CF-Related Liver Disease

Pathophysiology

Clinical Presentation

Diagnostic Criteria

Screening and Monitoring Tests

Non-CF Liver Disease

CF-Related Liver Disease (CFLD) or Hepatobiliary Disease

CFTR is expressed on the apical surface of cholangiocytes and gallbladder epithelial cells, but not hepatocytes[1]

In 2019, liver disease/liver failure accounted for 3.2% in overall mortality in the US.[2]

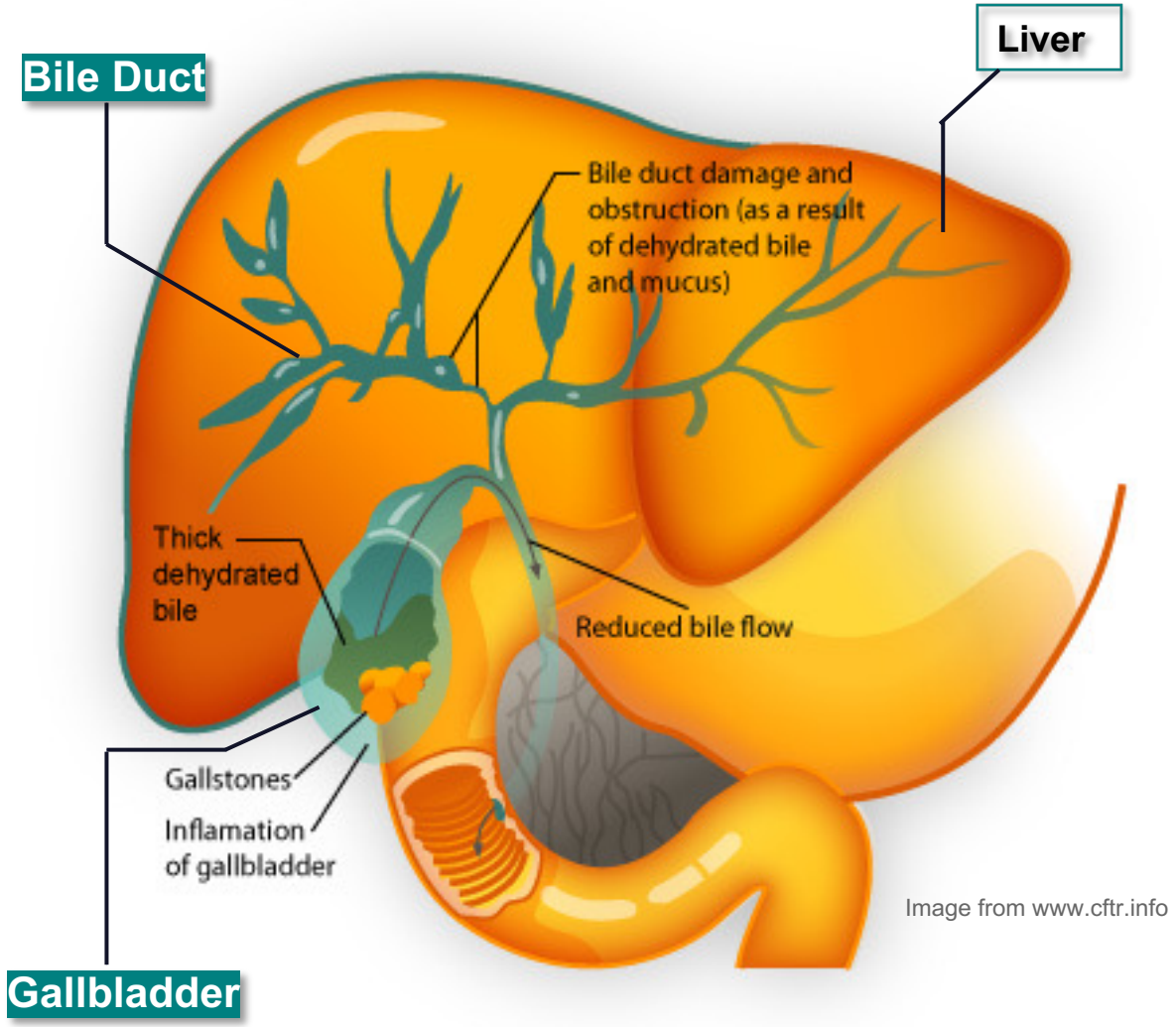
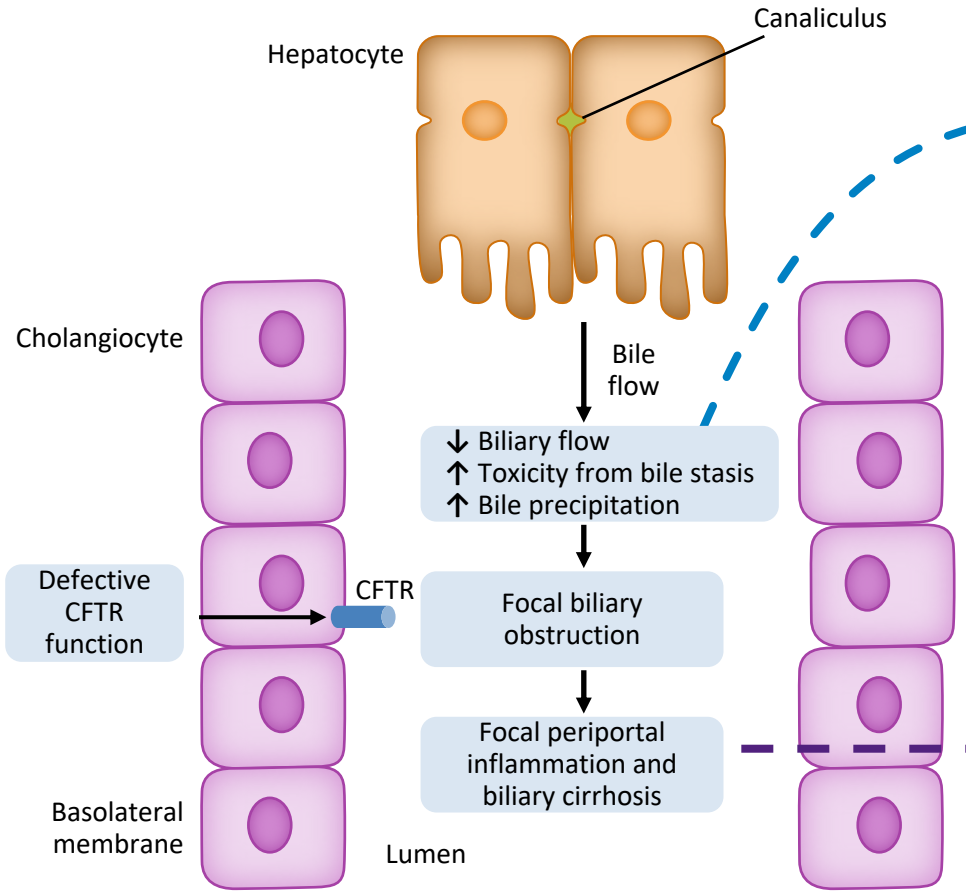


Image from www.cftr.info

CFTR, cystic fibrosis transmembrane conductance regulator.

1. Kelly T, et al. *Dig Dis Sci*. 2015;60:1903-1913. 2. Cystic Fibrosis Foundation (CFF) Patient Registry 2019 Annual Data Report. Bethesda, Maryland ©2020 CFF.

