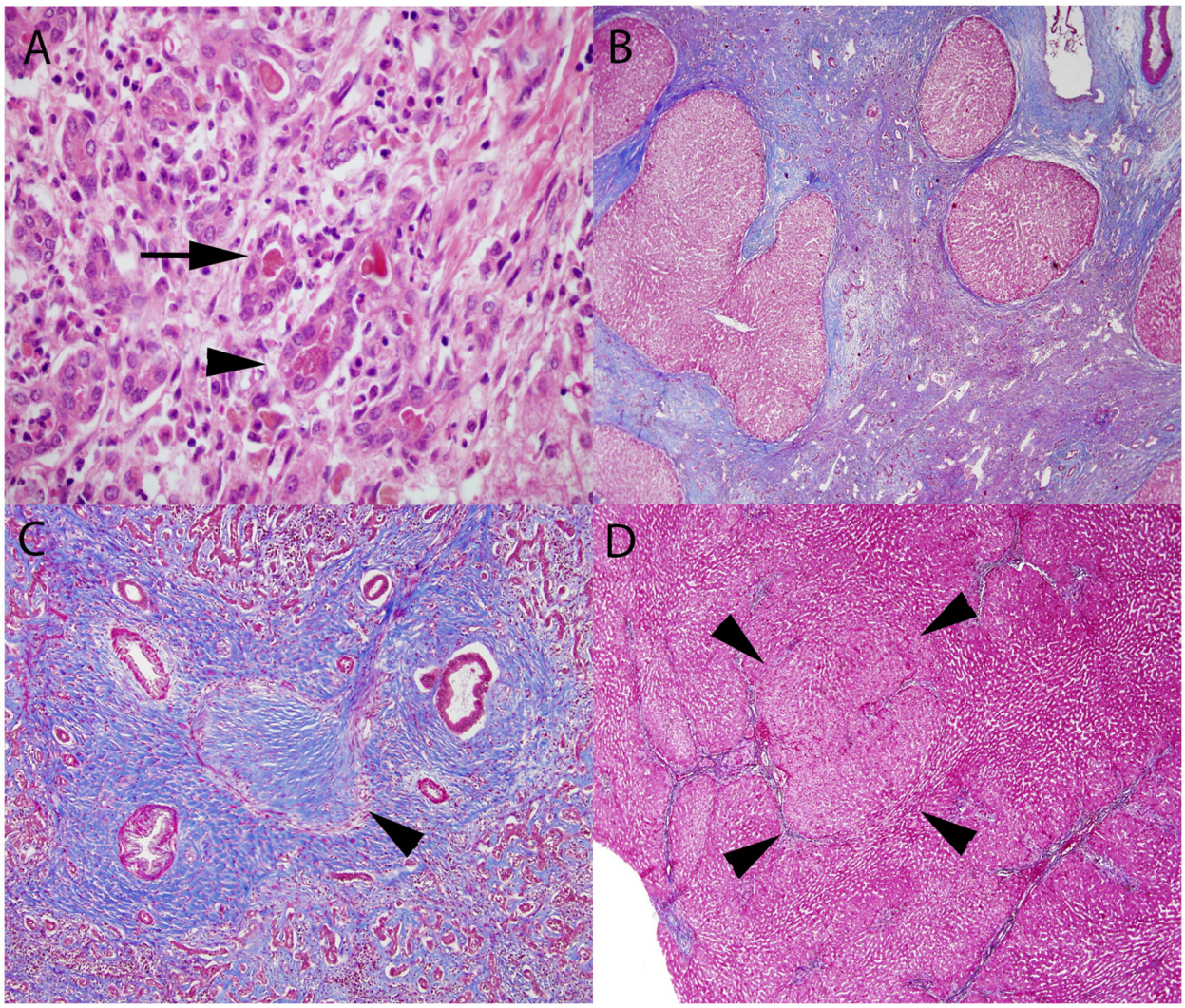

Figure 1.

Cholangiolar cholestatsis with bile plugs (long arrow) and granular debris (arrowhead) (H&E, 600x). (B) Focal biliary cirrhosis (elsewhere on the section of the architecture was intact) (Masson trichrome, 40x) (C) Portal venous occlusion with dense fibrosis (arrowhead) (Masson Trichrome, 100x). (D) Nodularity seen in region with the appearance of nodular regenerative hyperplasia (arrowheads outline nodule) (Masson trichrome, 40x). (Images courtesy of Dr. David Kleiner).

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Table 1

Diagnostic tools used to identify CFLD by the CF Foundation, Debray Criteria, and Koh Criteria

	CF Foundation		**Debray Criteria**	**Koh Criteria**
	CFLD with Cirrhosis +/−Portal Hypertension	***CFLI without Cirrhosis or Portal Hypertension***		
Histology	X	X	X	X
Laparoscopy	X			
Physical Examination	X		X	
Serum Blood Tests		X	X	X
Imaging	X	X	X	X
VCTE				X
Noninvasive biomarkers				X

Based on Debray et. al. (14), Flass et. al. (15), Koh et. al. (16)