Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

# Cystic Fibrosis-associated Liver Disease: A Review Article

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**ARTICLE INFO**

**Article type**
Review article

**Article history**
Received: 4 Feb 2018
Revised: 6 May 2018
Accepted: 11 Nov 2018

**Keywords**
Cystic Fibrosis
Diagnostic Methods
Liver Disease

**ABSTRACT**

Cystic fibrosis-associated liver disease (CFLD) is an important aspect of cystic fibrosis (CF), which manifests with various signs and symptoms. Lack of specific examinations for CFLD have made the diagnostic process of the disease time-consuming, and the disease is often identified after severe progress. Finding the associations between the outcomes of various clinical, biochemical, and sonography examinations could help specialists identify the disease in a timely manner. This review study aimed to determine the correlations between the outcomes of various diagnostic approaches based on the current literature. According to the literature, some studies have reported correlations between various diagnostic approaches, while other studies have reported no associations in this regard. This discrepancy could be due to the various manifestations associated with CF.

Please cite this paper as:
Kianifar HR, Rezaei Y, Khakshour A, Karami H, Khalesi M, Jafari SA, Kiani MA, Vakili V, Alamdaran SA. Cystic Fibrosis-associated Liver Disease: A Review Article. Rev Clin Med. 2018;5(4):146-149.

## Introduction

Cystic fibrosis (CF) is the most prevalent life-shortening, autosomal, recessive disease in several areas across the world, such as the United States, Europe, and Australia. The incidence of CF has been reported to be 1:3,500 cases per live births (1,2). Currently, the life expectancy of CF patients has increased to more than 40 years in developed countries owing to the advancement in the management of the disease (3). However, CF is still associated with multiple complications, such as hepatic cirrhosis, pulmonary failure, diabetes, and osteoporosis.

Among various complications of CF, liver disease is considered important due to its high prevalence and risk of mortality (4). According to the definition proposed by North America, cystic fibrosis-associated liver disease (CFLD) is indicated by the presence of liver cirrhosis and portal hypertension, persistent increase in liver enzymes, fibrosis, steatosis, and abnormal changes in ultrasound patterns (5,6). The global prevalence of CFLD has been reported to be 37.9%. According to statistics, approximately 2.5% of the overall mortality in the patients with CF is associated with liver disease, which is known as the third leading cause of death in these patients (7).

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To date, liver biopsy has been the most conventional approach for the assessment of CFLD. However, this technique is invasive and occasionally leads to severe complications in the patients (8).

Among various diagnostic methods, minimally invasive and noninvasive techniques for the diagnosis and management of CFLD have attracted the attention of specialists (9). Furthermore, early diagnosis of CFLD is of paramount importance due to the possible positive effects of ursodeoxycholic acid therapy, and there is an urgent need for the development of the trial of its prophylactic use.

Some of the routine procedures for the diagnosis of CFLD include determining the clinical characteristics, biochemical tests, and sonography. Evidently, finding a rational correlation between various assessments could further support the early detection of CFLD.

This review study aimed to present the results of previous studies regarding the correlations between the outcomes of various diagnostic approaches for CFLD.

## Literature Review

### *Clinical Features of CFLD*

Detection of CFLD is challenging since it is often a subclinical disease and manifests with a wide variety of signs and symptoms. The clinical features of CFLD could help specialists to suspect the disease and prescribe further examinations for the patients in order to confirm the diagnosis (10). In a study, Lamireau et al. have demonstrated that CFLD is more common in younger children (prevalence: 41%) at the age of 12 years. Similarly, Colombo et al. have reported that the incidence rate of liver disease is higher in the patients with the history of meconium ileus, male patients, and those with severe genotypes (11).

In addition to sever genotypes, factors such as pancreatic insufficiency and severe pulmonary disease have been reported to cause CFLD. In a study conducted on 288 patients with CF, 256 cases had pancreatic insufficiency, and approximately one-third of these patients (n=80) were diagnosed with liver disease. Some studies have also described the other manifestations of CFLD, including portal hypertension, neonatal cholestasis steatosis, elevation of liver transaminases, lack of alkalization, and bile dehydration (12).

In this regard, the findings of Corbett indicated poor growth and deteriorated nutritional status in the patients with CFLD (13). Furthermore, factors such as the history of jaundice, changes in the stool pattern/color, abdominal pain, weight loss, and family history of liver diseases should be considered in the patients with elevated levels of liver aminotransferases who are the potential cases of liver diseases (12). According to the study by Ciuca et al., evaluation for portal hypertension, liver cirrhosis, and pancreatic insufficiency should be considered as the initial assessment of CFLD.

