Baseline Ultrasound and Clinical Correlates in Children with Cystic Fibrosis

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Baseline ultrasound and clinical correlates in children with cystic fibrosis


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Trial registration ClinicalTrials.gov: NCT01144507
Abstract

Objective—To investigate the relationship between abdominal ultrasound (US) findings and demographic, historical and clinical features in children with CF.

Study design—Children age 3-12 years with CF without known cirrhosis, were enrolled in a prospective, multi-center study of US to predict hepatic fibrosis. Consensus US patterns were assigned by 3 radiologists as normal, heterogeneous, homogeneous, or cirrhosis. Data were derived from direct collection and U.S. or Toronto CF registries. Chi-square or ANOVA were used to compare variables among US groups and between normal and abnormal. Logistic regression was used to study risk factors for having abnormal US.

Results—Findings in 719 subjects were normal (n=590, 82.1%), heterogeneous (64, 8.9%), homogeneous (41, 5.7%), and cirrhosis (24, 3.3%). Cirrhosis (p=0.0004), homogeneous (p<0.0001) and heterogeneous (p=0.03) were older than normal. More males were heterogeneous (p=0.001). More heterogeneous (15.0%, p=0.009) and cirrhosis (25.0%, p=0.005) had CF-related diabetes or impaired glucose tolerance versus normal (5.4%). Early infection with Pseudomonas aeruginosa (<2 years old) was associated with a lower risk (OR 0.42, p=0.0007) of abnormal. Ursodeoxycholic acid use (OR 3.69, p<0.0001) and CF-related diabetes (OR 2.21, p=0.019) were associated with increased risk of abnormal.

Conclusions—Unsuspected cirrhosis is seen in 3.3% of young patients with CF, heterogeneous in 8.9%. abnormal US is associated with CF-related diabetes, and early P aeruginosa is associated with normal US. Prospective assessment of these risk factors may identify potential interventional targets.

Keywords
Sonography; imaging; risk; hepatobiliary; CFTR dysfunction

There are significant limitations in the identification and classification of liver disease in patients with CF. This gap primarily reflects a lack of reliable, sensitive, and specific diagnostic markers of liver involvement in CF prior to the development of clinically evident disease.
cirrhosis with portal hypertension. A mild degree of liver involvement is common among patients with CF, but most natural history studies suggest a prevalence of multilobular cirrhosis in CF of between 5 and 15%. Virtually all cases are identified before 20 years of age, indicating that advanced liver disease in CF is a disorder of children.

A heterogeneous echogenicity pattern of the liver on abdominal ultrasound (US) has been suggested to identify patients with CF at increased risk for cirrhosis. Between 9 and 25% of children with CF are reported to have a heterogeneous pattern on US. In a single center study, 67% of patients with a heterogeneous pattern on US progressed to features consistent with cirrhosis and 46% of these progressed to portal hypertension with an average follow-up of 10 years. In patients with a normal echogenicity pattern on US, only 7-13% developed US findings of cirrhosis and 5-7.5% progressed to portal hypertension. Thus, patients with a heterogeneous pattern of the liver on US demonstrated a 5.2 fold increased incidence of cirrhosis and a 6.1 fold increased incidence of portal hypertension compared with children with a normal echogenicity pattern.

In prior studies, sample size has limited the ability to investigate potential correlations between demographic, historic or clinical factors and US findings. We hypothesized that there would be demographic and clinical features associated with each US pattern. Specifically, we sought to determine if early or current nutritional status, early infections, antibiotic use and access to care were associated with abnormal baseline US.

**Methods**

The Cystic Fibrosis Liver Disease Network (CFLD-NET) is a North American multicenter group conducting a prospective study investigating the utility of abdominal US to identify young children at risk for the development of cirrhosis (Prediction by Ultrasound of the Risk of Hepatic Cirrhosis in Cystic Fibrosis [PUSH]; ClinicalTrials.gov: NCT01144507). Official registration for this trial was delayed due to administrative issues requiring clarification by the multiple sponsors. As such, 146 of the 722 subjects (20%) reported in this study were enrolled prior to the registration approval date of June 14, 2010. However, no data were examined, and no interval analysis was conducted prior to registration. The protocol was reviewed and approved by the Institutional Review Boards at all participating centers. Study subjects were recruited from 11 CF centers within the network. All guardians provided informed consent and appropriate assent was obtained. Children 3-12 years of age were eligible for the study based on the following inclusion criteria: (1) diagnosed with CF as determined by a sweat chloride of >60 mEq/L or two disease-causing CFTR genetic mutations with evidence of end organ involvement; (2) enrolled in either the United States or Toronto CF registry; and (3) diagnosed with pancreatic insufficiency as indicated by one of the following: CFTR mutations associated with pancreatic insufficiency, fecal elastase <100 micrograms/gm (at any time), or 72 hour fecal fat with coefficient of fat absorption <85% (at any time).

