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Validation of the Williams ultrasound scoring system for the diagnosis of liver disease in cystic fibrosis

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Abstract

Objectives: To describe the hepatic abnormalities revealed by ultrasound examination of cystic fibrosis (CF) patients followed at the CF Outpatient Clinic at the Federal University of Minas Gerais; to compare ultrasound data with clinical and biochemical parameters; to validate the Williams ultrasound score for the diagnosis of liver disease in CF.

Methods: Seventy cystic fibrosis patients were followed prospectively and underwent clinical, biochemical and ultrasound examinations. The ultrasound findings were compared to the results of the clinical and biochemical examinations. Clinical and biochemical criteria were used as the gold standard for the validation of the Williams ultrasound score. We calculated the sensitivity, specificity, and positive and negative predictive values for the Williams score. The patients were divided into two groups: normal (score = 3) or abnormal (score > 3) ultrasound examination.

Results: Ten patients met the clinical and/or biochemical criteria for liver disease (14.3%). All of them presented some abnormality on ultrasound examination of the liver. Abnormalities of the hepatic parenchyma, edge and periportal fibrosis were statistically more frequent in these patients. The Williams ultrasound score showed high specificity (91.7%; CI 80,9-96,9), but low sensitivity (50%; CI 20,1-79,9) for the diagnosis of liver disease.

Conclusions: The Williams ultrasound score was not a good screening tool when compared to the clinical and biochemical examinations. Since there are currently no adequate tests that can be used to diagnose liver disease, we recommend a sequential evaluation combining clinical, biochemical and ultrasound examinations for the diagnosis of liver disease in CF.

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Introduction

As cystic fibrosis (CF) patients increasingly survive longer, the hepatobiliary manifestations of the disease have become a diagnostic and therapeutic challenge. Based on clinical criteria alone, liver disease is found in 1.4 to 7% of patients with CF.[1,2] When, however, biochemical indicators and ultrasound are also included, the prevalence increases significantly.[3,4] Accurate and timely diagnosis of hepatic involvement is desirable due to the therapeutic availability of ursodeoxycholic acid (UDCA). While its efficacy has not yet been proven, early identification appears to be important since these patients respond better than do those with advanced cirrhosis.[5]

The limitations of clinical examination and liver biopsy and the controversy surrounding biochemical screening

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make the development of new non-invasive imaging techniques, such as ultrasound, for the earlier diagnosis of this hepatopathy.[6,7] There are reports that abnormalities on ultrasound examination are strong indicators of liver disease, offering high sensitivity and specificity for detecting chronic liver disease.[8,9] Abdominal ultrasound can show increased echogenicity of the hepatic parenchyma, suggestive of steatosis or cirrhosis and varices and vascular shunts, indicative of portal hypertension.

Williams et al.[6] developed an ultrasound scoring system to aid in the identification of patients with liver disease associated with CF, based on three characteristics: gross nodularity of the parenchyma, nodularity of the liver edge and increased periportal echogenicity (Table 1). A score of 3 entails an entirely normal liver, while any higher score is indicative of varying degrees of liver abnormality, up to scores of 8-9, which suggest established cirrhosis. The authors concluded that this score is useful not just to identify patients with cirrhosis (scores 8-9), but also for a subset of patients with less advanced disease (scores 4-7), making earlier diagnosis possible and, in the future, allowing treatment with UDCA to be monitored. They also found that the diagnostic method had a high level of reproducibility.

The objective of this study is to describe the hepatic abnormalities viewed in the ultrasound scans of CF patients at the Cystic Fibrosis Outpatients Clinic at the *Hospital das Clínicas* of UFMG, to compare these ultrasound findings with biochemical and clinical criteria and validate the Williams score for the diagnosis of CF-associated liver disease.

Methods

Seventy patients with confirmed CF diagnoses were followed-up prospectively and subjected to clinical, biochemical and ultrasound examinations during the period between March 1999 and June 2000.