CFTR Defects May Lead to Hepatobiliary Disease and Manifestations in the Gastrointestinal Tract[1,2]



↓ Bile flow, ↓ bile pH, and ↑ bile precipitation may contribute to:[3]

- Low pH in the small intestine
- Fat malabsorption

Gut-liver axis hypothesis[1]

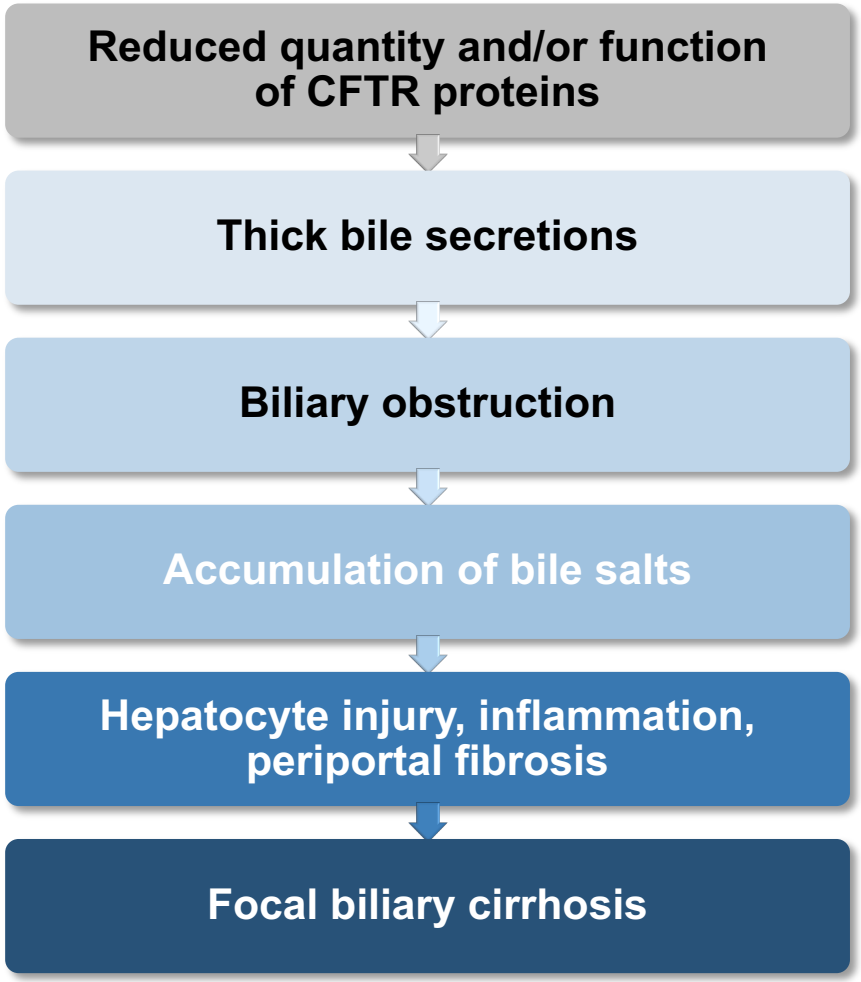
Intestinal inflammation and ulceration, pathogenic bacterial overgrowth, and ↑ permeability may lead to liver disease[4]

Figure adapted from Ooi CY, et al. 2016[1]

CFTR, cystic fibrosis transmembrane conductance regulator.

1. Ooi CY, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:175-185. 2. Sakiani S, et al. *Clin Liver Dis*. 2019;23:263-277. 3. Li L, et al. *Dig Liver Dis*. 2014;46:865-874. 4. Flass T, et al. *PLoS One*. 2015;10:e0116967.

Pathophysiology of CFLD



- Impaired CFTR function leads to bile salt accumulations due to thickened, inspissated bile secretions and biliary obstructions from plugging[1]
- Biliary dysfunction likely contributes to hepatocyte injury and inflammation resulting in hepatic fibrosis[2–4]
- Focal biliary cirrhosis may progress to multilobular cirrhosis, leading to portal hypertension, splenomegaly, hypersplenism[5] and associated complications of gastric or esophageal variceal bleeding[6]
- Biliary cirrhosis and portal hypertension can be co-existing risk factors for early mortality[1,7]

CFTR, cystic fibrosis transmembrane conductance regulator.

1. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962. 2. Flass T, et al. *J Cyst Fibros*. 2013;12:116-124. 3. Kelly T, et al. *Dig Dis Sci*. 2015;60:1903-1913. 4. Sokol RJ, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:S1-S23. 5. Ooi CY, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:175-185. 6. Gelfond, D, et al. *Clin Gastroenterol Hepatol*. 2013;11:333-342. 7. Kamal N, et al. *Curr Opin Gastroenterol*. 2018;34:146-151.

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CFLD is an Early Manifestation of CF

Natural history is not well understood[1]

- Clinically significant hepatobiliary manifestations of CF are reported in 15–30% of children[1]

Incidence[2]

- Highest during the first decade of life (1.8 cases per 100 patient years, incidence rate of 2.5% in first decade)
- Declining in the second decade

5–10% of individuals with CF develop cirrhosis during the first decade of life[3]

Steatosis, the most common identified histological abnormality, is found in up to 70% of liver biopsies from children with suspected CFLD[1,4]

Independent Risk Factors for Developing CFLD[2,5-7]

- Male sex
- History of meconium ileus
- Poor nutritional status
- Pancreatic insufficiency
- Minimal function *CFTR* genotype

CFLD, CF-related liver disease

1. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29(12):1954-1962. 2. Colombo C, et al. *Hepatology*. 2002;36(6):1374-1382. 3. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11(4):333-342. 4. Lewindon PJ, et al. *Hepatology*. 2011;53(1):193-201. 5. Colombo C, et al. *J Pediatr Gastroenterol Nutr*. 2006;43(Suppl 1):S49-S55. 6. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153-1163. 7. Boelle PY, et al. *Hepatology*. 2019;69(4):1648-1656.

Clinical Presentation of CFLD is Variable

CFLD encompasses a wide spectrum of hepatobiliary conditions[1]

The Cystic Fibrosis Foundation classifies CFLD into 3 categories[2]:

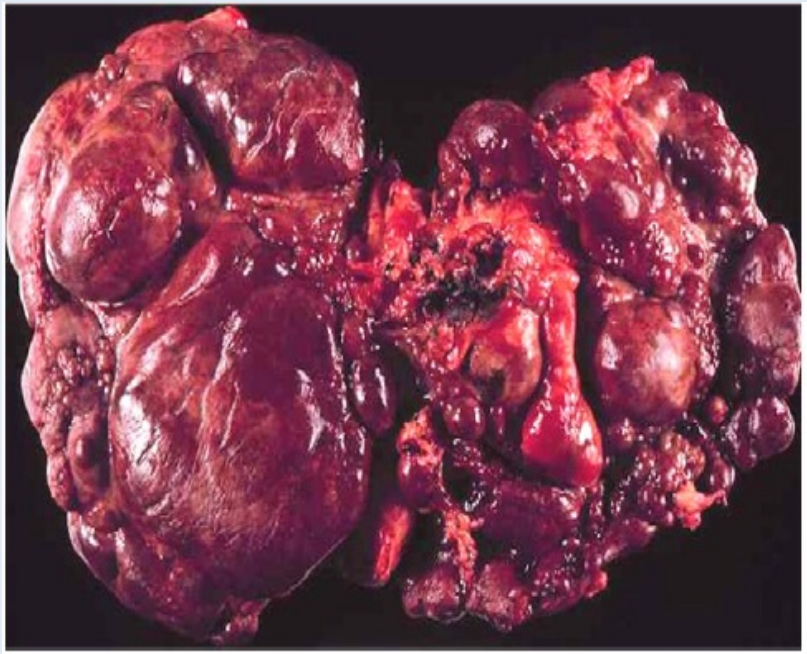
1. **CFLD <u>with</u> cirrhosis ± portal hypertension**
   Based on clinical exam/imaging, histology, laparoscopy
2. **Liver involvement <u>without</u> cirrhosis or portal hypertension consisting of ≥1 of the following:**
   a) Persistent AST, ALT, GGT >2 x ULN
   b) Intermittent elevations of the above laboratory values
   c) Steatosis (histologic determination)
   d) Fibrosis (histologic determination)
   e) Cholangiopathy (based on ultrasound, MRI, CT, ERCP)
   f) Ultrasound abnormalities not consistent with cirrhosis
3. **<u>Preclinical disease</u>: No evidence of liver disease on exam, imaging or laboratory values**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; GGT, gamma glutamyl transpeptidase; MRI, magnetic resonance imaging; ULN, upper limit of normal.

1. Kamal N, et al. *Curr Opin Gastroenterol*. 2018;34:146-151. 2. Leung DH, et al. *J Cyst Fibros*. 2017;16(Suppl 2):S50-S61.

Severe CFLD

- Defined by the presence of cirrhosis with portal hypertension[1]
- Liver cirrhosis is the most important non-pulmonary cause of death in individuals with CF[2]
- Cirrhotic CFLD with portal hypertension is associated with a lower median age at death[3]
- Occurs in ~5% of patients with CF and is associated with the presence of the *SERPINA1* (Alpha-1 antitrypsin) *Z* allele[1]
- Complications associated with the development of portal hypertension include esophageal or gastric varices and variceal bleeding[2]



Multilobular nodules in the explant of a liver from a patient with CF related cirrhosis[4]

Image reprinted from Flass T, et al. *J Cyst Fibros*. 2013;12:116-24 with permission from Elsevier.