### *Diagnosis of CFLD*

### *Biochemical Tests*

The serum activity assessment of transaminases is the most common test performed for the diagnosis of liver disease. However, the elevation of liver enzyme levels is frequent in the patients with CF, so that it would not be associated with severe liver disease in all the cases.

Liver function test (LFT) was investigated in a cohort prospective study in this regard. According to the obtained results, approximately 25% of the patients had abnormal LFT, and in only 13% of the cases, a significant association was observed between elevated LFT and clinical outcomes (14).

In another research, Lindblad et al. assessed the pathological morphology of liver biopsies in several patients, and only a slight increase was observed in their serum transaminase levels (15). On the other hand, various study have indicated that children with CF, who were affected by multilobular biliary cirrhosis and severe fibrosis, had normal liver enzymes (14,16).

In a review study conducted by Williams during a nine-year period, the authors reported that the results of biomarker tests differed from sonographic findings, and no correlations were observed in this regard. In addition, in 3% of the patients with persisting abnormalities of the liver echo texture and persisting splenomegaly, the level of aspartate aminotransferase were within the normal range. In the mentioned study, 725 ultrasound examinations were performed (16).

Ling et al. followed-up 124 patients with CF for the evidence of liver disease for four years (17). According to the findings, 40% of the patients with abnormal clinical or ultrasound examinations had biochemically increased aminotransferase levels. During the follow up, 48% of the patients were observed to have liver abnormalities in the clinical, biochemical, and ultrasound examinations. Some of the previous studies in this regard have also confirmed the correlation between ultrasonographic findings in the patients with CF with their clinical and biochemical characteristics (18). Overall, Ling concluded that ultrasound and the clinical examination of abnormalities based on biochemical tests could result in the prompt identification of CF in the patients (19).

### *Ultrasonography*

Currently, liver biopsy is considered to be the most common reference standard for the assess-

ment of liver fibrosis. However, it is an invasive method associated with patient discomfort and severe complications in rare cases. Over the past years, extensive research has been focused on the evaluation of noninvasive methods for the assessment of liver fibrosis (9).

Ultrasound is a noninvasive, cost-effective, and highly valuable technique for the diagnosis of hepatic steatosis, cirrhosis, and the complications caused by portal hypertension (e.g., ascites and splenomegaly). However, ultrasound cannot reliably exclude early liver disease (20).

According to the results obtained by Leung et al., sonography abnormalities were observed in 18% of the patients with pancreatic insufficiency in CF. The findings of the mentioned research are consistent with the current literature in this regard. Although 3.3% of the patients with no evidence of liver disease (e.g., portal hypertension and thrombocytopenia) had cirrhosis based on their ultrasound results. This could be due to the appearance of cirrhosis early in life. Furthermore, no correlations were reported between meconium ileus, malnutrition, deteriorated FEV1, and ultrasound results. However, Leung claimed that meconium ileus is the potential risk factor for a homogenous ultrasound pattern (21).

Another study in this regard was conducted on an extensive infant population, and the results demonstrated no significant difference between meconium ileus and development of liver disease in the patients with CF (22). Moreover, Colombo investigated 177 patients with CF with a 14-year follow-up. According to the results of the mentioned study, the ultrasonographic patterns of 10% of the cases showed the signs of cirrhosis, while there was no evidence of portal hypertensions (11).

In a recent study performed on 174 patients with CF, all the cases were followed-up daily for clinical, biochemical, and ultrasonography results. According to the findings, three children developed CFLD during infancy, along with the signs of portal hypertension. The outcome of ultrasonography also confirmed the progression of portal hypertension. According to the literature, multilobular cirrhosis with the development of portal hypertension is a major liver disease in the patients with CF (6,23).

## Conclusion

Testosterone has several functions that we mentioAccording to the current literature, liver abnormalities have been reported in some of the patients with CF along with normal biomarkers, while some studies have demonstrated that the improper function of the liver was evident in the clinical, biochemical, and ultrasound assessments of these patients. The discrepancies between the findings could be due to the wide range of liver disease manifestations, which may lead to various results in different investigations.

With respect to ultrasonography, a correlation has been reported between ultrasound patterns and clinical data in some studies, while other studies have denoted no such association. In fact, the correlations of various clinical symptoms have been reported variably in different studies. To obtain better results, it is suggested that specific research be conducted independently on the prevalent types of liver diseases to determine the correlations between various assessments.

## Acknowledgements

None.

## Conflict of Interest

The authors declare no conflict of interest.

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