The liver disease diagnoses were defined by means of clinical and/or biochemical criteria.[4,5] The clinical examination was considered abnormal when the presence of a palpable spleen and/or hepatomegaly, defined as the presence of a palpable liver more than 2.5 cm below the right costal margin (RCM), of firm consistency. Abnormal biochemistry was defined as a significant and persistent increase, of at least 1.5 times the upper limit of the reference range, of at least two of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) or gamma-glutamyltranspeptidase (GGT), for a period of more than 6 months. Other causes of liver disease, such as Wilson's disease, hepatitis B and C, deficiency of alpha-1-antitrypsin and auto-immune hepatitis, were ruled out.

The patients underwent the hepatobiliary ultrasound examination at the Radiology Service of the *Hospital das Clínicas* at UFMG. All examinations were performed by the same ultrasound operator with no regard to the clinical and biochemical situation of the patients. The apparatus employed was from the Siemens Prima line, a multi-frequency (2.6 to 5.0 MHz) Sonoline Prima, with convex probe.

Abnormalities in the echogenicity of the hepatic parenchyma and edge were noted as was periportal fibrosis (Table 1), in accordance with the scoring devised by Williams et al.[6] Signs suggestive of steatosis, the presence of ascites and collateral portal system damage were noted in addition to measurements for the liver, spleen and gallbladder taken with the electronic pachymeter. The right lobe of the liver was measured from the phrenic cupola to its lower edge, at the level of the right hemiclavicular line, to the right of the gallbladder bed and the left lobe, in turn, from the phrenic cupola to the lower edge, at the level of the sagittal line. The longitudinal axis of the spleen was measure at the level of the medial axillary line and the anterior-posterior along the left flank. Reference values for liver and spleen measurements for the different age groups were taken from a study by Konus et al.[10]

The database was developed and analyzed on Epi-Info version 6.0 public-domain software.

In order to validate the ultrasound test, the clinical and biochemical criteria were taken as the gold standard. The Fleiss quadratic method was then used to calculate sensitivity (s), specificity (sp), positive predictive value (PPV) and negative predictive value (NPV) with their respective confidence intervals (95% CI) for the Williams score. For the calculations the patients were split into two groups: normal ultrasound results (score = 3) or abnormal (score > 3).

Table 1 - Ultrasound scoring system to aid in the identification of patients with liver disease associated with CF developed by Williams et al.[6]

Score	1	2	3
Hepatic parenchyma	normal	intermediate	irregular
Liver edge	smooth	–	nodular
Periportal fibrosis	absent	moderate	severe

In order to compare ultrasound findings of steatosis, portal involvement and hypotrophic bladder with the results of the clinical and biochemical examinations, two-tailed Fisher's exact test was used. The Kruskal-Wallis test was used to compare median Williams scores between those with and without hepatopathies.

The study was approved by the Committee for Ethics in Medical Research at UFMG. Parents, guardians and/or the patients themselves (those aged more than 14 years) gave consent to participation.

Results

Seventy patients, seen regularly at the outpatients clinic, participated in the study. Their ages varied from 0.6 to 24.5 years (mean 10.9±6.4 and median of 10.6 years). Forty-two patients (60%) were male. Ten patients met the clinical and/or biochemical criteria for liver disease (14.3%). The ultrasound findings for the 70 patients are listed in Table 2.

Table 2 - Ultrasound findings for 70 patients

Finding	Simple frequency	Relative frequency
Abnormal Williams score	10	14.3
Parenchyma abnormality	8	11.4
Hepatic edge abnormality	3	4.3
Periportal fibrosis	6	8.6
Hepatomegaly	6	8.6
Splenomegaly	5	7.1
Steatosis	8	11.4
Collateral veins of the *porta vena* system	2	2.9
Atrophic vesicle (AV)	7	10
Ultrasound with at least one of the findings mentioned above	23	32.9
Abnormal ultrasound without AV	17	24.3
Normal ultrasound	47	