1. Bartlett JR, et al. *JAMA*. 2009;302:1076-1083. 2. Debray D, et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. 3. Pals FH, et al. *J Cyst Fibros*. 2019;18:385-389. 4. Flass T, et al. *J Cyst Fibros*. 2013;12:116-24.

Severe CFLD is Associated with Lower Median Age at Death

Age of Death and Proportion of Death per Age Category		
	CF Cirrhosis (CFC)	**CF Without Cirrhosis**
Deceased patients	22	63
<25 years	10 (45%)	11 (17%)[a]
25–40 years	8 (36%)	28 (44%)
>40 years	4 (18%)	24 (38%)[a]
Median age at death (years)[b]	27 (18–38)	37 (27–45)[a]

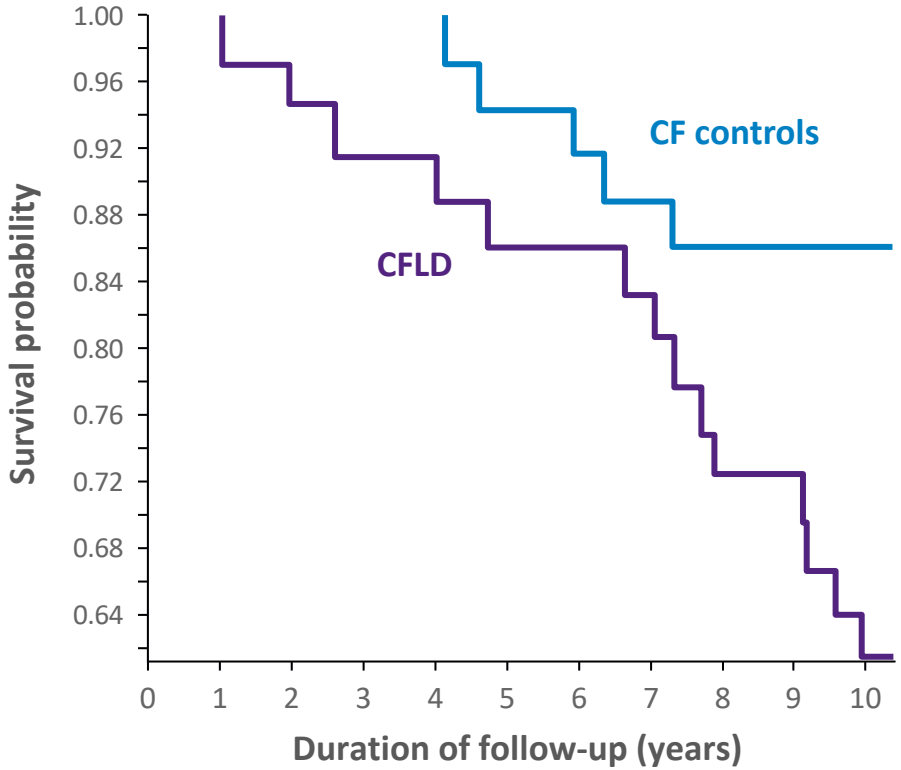
The median age at death was 10 years sooner in the CFC group compared with the CF group without cirrhosis

CFC, CF Cirrhosis (cirrhotic CFLD with portal hypertension). [a]*P* value <0.05 was considered statistically significant (Mann-Whitney U test). [b]Medians with interquartile range (IQR: 25th percentile to 75th percentile).

Pals FH, et al. *J Cyst Fibros*. 2019;18:385-389.

CFLD is Associated with Reduced Survival

Probability of Survival for Individuals with CFLD Compared with Matched CF Controls



Kaplan-Meier plot showing the probability of survival following a 10-year follow-up period in individuals with CFLD (purple line, n=36) compared with CF controls (pair matched for age and sex) with no evidence of liver disease (blue line, n=36) (Log Rank Test *P*=0.02)

In a cohort of 72 patients with CF followed over 10 years:

- Patients with CFLD had ~3 times the risk of death versus those without liver disease (38.9% vs 13.9%)
- 64% of those who died with CFLD were female

Study limitations include:

- The baseline control population may have been sicker than the general pediatric CF population in Ireland because of enrollment occurring only during hospital visit
- Diagnosis of portal hypertension CFLD is imprecise
- Calculations may have underestimated mortality risk for those with CFLD

Rowland M, et al. *J Cyst Fibros*. 2015;14:120-126.

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Diagnostic Criteria for CFLD

A diagnosis of progressive CFLD is made if ≥2 of the following are present (as suggested by experts from the NIH/CFF CFLD Clinical Research Workshop and Europe)[1,2]:

Hepatomegaly (e.g., liver edge palpable >2 cm below the costal margin) and/or **splenomegaly,** confirmed by ultrasonography

Ultrasonographic evidence of coarseness, nodularity, increased echogenicity, or portal hypertension

Abnormalities of ALT, AST, and GGT above laboratory ULN for >6 months, after excluding other causes of liver disease

Liver biopsy showing focal biliary cirrhosis or multilobular cirrhosis (if performed)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFF, Cystic Fibrosis Foundation; GGT, gamma glutamyl transpeptidase; NIH, National Institutes of Health; ULN, upper limit of normal.

1. Leung DH, et al. *J Cyst Fibros*. 2017;16(Suppl 2):S50-S61. 2. Debray D, et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36.

Liver Function Tests Variability

Transient elevations can be seen in up to 50% of infants and young children with CF and often normalize within 2 to 3 years of age[1,2]

In a longitudinal study of 298 children diagnosed with CF, 93% had at least one abnormal ALT value and 31% had persistently (>6 months) elevated ALT values (≥2 x ULN) by 21 years of age[3]

Transient elevations may result from malnutrition, concurrent illness, or be drug related; they may not be specific for CFLD[4]

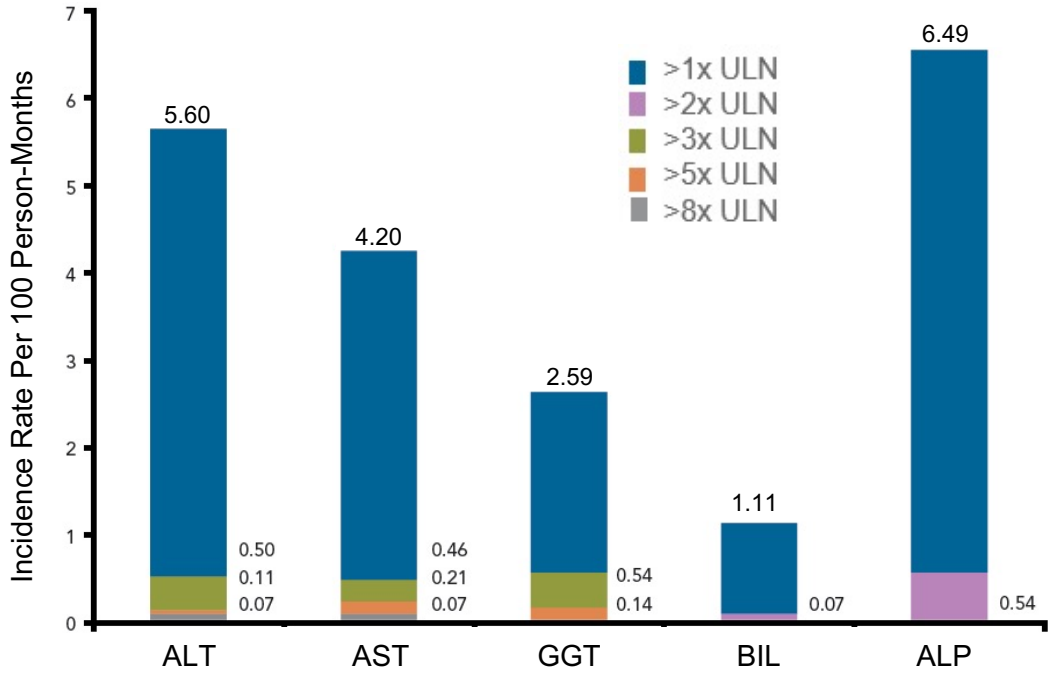
Majority of the patients with CF will develop LFT elevations; but only 10% will develop cirrhosis[4]

ALT, alanine aminotransferase; LFT, liver function test; ULN, upper limit of normal.

1. Gelfond D, et al. *Clin Gastroenterol Hepatol*. 2013;11:333-342. 2. Debray D, et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. 3. Woodruff SA, et al. *J Cyst Fibros*. 2017;16:139-145.
4. Kamal N, et al. *Curr Opin Gastroenterol*. 2018;34:146-151.

Liver Function Test Abnormalities in Patients With Cystic Fibrosis

Incidence rates for each LFT parameter[1]



Analysis of 645 patients* randomized to placebo arms in CF clinical trials with ≥8 weeks of follow-up (average of 5.6 months)[1]:

- Incidence rates of LFT elevations were highest for ALP abnormalities, followed by ALT abnormalities**
- Patients with normal ALT and AST levels at baseline (n=506), approximately 50% had ≥1 LFT abnormality >1 x ULN during follow-up, some potentially clinically significant
- Patients with abnormal ALT or AST levels at baseline (n=139) had considerably higher incidence of potentially clinically significant LFT abnormalities during follow-up

Transient elevations in ALT or AST occur in 53-93% of patients with CF by age 21[2]

*Patients with CF ≥6 years of age, on standard CF treatments; **The true incidence may be underestimated due to strict trial exclusion criteria
ALT or AST abnormality defined as a measurement of ALT or AST >1x ULN; potentially clinically significant LFT abnormality defined as ALT/AST/GGT >3 x ULN
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, total bilirubin; GGT, gamma glutamyl transpeptidase; LFT, liver function test; ULN, upper limit of normal.

1. Seliger V, et al. Poster presented at: 39th European Cystic Fibrosis Conference; June 8-11, 2016; Basel, Switzerland. ©2016 Vertex Pharmaceuticals Incorporated. 2. Kamal N, et al. *Curr Opin Gastroenterol*. 2018;34:146-151.

Challenges Associated with Diagnosing CFLD

CFLD is likely underdiagnosed for several reasons:

- Frequently asymptomatic[1]
- Wide spectrum of manifestations ranging from neonatal cholestasis, elevation of liver transaminases, steatosis, gallbladder abnormalities, and development of biliary cirrhosis with or without portal hypertension[1–3]
- No single diagnostic test has been shown to accurately diagnose CFLD[2]
- No global consensus regarding the precise diagnostic criteria[1]

1. Debray D, et al. *J Pediatr Gastroenterol Nutr*. 2017;65:443-448. 2. Kamal N, et al. *Curr Opin Gastroenterol*. 2018;34:146-151. 3. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962.

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Current Yearly Recommendations to Screen for CFLD

All patients with CF need annual follow-up to evaluate CFLD (development of cirrhosis, portal hypertension, or liver failure) starting in early childhood[1,2]

Annual screening is recommended with[1-3]:

- Physical examinations to screen for hepatomegaly or splenomegaly
- Conventional liver function tests
- Monitoring for declining platelet counts
- Abdominal imaging for patients with persistently abnormal hepatic enzymes

1. Leung DH, et al. *J Cyst Fibros*. 2017;16(Suppl 2):S50-S61. 2. Debray D, et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. 3. Sakiani S, et al. *Clin Liver Dis*. 2019;23:263-277.

Conventional Liver Function Tests

A yearly panel of liver blood tests for all patients with CF is recommended[1]

Liver Function Tests
• ALT
• AST
• GGT
• ALP
• Total bilirubin

Monitoring (every 3 to 6 months) should be initiated if any of these serological markers are above 1.5 x ULN[2]

Persistently elevated levels (>1.5 x ULN for ≥6 months without other explanation) probably indicate a liver abnormality[2]

Further evaluation of the synthetic function of the liver (e.g., albumin or prothrombin time) should be considered[2]

Potential limitations

- Transaminase elevations (ALT or AST) or cholestasis parameters (ALP or GGT) are frequently mild or intermittent[1,3]
- Abnormalities tend not to correlate with histological findings[1]

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; ULN, upper limit of normal.

1. Debray D, et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. 2. Kelly T, et al. J. *Dig Dis Sci*. 2015;60:1903-1913. 3. Gelfond D, et al. *Clin Gastroenterol Hepatol*. 2013;11:333-342.

Liver Chemistries: Markers of Hepatocyte Integrity

Test	Description	Significance of abnormal value
Alanine aminotransferase (ALT)	An enzyme primarily in the liver[1,2]	• Hepatocyte injury or death[1,2] • More specific for hepatic injury than AST[1,3]
Aspartate aminotransferase (AST)	An enzyme in the liver, cardiac muscle, skeletal muscle, kidney, and brain[1]	• Hepatocyte injury or death, or extrahepatic disorders[1,2,3] • AST elevation without ALT elevation may suggest cardiac or muscle disease[1]

Hepatocellular damage releases the enzymes ALT and AST into the circulation at disproportionate levels as compared with alkaline phosphatase levels[1,3]

Slight ALT or AST elevations (within 1.5 x ULN) do not always indicate liver disease[4]
Mild ALT and AST elevations (<5 x ULN) are common in primary care[3]
Evaluations >5 x ULN should prompt immediate evaluation[3]

ULN, upper limit of normal

1. Kwo PY, et al. *Am J Gastroenterol.* 2017;112:18–35. 2. Mayo Clinic. Liver Function Tests. https://www.mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595 Accessed February 2021.
3. Oh RC, et al. *Am Fam Physician*. 2017;96(11):709-715. 4. Johnston DE. *Am Fam Physician*. 1999;59(8):2223-30.

Liver Chemistries: Markers of Bile Duct Function

Test	Description	Significance of abnormal value
Alkaline phosphatase (ALP)	An enzyme in hepatocytes, bone, placenta, intestine, and kidney[1] • Bone is the most common extrahepatic origin[1]	• Elevated with bile duct obstruction, liver injury and certain bone diseases[1,2] • May be elevated in children, pregnancy, and elderly[1,3] • Disproportionate elevation in ALP as compared with AST and ALT define cholestatic injury[1] • May be fractionated to delineate if origin is bone, intestinal, or hepatic[1]
Gamma-glutamyltransferase (GGT)	An enzyme on membranes of cells with high secretory or absorptive activities; abundant in the liver, kidney, pancreas, intestine, and prostate, but not in bone[3,4]	• More sensitive than ALP and transferases in detecting bile duct obstruction[3] • GGT rises earlier and remains elevated longer than other liver enzymes[3] • Elevated GGT combined with elevated ALP suggests hepatic origin[1] • Should not be used as a screening test for liver disease if other liver enzymes are normal[1]

1. Kwo PY, et al. *Am J Gastroenterol.*2017;112:18–35. 2. Mayo Clinic. Liver Function Tests. https://www.mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595 Accessed February 2021.
3. Cabera-Abreu JC. *Ann Clin Biochem.*2002;39:22-25. 4. Green RM, et al. *Gastroenterol*. 2002;123:1367-84.