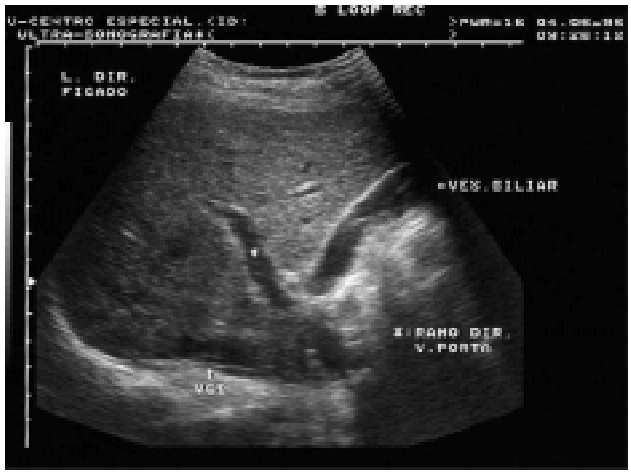

Figure 1 - Ultrasound scan showing the biliary vesicle and the right hepatic lobule, especially the right branch of the vena porta and the branch of segment 5, which exhibits mild echogenic thickening, with no other alterations

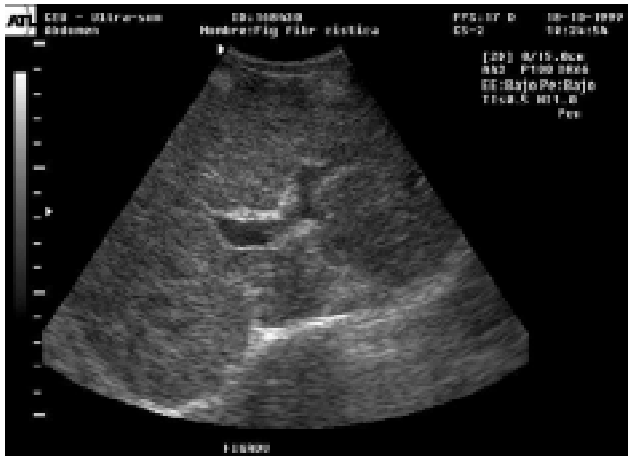

Figure 2 - This patient presents with severe hepatopathy (compare with Figure 1). Subcostal portion with severe periportal fibrosis and increase in the fiber-like tissue covering the liver - findings compatible with cirrhosis

When the points from the Williams score were summed, 10 of the 70 CF patients (14.3%) exhibited abnormal ultrasound liver scans, i.e. had score above 3 (Figures 1 and 2). Only one patient (Figure 3) presented a score suggestive of established cirrhosis (> 7). The nine remaining patients presented intermediate scores, i.e. 4 to 7.

All patients who, according to clinical and/or biochemical criteria, had hepatopathies exhibited some type of abnormality on the ultrasound scan (Table 3). Just half of these patients presented a Williams score greater than 3, varying from 4 to 8. Four patients presented intermediate scores (scores 4 to 7), while just one exhibited established cirrhosis (score > 7). The most frequently encountered abnormality was of the parenchyma (50%), followed by periportal fibrosis and liver edge nodularity. Steatosis was visible in two patients and an atrophic gallbladder in just one (Figures 4 and 5). Portal system involvement was detected in two patients.

Altered hepatic parenchyma and edge and periportal fibrosis were found more frequently among those with hepatopathies, with this difference being statistically significant. The hepatic parenchyma was found altered in 50% of the patients with hepatopathies and just 5% of those without ($p = 0.001$). Liver edge abnormalities were not described in any of the patients without liver disease, but were found in 30% of those with ($p = 0.02$). Periportal fibrosis was reported in 40% of hepatopathy patients and in just 3.3% of those without hepatopathies ($p = 0.003$). The ultrasound score for the hepatopathy subset was significantly

greater than for the non-hepatopathy set (means of 4.6 and 3.08, respectively, for with and without hepatopathies, p = 0.0037). All told, either taken in isolation or grouped, scores had low sensitivity, but were highly specific for liver disease diagnosis (Table 4).