Liver Chemistries: Markers of Hepatocellular Function

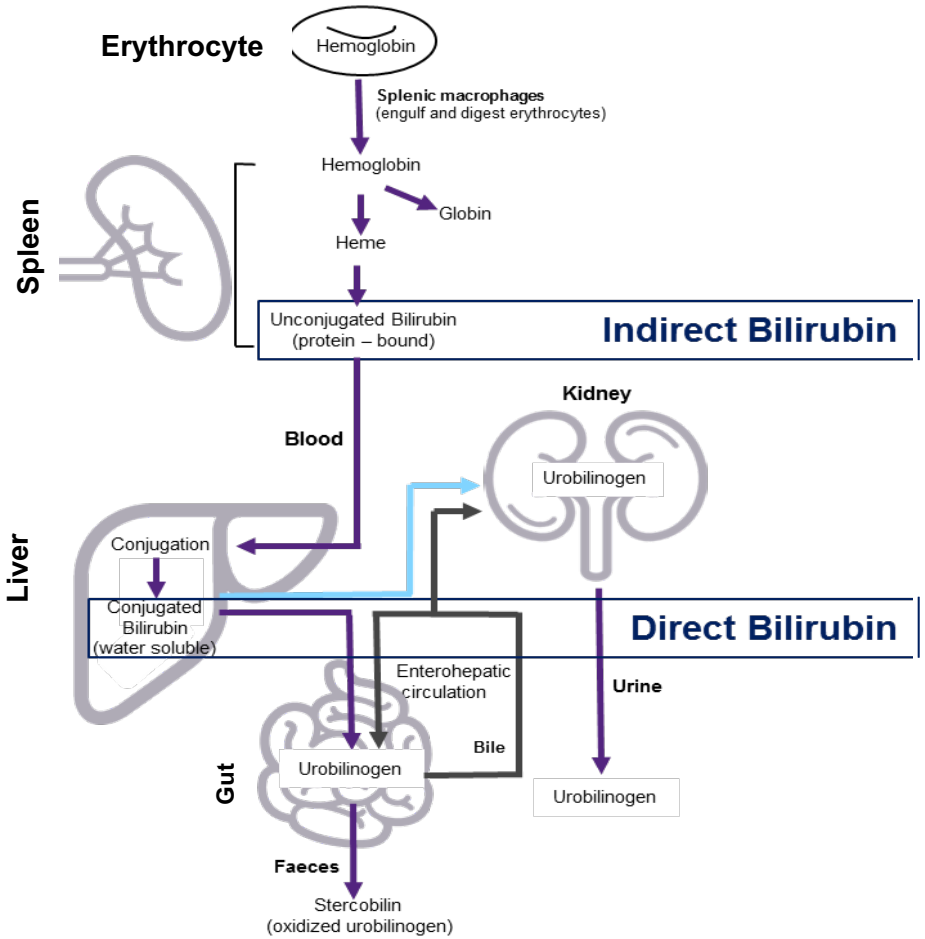
Test	Description	Significance of abnormal value
Serum albumin	• A plasma protein exclusively synthesized by the liver[1]	• Low albumin levels may be due to poor nutritional status, severe illness with protein catabolism, nephrosis, malabsorption and GI tract abnormalities[2] • Levels difficult to interpret since albumin has a half-life of 3 weeks causing serum levels to change slowly[1,3]
Prothrombin time (PT)	• Prothrombin is a clotting factor made by the liver[4] • Measurement of time for a clot to form in the blood[1,4]	• Elevated PT may indicate a decreased ability of the liver to synthesize clotting factors[5] • PT is a more sensitive measure of liver function than albumin because PT may be prolonged in pts with acute liver disease[1] • Prolonged PT may occur in patients with vitamin K deficiency due to cholestasis or fat malabsorption[3] • PT results are standardized as an International Normalized Ratio (INR)[6]

Serum albumin and PT may be important indicators of hepatic synthetic function, although neither is specific for hepatic disease[2]

1. Kwo PY, et al. *Am J Gastroenterol.*2017;112:18–35. 2. Green RM, et al. Gastroenterol. 2002;123:1367-84. 3. Johnston DE. Am Fam Physician. 1999;59:2223-30. 4. MedlinePlus. https://medlineplus.gov/encyclopedia.html Accessed January 2021. 5. Starr SP, et al. *Am Fam Physician*. 2011;84:1353-9. 6. Kovacs MJ, et al. *Thromb Haemost*. 1994;71:727-30.

Bilirubin: Marker of Hepatocellular Function or Cholestasis

Bilirubin Normal Metabolism[1]



Bilirubin is a bile pigment derived from the degradation of hemoglobin during the normal and abnormal destruction of red blood cells and is metabolized through the digestive system as part of the bile from the liver[2]

Total Bilirubin[3] = **Indirect Bilirubin (non-hepatic)** ✚ **Direct Bilirubin (hepatic)**

Bilirubin circulates in the bloodstream in two forms[1]:

- Indirect (unconjugated) bilirubin is the lipid soluble form that circulates in loose association with plasma proteins
- Direct bilirubin has been taken by the liver cells and conjugated to form a water-soluble bilirubin diglucuronide

Hyperbilirubinemia results from disorders of one or more of the metabolic steps[3]:

- Abnormal processing and breakdown of red blood cells
- Any disorder that destroys a large quantity of liver cells or disrupts the liver cell function

1. Lester R, et al. *N Engl J Med*. 1964;270;779-786. 2. Dorland's Illustrated Medical Dictionary, 27th edition, page 205. 3. Levitt DG, Levitt MD. *Clin Exp Gastroenterol*. 2014;7:307-328.

Elevated Bilirubin – Differential Diagnosis

Predominance of Direct (Conjugated) Bilirubin

- Extra-hepatic obstruction:
  - Common duct abnormalities: calculi, neoplasm, stricture, cyst, sclerosing cholangitis
- Ampullary carcinoma
- Metastatic carcinoma
- Pancreatic carcinoma, pseudocyst
- Recurrent benign intrahepatic cholestasis
- Hepatocellular disease: hepatitis, cirrhosis
- Drugs: estrogens, phenothiazines, captopril, methyl-testosterone, labetalol
- Cholestatic jaundice of pregnancy
- Hereditary disorders: Dubin-Johnson syndrome, Rotor's syndrome

Predominance of Indirect (Unconjugated) Bilirubin

- Neonatal jaundice
- Hemolysis: hereditary and acquired hemolytic anemias
- Inefficient marrow production
- Impaired hepatic conjugation: chloramphenicol, pregnanediol
- Hereditary disorders: Gilbert's syndrome, Crigler-Najjar syndrome

Ferri's Clinical Advisor, Instant Diagnosis and treatment, 2003 Edition, Page 1108, Box 2-149.

CFLD: Conventional Abdominal Ultrasound

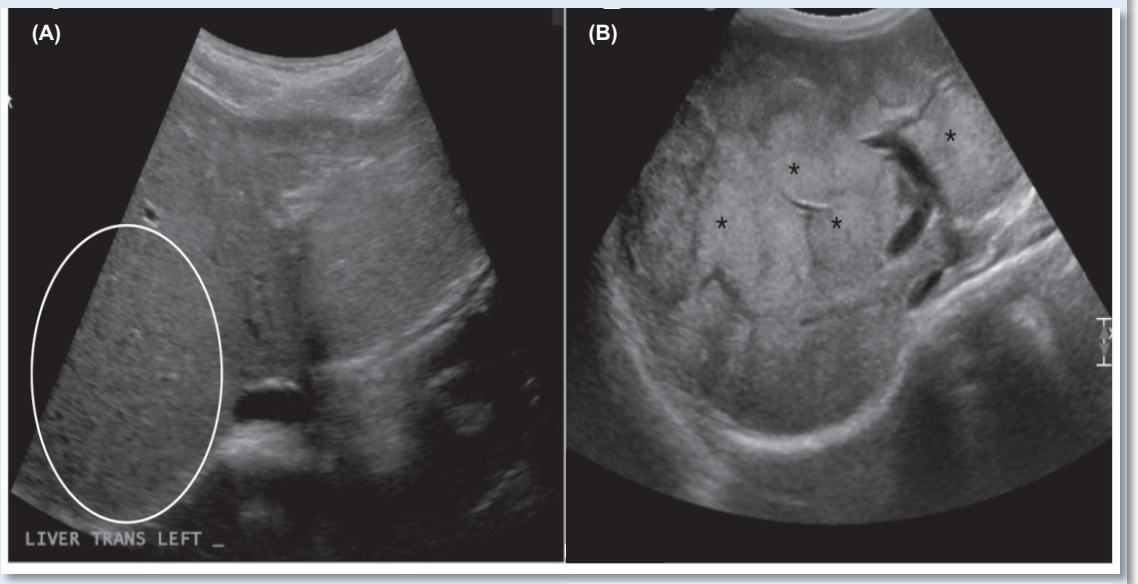
- Visualizes the liver, spleen and biliary tree, and measures both direction and intensity of portal and hepatic blood flow[1]
- Detects subclinical findings suggestive of cirrhosis, including coarseness of liver parenchyma, nodularity of the liver edge, and increased periportal echogenicity[1]
- Can exclude gallstones or common bile duct stones as a cause of intermittently elevated GGT[1]
- In patients 3–12 years of age, heterogeneous pattern had a 9.3-fold relative risk (CI: 2.8, 31.3) for the development of advanced CFLD[2]

Limitations

- Interobserver variability[3,4]
- Early changes may be overlooked[4]
- Difficulty differentiating fat from fibrosis[5]

Ultrasonography of the liver[1]

Gray-scale ultrasound imaging of varying forms of CF liver cirrhosis



(**A**) A focal area of micronodularity (circled) in the liver of a patient with CF with focal biliary cirrhosis

(**B**) Multiple and large nodules (asterisks) throughout the liver of a patient with CF and multilobular cirrhosis

CI, confidence interval; GGT, gamma glutamyl transpeptidase. Images courtesy of Roger Harned, MD, University of Colorado, Aurora, CO.

1. Leung DH, et al. *J Cyst Fibros*. 2017;16(Suppl 2):S50-S61. 2. Narkewicz M, et al. NACFC 2018 Late Breaker Abstract #807. 3. Flass T, et al. *J Cyst Fibros*. 2013;12:116-124.
4. Colombo C, et al. *J Pediatr Gastroenterol Nutr*. 2006;43(Suppl 1):S49-S55. 5. Lewindon PJ, et al. *Hepatology*. 2011;53:193-201

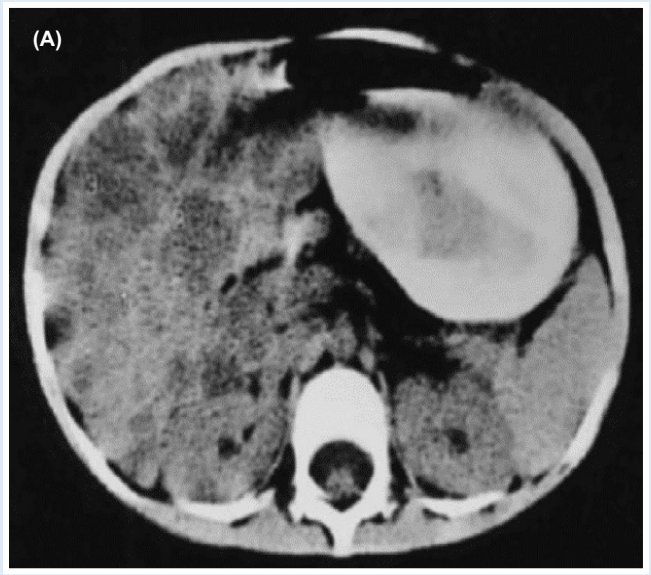
CFLD: Computed Tomography (CT)

- Allows high-resolution visualization and evaluation of the entire abdomen[1]
- Evaluates liver parenchyma in patients who have developed macronodular cirrhosis and portal hypertension[2]

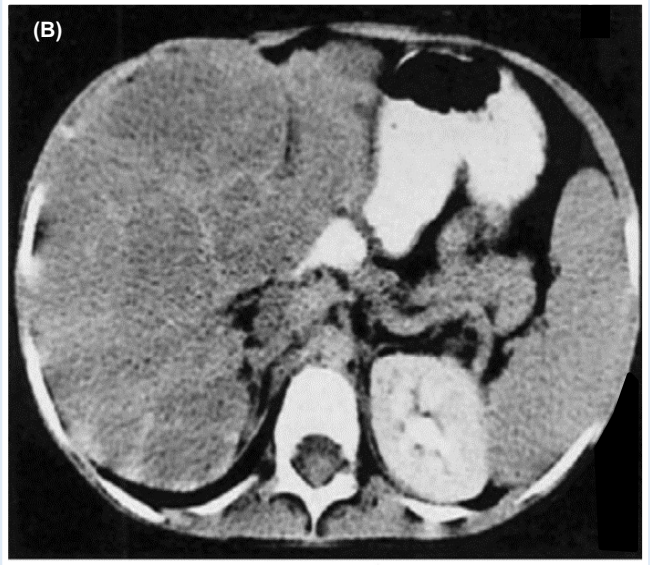
Limitations

- Radiation exposure[1]
- Cost[1]
- Sedation is required for young patients[3]

Cross-sectional images of the liver acquired using CT



(A) CT scan of the liver of a 7-year-old patient with CF showing lobular fatty structures (1 to 2 cm in size) causing irregular liver contour and heterogeneity in the liver parenchyma. The normal liver parenchyma (hyperattenuating on CT scans) appears squeezed in between these pseudomasses simulating the rim of a mass[2]



(B) CT scan of a 4-year-old patient with CF showing the typical but more diffuse form of pseudomass appearance. The spared (non-fatty) parenchyma of the liver is visualized as hyper-attenuating rims around fatty areas[2]

Images reproduced with permission from Akata D, Akhan O. 2007.

1. Colombo C, et al. *J Pediatr Gastroenterol Nutr*. 2006;43(Suppl 1):S49-S55. 2. Akata D, Akhan O. *Eur J Radiol*. 2007;61:11-17. 3. Loeve M, et al. *Eur Respir J*. 2013;42:844-857.

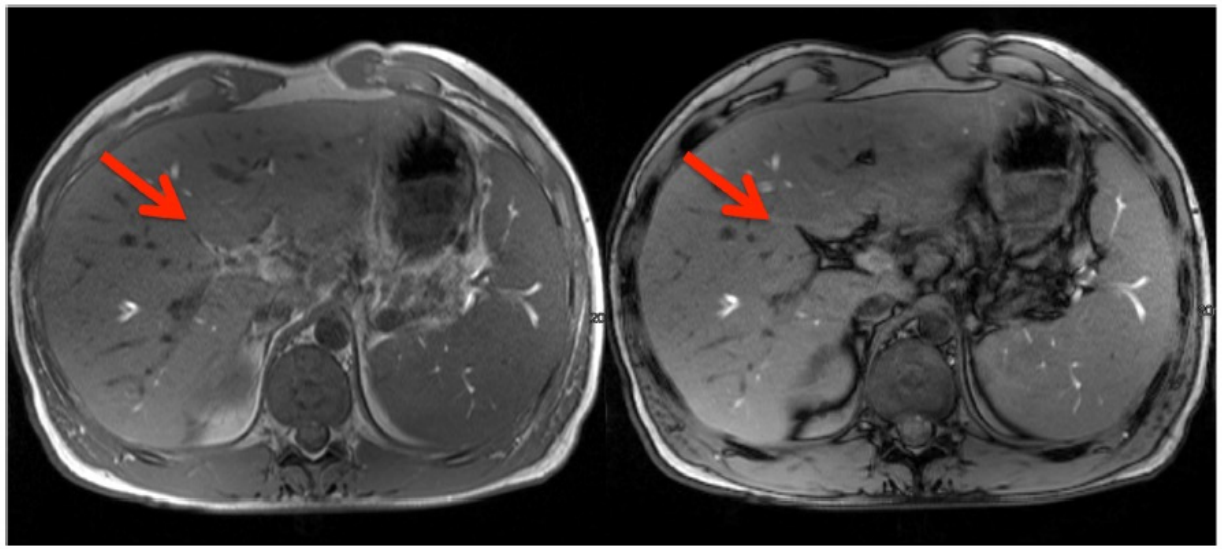
CFLD: Magnetic Resonance Imaging (MRI)

- Increasingly used to help confirm disease when there is clinical suspicion of CF cirrhosis[1]
- Magnetic resonance cholangiography detects abnormalities in intrahepatic and extrahepatic bile ducts, as well as significant periportal fibrosis and nodularity in the liver parenchyma[2–4]
- Recently developed MRI modalities can accurately determine liver fat content and may aid in the detection of hepatic steatosis[4]

Limitations

- Cost[5]
- Sedation required for young patients[5]
- Bile duct lesions detected in many patients both with and without confirmed CFLD, so MRI has not been recommended for routine use in the diagnosis of CFLD[6]

Images of the liver acquired using MRI



A 23-year-old patient with CF:

T1-weighted in-phase and opposed-phase images demonstrate periportal fat deposition as a band-like signal intensity loss on the opposed-phase image compared with the in-phase image along the fissure of the porta hepatis[3]

Image reproduced with permission from Poetter-Lang S, et al. 2019.

1. Leung DH, et al. *J Cyst Fibros*. 2017;16(Suppl 2):S50-S61. 2. Akata D, et al. *Eur J Radiol*. 2007;61:11-17. 3. Poetter-Lang S, et al. *Eur Radiol*. 2019;29:1048-1058. 4. Flass T, et al. *J Cyst Fibros*. 2013;12:116-124.
5. Colombo C, et al. *J Pediatr Gastroenterol Nutr*. 2006;43(Suppl 1):S49-S55. 6. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962.