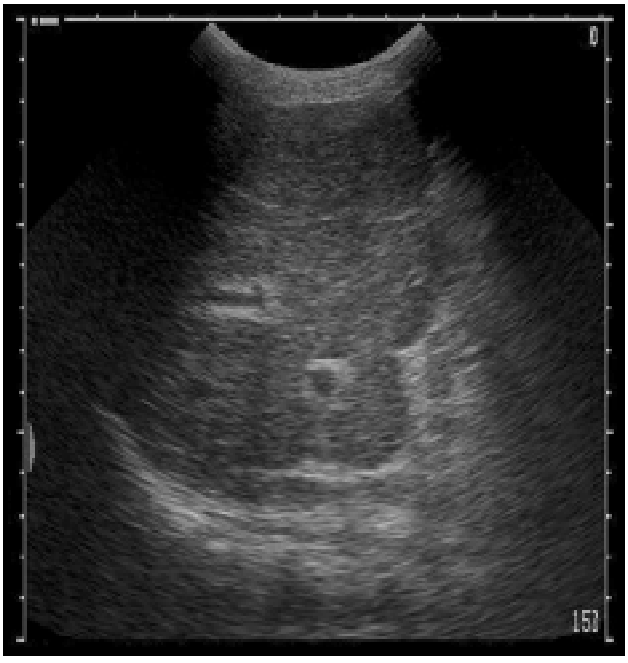

Figure 3 - Ultrasound scan showing the right hepatic lobule with evident periportal echogenic thickening, increase in the fiber-like tissue and irregular borders - severe hepatopathy, with alterations compatible with cirrhosis

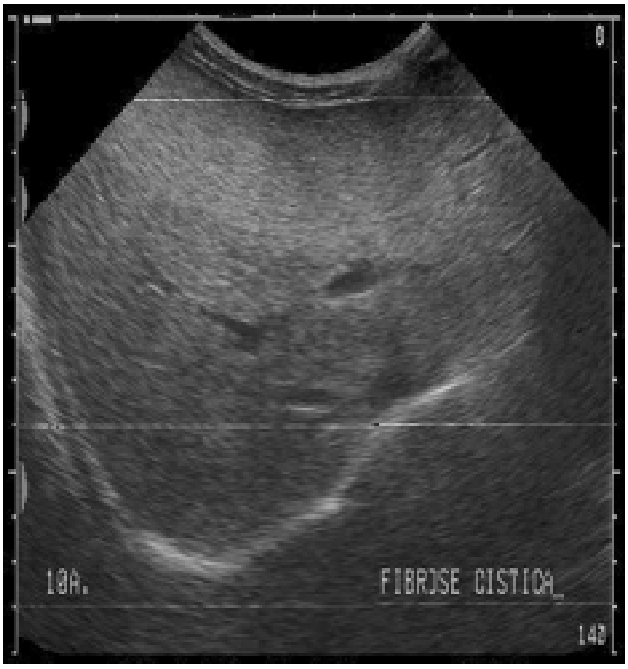

Figure 4 - Subcostal portion of the right hypochondrium showing the hyperechogenic liver ("shining"), which is compatible with diffuse steatosis

Five patients had abnormal Williams scores (in all cases the score was 4), but did not meet clinical and biochemical criteria for liver disease. Neither did they exhibit either hepatomegaly or splenomegaly on ultrasound. Two patients exhibited a palpable liver, with normal density, less than 2.5 cm from the RCM. The other three patients did not have livers that were palpable to physical examination.

The two patients that exhibited mild periportal fibrosis (scoring 2), did not present biochemical alterations or abnormalities on physical examination. In these cases esquistosomosis was ruled out. The three patients who exhibited mild parenchymal abnormalities (scoring 2) exhibited the following biochemical anomalies:

Patient 1: AST = 1.2 times the upper reference value (URV), other enzymes within normal limits.

Patient 2: AST = 1.2 times the URV, ALT = 1.1 times the URV.

Patient 3: GGT = 1.8 times the URV, FA = 1.1 times the URV, AST at the upper limit for the reference range.

Evidence of collateral circulation in the portal system was observed in two of the ten hepatopathy patients. None of the patients in the subset without hepatopathies exhibited this abnormality, which difference was statistically (p = 0.0186). In contrast, the presence of steatosis and atrophic gallbladder was no different between the two groups. There were three cases of steatosis among the liver disease patients and five among those without (p = 0.08) and one case of atrophic bladder among the hepatopathy patients and six among the remainder of the sample (p = 1.0).

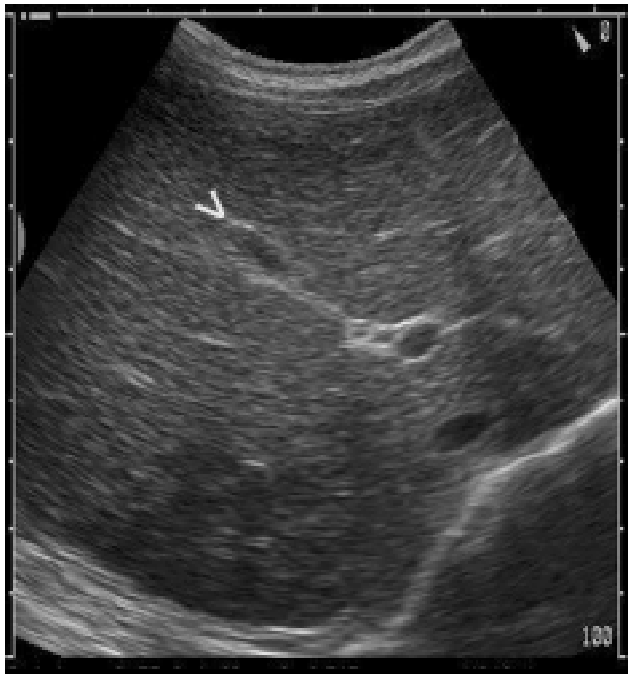

Figure 5 - Subcostal portion showing mild to moderate increase in the fiber-like tissue of the liver, with reduced biliar vesicle and thickened walls

Table 3 - Ultrasound abnormalities of 10 patients with hepatopathy associated with cystic fibrosis

	Parenchyma*	Hepatic edge*	Periportal fibrosis*	Score*	Other
1	1	1	1	3	HM
2	1	1	1	3	Steatosis
3	3	3	2	8	Collateral veins and SM
4	2	1	2	5	Collateral veins and HSM
5	2	3	2	7	SM
6	1	1	1	3	HM and steatosis
7	2	1	1	4	Steatosis and HM
8	2	3	2	7	AV and HSM
9	1	1	1	3	HM
10	1	1	1	3	SM

* Score according to Williams.[6]
HM = hepatomegaly; SM = splenomegaly; HSM = hepatosplenomegaly; AV = atrophic vesicle.

Table 4 - Williams score validation considering clinical and/or biochemical criteria with gold standard

Score	Hepatopathy Yes	Hepatopathy No	s*	e*	PPV*	NPV*
Hepatic parenchyma						
> 1	5	3	50%	95%	62.5%	92%
= 1	5	57	(20.1-79.9)	(85.2-98.7)	(25.9-89.8)	(81.5-97)
Hepatic edge						
> 1	3	0	30%	100%	100%	89.6%
= 1	7	60	(8.1-64.6)	(92.5-100)	(31-100)	(79.1-95.3)
Periportal fibrosis						
> 1	4	2	40%	97%	66.7%	90.6%
= 1	6	58	(13.7-72.6)	(87.5-99.4)	(24.1-94)	(80.1-96.1)
Williams score						
> 3	5	5	50%	91.7%	50%	91.7%
= 3	5	55	(20.1-79.9)	(80.9-96.9)	(20.1-79.9)	(80.9-96.9)

* The values between parenthesis are the respective confidence intervals (95%CI).
PPV = positive predictive value; NPV = negative predictive value.