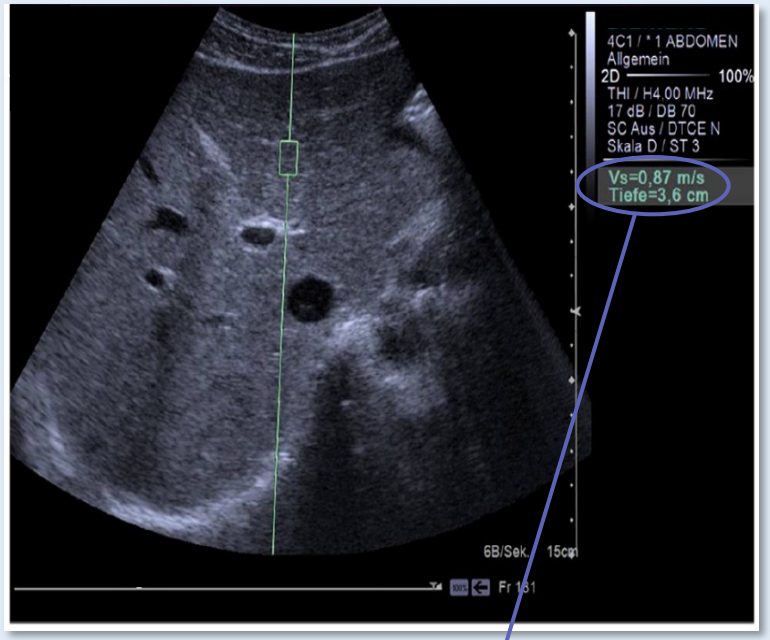
CFLD: Acoustic Radiation Force Impulse (ARFI)

- A novel elastography method performed with conventional ultrasound probes during a routine abdominal ultrasound scan[1]
- Involves mechanical excitation of tissue using acoustic pulses at an ROI that leads to localized tissue displacements, resulting in shear-wave propagation away from the region of excitation, that is tracked using ultrasonic, correlation-based methods[1,2]
- Results expressed in meters per second (range: 0.5 to 5.5 m/s)
- Examination takes ~10 to 15 minutes[1]

Limitations

- Technology not yet widely adopted[2]
- Measurements are subjective, as variability is introduced with operator-dependent selection of ROI and difficult to control magnitude of applied stress[3]
- Requires further validation against other objective measures of fibrosis[4]

Ultrasound scan with ARFI velocity measured



ARFI velocity within the ROI measures: 0.87 m/s

B-mode ultrasound of the right liver lobe with the ROI placed 2 cm below the liver capsule with a depth of 3.6 cm below the skin[1]

ROI, region of interest. Image reproduced with permission from Friedrich-Rust M, et al. 2013.

1. Friedrich-Rust M, et al. *J Cyst Fibros*. 2013;12:431-439. 2. Cañas T, et al. *Biomed Res Int*. 2015;2015:517369.
3. Sigrist RMS, et al. *Theranostics*. 2017;7:1303-1329. 4. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962.

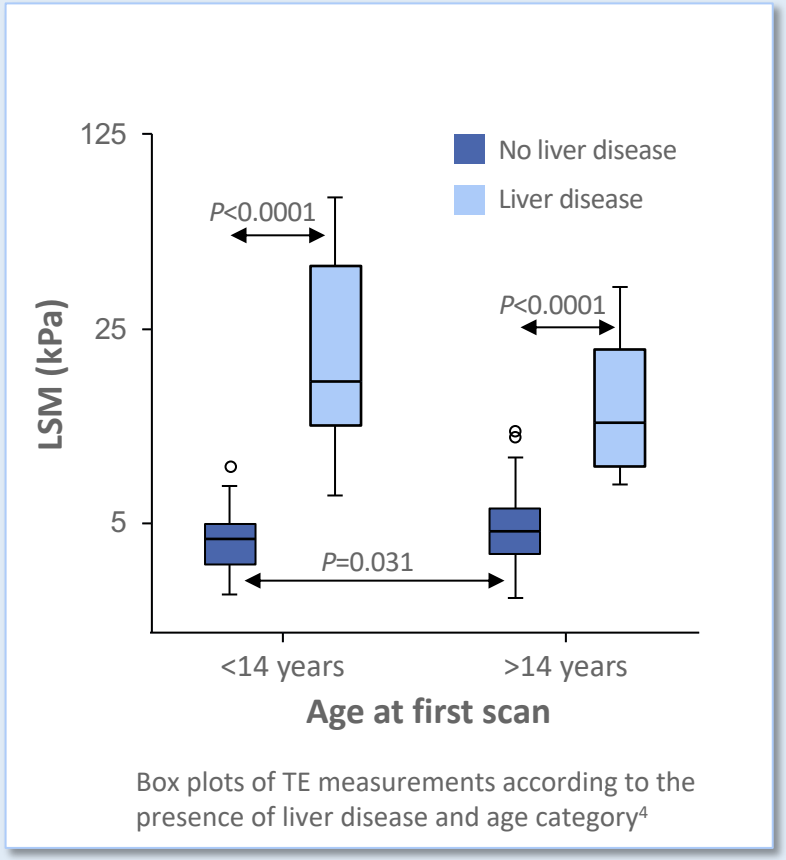
CFLD: Transient Elastography (TE)

- Uses a low frequency acoustic wave transmitted through the liver via a probe (placed on the skin)[1]
- Velocity of wave propagation is directly proportional to the stiffness of the liver due to its collagen fiber content[1,2]
- A rapid and noninvasive tool to assess presumed liver fibrosis in CF,[3] and may be capable of detecting and tracking early-stage CFLD progression[4–6]
- Results reported in kPa[3]
- Examination takes ~5 minutes[2–4]

Limitations

- Technology not yet widely adopted[1]
- Cost – requires additional hardware (in contrast to ARFI)[7]
- Requires further validation against other objective measures of fibrosis[8]

TE measurements of liver stiffness



Box plots of TE measurements according to the presence of liver disease and age category[4]

ARFI, acoustic radiation force impulse; LSM, liver stiffness measurement. Image adapted with permission from Van Biervliet S, et al. 2016.

1. Flass T, et al. *J Cyst Fibros*. 2013;12:116-124. 2. Friedrich-Rust M, et al. *J Cyst Fibros*. 2013;12:431-439. 3. Aqul A, et al. *J Pediatr Gastroenterol Nutr*. 2017;64:505-511.
4. Van Biervliet S, et al. *Ultrasound Med Biol*. 2016;42:848-854. 5. Klotter V, et al. *PLoS One*. 2017;12:e0178784. 6. Gominon AL, et al. *J Pediatr Gastroenterol Nutr*. 2018;66:455-460.
7. Engelmann G, et al. *World J Hepatol*. 2017;9:409-417. 8. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962.

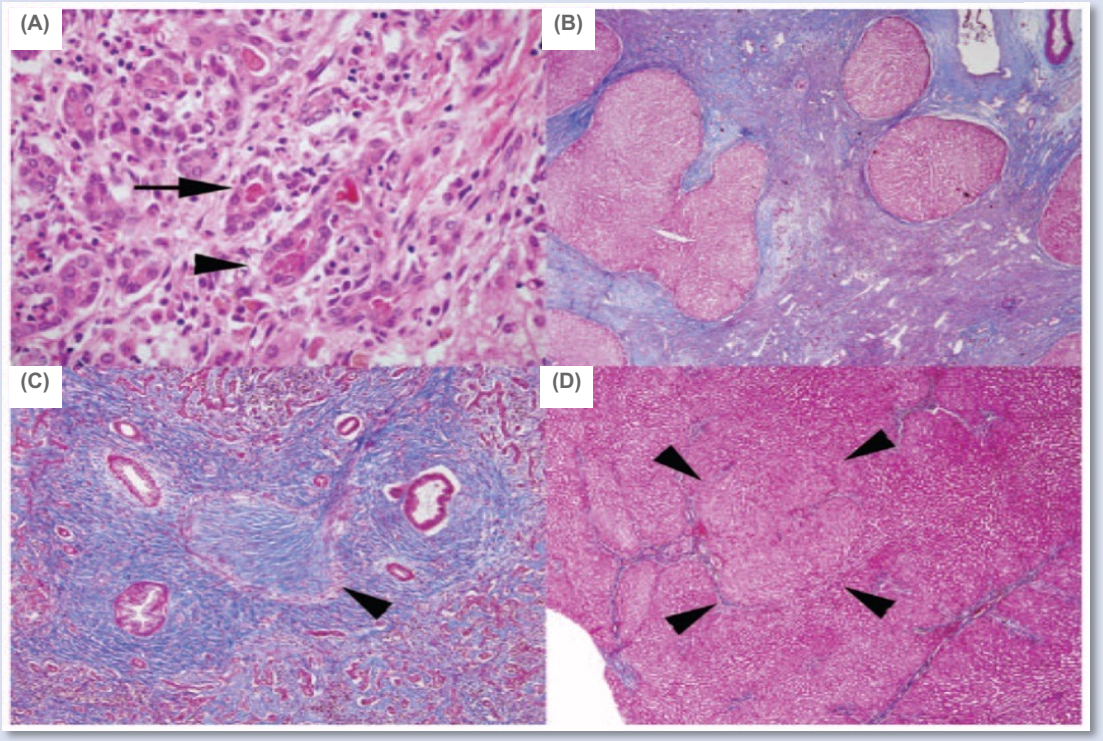
CFLD: Liver Biopsy

- Described as the “gold standard” for diagnosing and staging CF liver disease[1–3]
- Can inform on the predominant type of lesion (steatosis or focal biliary cirrhosis) and extent of portal fibrosis[4]