Discussion

Abdominal ultrasound is the imaging study most widely used for the diagnosis of hepatobiliary involvement in CF. It is a test that is fast, safe, non-invasive, relatively accessible and particularly appropriate for the pediatric age group, and can be performed repeatedly. Sokol & Durie,[5] however, consider ultrasound scans to be of little utility for the detection of CF-related liver disease, because steatosis appears similar to periportal fibrosis, both of which are very common among CF patients. Despite these limitations, ultrasound is ever more widely employed.

In hepatology, ultrasound findings are often verified by liver histopathology. In CF, however, samples obtained by percutaneous puncture biopsy may not be representative because of the focal nature of the condition.[3-6] Clinical and biochemical diagnostic criteria also present limitations for the diagnosis of liver disease in CF, although they nevertheless continue to be the most often used follow-up methods. According to recommendations by the Cystic Fibrosis Foundation in the USA,[5] patients should be examined carefully at each visit, with liver and spleen measurements being recorded. A palpable liver more than 2.5 cm below the RCM should be considered abnormal at any age. Liver displacement secondary to lung disease can be differentiated from a diseased liver by means of its consistency and that of its edge. A liver that is palpable below the 2.5 cm limit purely as a result of pulmonary drift, should be soft and have a fine, smooth edge. A palpable spleen should also always be considered abnormal.

Laboratory tests of AST, ALT, AP and GGT should be performed annually, even though their levels do not preserve a strict relationship with the degree of fibrosis. When the result of the enzyme assay exceeds 1.5 times the reference range's upper limit, tests should be repeated at shorter intervals (3 to 6 months). Because of the frequent fluctuation of these enzymes in CF, results should be only considered significant if they remain abnormal (for more than 6 months). Patients presenting transitory enzyme alterations should be followed-up and subjected to a more complete evaluation before been classed as having liver disease. Differential diagnosis should be performed to rule out other causes of liver disease, such as viral hepatitis. In the event that enzyme levels continue abnormal, ultrasound examination should be performed.[5]

Neither liver histology, nor scintigraphy, or serum assay for liver fibrosis markers and bile salts have proven to be good for screening to date. This being so, for the present study clinical and biochemical criteria were used as the gold standard for validating the Williams score for CF-related liver disease diagnosis.

Patriquin et al.[11] compared ultrasound findings with hepatic biochemistry alterations (AST, ALT and GGT). Nineteen percent of the 195 patients studied exhibited ultrasound abnormalities. Sixty-three percent of the patients who presented altered ultrasound results also exhibited biochemical abnormalities, while just 21% of the patients with normal ultrasound findings had biochemical abnormalities ($p < 0.001$). The association between biochemical findings and specific ultrasound findings was also studied. Non-specific findings, such as parenchymal hypoechogenicity, exhibited little association with biochemical alterations. In contrast, 57% of steatosis cases were associated with biochemical findings, with the equivalent percentage for cirrhosis being 82%. All of the patients with signs of portal hypertension on ultrasound also presented biochemical alterations. McHugo et al.[12] also reported a positive correlation between ultrasound and biochemical findings, recording a prevalence of 26% of ultrasound abnormalities among the patients studied. Williams et al.[6] observed a good level of correlation between their ultrasound score and clinical and laboratory parameters suggestive of liver disease. Markers for portal hypertension, such as spleen size, splenic vein diameter and the presence of porto-systemic involvement exhibit a strong correlation with the proposed scoring system. The sensitivity and specificity of the Williams score had not yet been defined however.

In our research we found ultrasound liver abnormality prevalence (24.3%) comparable with reports in the literature. There was correspondence between the Williams ultrasound findings score and clinical and biochemical abnormalities suggestive of liver disease. Hepatic parenchyma and edge abnormalities, the presence of periportal fibrosis and porto-systemic involvement were more frequent among those with hepatopathies, with statistically significant differences. Liver disease patients had significantly higher ultrasound scores than did patients without liver disease ($p = 0.0037$).

The Williams score exhibited elevated specificity (91.7%) and low sensitivity (s = 50%) for the diagnosis of liver disease. It does not, therefore, constitute a good screening test, when compared with clinical and biochemical examination despite its creators having recommended it. Nevertheless, it did prove highly specific, and with a high NPV, i.e. a normal ultrasound score (of 3) makes the possibility of liver involvement unlikely. Based on these results, the Williams score should be considered as an adjutant for the diagnosis of liver disease associated with CF, as recommended by Sokol & Durie.[5]

On the other hand, Ling et al.[13] report that ultrasound findings, in common with biochemical ones, can be intermittent. It is worth pointing out that, in the present study, the three patients who exhibited parenchymal alteration on ultrasound (Williams score = 4), without meeting the criteria for liver disease associated with CF, did exhibit discrete alterations to the activities of some hepatic enzymes. The 1.5 times URF cutoff, considered liberal by Lindblad et al.[14], may, therefore, be excluding patients with early-stage liver abnormalities. Only continued observation can reveal whether these alterations are transitory or the initial manifestation of chronic liver disease.

Since there is not yet any single test which, used in isolation, offers adequate sensitivity, the recommendation is to utilize clinical examination, biochemical testing and ultrasound scans for the diagnosis of liver disease associated with CF, always serially.

References

1. Feigelson J, Anagnostopoulos C, Poquet M, Pecau Y, Munck A, Navarro J. Liver cirrhosis in cystic fibrosis - therapeutic implications and long term follow up. Arch Dis Child. 1993;68:653-7.
2. FitzSimmons SC. The changing epidemiology of cystic fibrosis. J Pediatr. 1993;122:1-9.
3. Colombo C, Apostolo G, Ferrari M, Seia M, Genoni S, Giunta A, et al. Analysis of risk for the development of liver disease associated with cystic fibrosis. J Pediatr. 1994;124:393-9.
4. Fagundes EDT, Roquete MLV, Penna FJ, Reis FJC, Duque CG. Triagem diagnóstica da hepatopatia da fibrose cística. J Pediatr (Rio J). 2002;78:389-96.
5. Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. J Pediatr Gastroenterol Nutr. 1999;28 Suppl:S1-13.
6. Williams SGJ, Evanson JE, Barret N, Hodson ME, Boultbee JE, Westaby D. An ultrasound scoring system for the diagnosis of liver disease in cystic fibrosis. J Hepatol. 1995;22:513-21.
7. Williams SM, Goodman R, Thomson A, McHugh K, Lindsell DRM. Ultrasound evaluation of liver disease in cystic fibrosis as part of an annual assessment clinic: a 9-year review. Clin Radiol. 2002;57:365-70.
8. Joseph AEA, Saverymuttu SH, al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol. 1991;43:26-31.
9. Bloom SL, Ireland A, Ryley NG, Chapman RW, Lindsell D. Correlation between hepatic ultrasound and histology. Eur J Gastroenterol Hepatol. 1992;4:39-42.

10. Konus OL, Ozdemir A, Akkaya A, Erbas G, Celik H, Isik S. Normal liver, spleen, and kidney dimensions in neonates, infants and children evaluation with sonography. Am J Roentgenol. 1998;171:1693-8.
11. Patriquin H, Lenaerts C, Smith L, Perreault G, Grignon A, Filiatrault D, et al. Liver disease in children with cystic fibrosis: US-biochemical comparison in 195 patients. Radiology. 1999;211:229-32.
12. McHugo JM, McKeown C, Brown MT, Weller P, Shah KJ. Ultrasound findings in children with cystic fibrosis. Br J Radiol. 1987;60:137-41.
13. Ling SC, Wilkinson AS, Hollmam AS, McColl J, Evans TJ, Paton JY. The evolution of liver disease in cystic fibrosis. Arch Dis Child. 1999;81:129-32.
14. Lindblad A, Glaumann H, Stradvik B. Natural history of liver disease in cystic fibrosis. Hepatology. 1999;30:1151-8.

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