Limitations

- Invasive procedure, discomfort, and requires anesthesia in children[5,6]
- Due to the patchy distribution of CFLD lesions, may underestimate the severity of lesions and is not a routine investigation in many CF units[1–4]
- Dual-pass biopsy specimens have been described to improve the accuracy of diagnosing CFLD, but discordance for the fibrosis stage occurred in 38% of biopsy pairs in one study[7]

Histology associated with CFLD [1]



(A) Cholangiolar cholestasis with bile plugs (long arrow) and granular debris (arrowhead)
(B) Focal biliary cirrhosis (elsewhere on the section the architecture was intact)
(C) Portal venous occlusion with dense fibrosis (arrowhead)
(D) Nodularity seen in region with the appearance of nodular regenerative hyperplasia (arrowheads outline nodule)

Images courtesy of David Kleiner, MD, PhD, National Cancer Institute, Bethesda, MD.

1. Kamal N, et al. *Curr Opin Gastroenterol*. 2018;34:146-151. 2. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11:333-342. 3. Flass T, et al. *J Cyst Fibros*. 2013;12:116-124. 4. Debray D, et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. 5. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962. 6. Leung DH et al. *J Cyst Fibros*. 2017;16(Suppl 2):S50-S61. 7. Lewindon PJ, et al. *Hepatology*. 2011;53:193-201.

Pathophysiology

Clinical Presentation

Diagnostic Criteria

Screening and Monitoring Tests

Non-CF Liver Disease

Non-CF Liver Disease

Many diseases may cause chronic liver disease (CLD)[1]

- Often gradual progression of injury leading to fibrosis, which when extensive becomes cirrhosis[2]
- Clinically, liver disease is non-cirrhotic or cirrhotic
- Synthetic liver function may vary over time and when lost, one enters end-stage liver disease[2]

Clinically, once CLD becomes cirrhotic liver disease, it is[3,4]:

- Compensated cirrhosis: no current symptoms

  OR

- Decompensated cirrhosis: currently symptomatic

Evaluating severity often falls to using the Child-Pugh Classification

- When undergoing liver transplant evaluation, the MELD (model for end-stage liver disease) score is used[5]

1. Younossi ZM, et al. *Clin Gastroenterol Hepatol*. 2011;9:524-530. 2. American Liver Foundation. https://liverfoundation.org/for-patients/about-the-liver/the-progression-of-liver-disease/ Accessed February 2021.
3. Goldberg D, et al. *Gastroenterology*. 2017;152:1090-1099. 4. Zipprich A, et al. *Liver Int*. 2012;32:1407-1414. 5. Peng Y, et al. *Medicine*. 2016;95:e2877.

Non-CF Grading of Liver Disease

Child-Pugh Classification[1,2,3]

- Assign points based on lab & clinical criteria
- Total correlates to severity of hepatic impairment
- As based on lab & clinical criteria, may move from one level of impairment to another based on factors affecting the liver (e.g., intercurrent illness, drugs, progression of underlying disease)

Points	1	2	3
Bilirubin* (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (sec prolonged) **or** INR	<4 <1.7	4–6 1.7–2.3	>6 >2.3
Encephalopathy	None	Mild	Marked
Ascites	None	Mild	Marked

Class	Severity	Score
A	Mild	<7
B	Moderate	7-9
C	Severe	>9

NOTE: Once a score of 7-9 or higher is met, patient is often in decompensated liver failure

*Values may differ for Primary Biliary Cirrhosis
INR, international normalized ratio; PT, prothrombin time

1. Pugh RNH et al *Br J Surg*. 1973;60 (8):646-649. 2. U.S. Department of Veterans Affairs. https://www.hepatitis.va.gov/cirrhosis/background/stages.asp Accessed February 2021.
3. Merck Manual. https://www.merckmanuals.com/medical-calculators/ChildTurPuScore.htm Accessed February 2021.

Combined Serum Biomarkers in Diagnosis of Drug Induced Liver Injury (DILI)

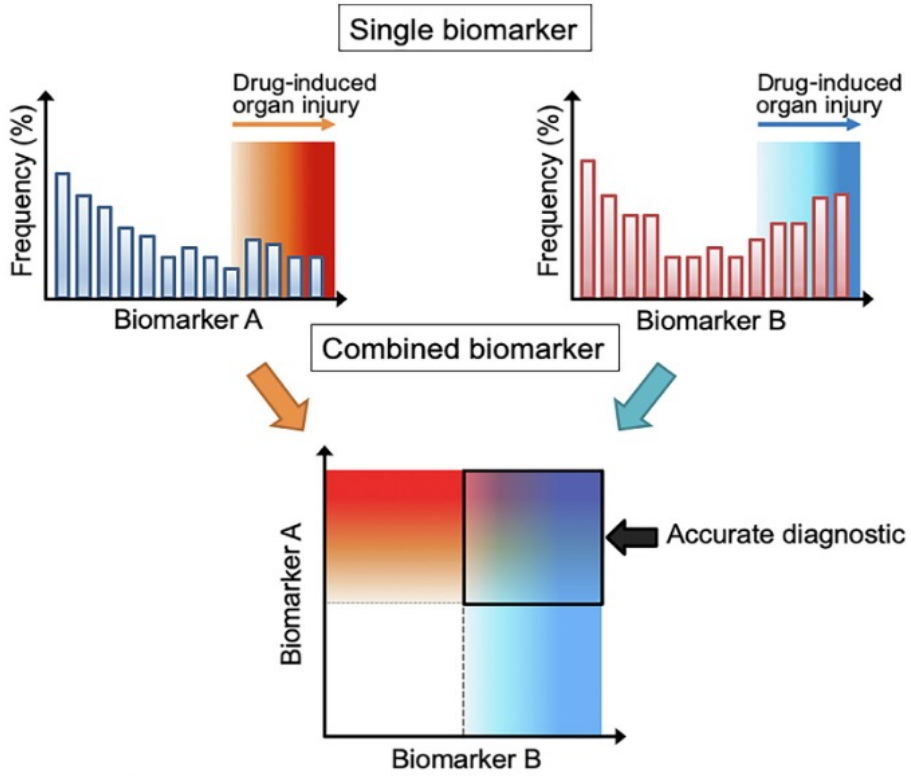
Aminotransferases are not specifically expressed in the liver, so they may also be elevated in rhabdomyolysis and myocardial infarction[1]

- Serum ALT activity level is the gold standard clinical chemistry marker of liver injury. ALT is primarily localized to the liver, with lower enzymatic activities found in skeletal muscle and heart tissue[2]
- AST is distributed in the heart, bone, skeletal muscle, as well as the liver[1]

In DILI, bilirubin excretion into bile decreases, and the concentrations of conjugated bilirubin and total bilirubin (including unconjugated bilirubin) in the serum are increased[1]

Definitions for DILI include one of the following thresholds[3]:
ALT ≥5 x ULN
ALP ≥2 x ULN after ruling out bone pathology, or
ALT ≥3 x ULN plus total bilirubin >2 x ULN

Combined biomarkers allow more sensitive and accurate diagnosis than single biomarkers[1]



ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

1. Tajima S, et al. *Biochem Pharmacol*. 2019 Dec;170:113664. 2. Giannini EG, et al. *CMAJ*. 2005;172:367-379. 3.Bessone F, et al. *Semin Liver Dis*. 2019;39:381-394.