Exclusion criteria were: known cirrhosis or portal hypertension (ie, splenomegaly, ascites), prior identification of *Burkholderia* species on respiratory cultures, or short bowel syndrome, defined as requiring any parenteral nutrition after 3 months of age.
Data collected included demographics, CFTR genotype, and abdominal US findings. The United States and Toronto CF registries were utilized for historical and clinical data, including medical insurance, symptoms at diagnosis, history of malnutrition, infection, lung function, complications, and medications. CF-related diabetes or impaired glucose tolerance is defined in the registries as 2-hour glucose levels of 140 to 199 mg per dL on the 75-g oral glucose tolerance test. US was performed with state-of-the-art equipment with both gray-scale and Doppler imaging at each site.

Grading followed the system of Williams et al. Liver echogenicity and contours were assessed to classify a patient into one of four US patterns. Normal denoted that the subject had normal hepatic echogenicity. Heterogeneous denoted that the subject had increased echogenicity that was diffusely patchy or limited to periportal regions. Homogeneous denoted that the subject had diffusely increased hepatic parenchymal echogenicity relative to renal echogenicity, absent or poor definition of portal venous and hepatic structures, and posterior beam attenuation with absent or incomplete diaphragm visualization. Cirrhosis pattern denoted that the subject had a heterogeneous echogenicity and coarse echotexture of the liver parenchyma and obvious nodularity of the liver contour.

A single radiologist from each center participating in the PUSH study read all the US studies locally. Participating radiologists underwent web based training for the grading of the US studies. A training set of representative images from each grade was developed by the lead radiologist. Validation of consistency (κ>0.7) in the readings was assessed with the training set prior to initiation of the study. In addition, the lead radiologist reviewed the first 5 ultrasound studies from every site for quality to ensure uniform quality and validated degree of concordance before study continuation. The same training set used for the radiologists was used to train the sonographers. In addition, there was a written guide documenting the required images for the sonographers.

At study entry, each enrolled subject, underwent a standardized abdominal US to include a survey examination of the entire abdomen and a detailed examination of the liver and spleen to assess for presence or absence of liver disease. The gray-scale images were the determinant of those who had longitudinal follow-up. US findings were independently graded as normal, heterogeneous, homogeneous or cirrhosis by 3 study radiologists randomly assigned from the different participating study sites in regular rotation and blinded to the results of the other interpretations. The consensus grade was assigned by majority. In rare cases, a 4th reader was invited to grade the ultrasound if there were 3 different grades, as a tiebreaker. If 4 different grades were submitted, the patient was excluded from the study.

**Statistical analyses**

We utilized descriptive statistics to describe demographic and clinical features, and medical history of patients in the normal and abnormal groups separately. ANOVA or Kruskal-Wallis test for continuous variables and Chi-square or Fisher's exact tests for categorical variables were used to test difference between the four groups. We then used logistic regression to determine risk factors for abnormal US findings (abnormal: heterogeneous, homogeneous, or cirrhosis) adjusting for age at US as a covariate. Each risk factor was included in the regression model individually. To investigate any potential negative impact
that different US grades had on lung function, we used a mixed effects model to test whether population mean forced expiratory volume in 1 second (FEV\(_1\) % predicted) trajectories significantly differed between the four US groups. Because FEV\(_1\) measurements are not reliably obtained in children under 6 years of age, we only included subjects older than 6 years of age at the time of screening US in this part of the analysis.

**Results**

Patients in this study were enrolled from January 21, 2010, to February 7, 2014; 722 subjects were enrolled and assigned a final US grade, but 719 were eligible and successfully matched to the US CF or Toronto registry (three were found to be ineligible after screening US). The distribution of the US findings and the demographic features are shown in Table I. The majority of subjects had a normal pattern (82.1%) with 8.9% heterogeneous, 5.7% homogeneous and 3.3% cirrhosis. Overall, 17.9% were abnormal. The subjects with heterogeneous, homogeneous, and cirrhosis patterns were all older than the normal group (Table I and Figure; Figure available at [www.jpeds.com](http://www.jpeds.com)). Heterogeneous subjects were more likely to be male (p=0.0018) and had differences in race distribution when compared with the normal group (p=0.02). There were no Hispanic subjects in the heterogeneous group compared with 8% of Hispanic in the normal group. More homogeneous patients were diagnosed with meconium ileus than normal subjects (p=0.015). There was no correlation between genotype and US pattern.

We then investigated the association of current nutritional status with US findings (Table II). Homogeneous subjects had a significantly higher BMI age adjusted z-score than normal subjects, but only 6/40 (15%) of homogeneous subjects had a BMI z-score of >1.5. More heterogeneous (15.0%) and cirrhosis (25.0%) patients were diagnosed with CF-related diabetes or impaired glucose tolerance compared with normal (5.4%) subjects. More homogeneous patients (11.4%, p=0.03) and patients with cirrhosis (25.0%, p=0.0006) were identified in the registry with non-cirrhotic liver disease compared with normal (3.1%) subjects.

There were no differences in proportion of Pseudomonas culture positivity between groups at the time of US (Table II). We studied the relationship between the change over time in pulmonary function as measured by FEV\(_1\) and US category for children over 6 years of age using a linear mixed effect model. We did not find any significant difference between groups in either rate of FEV\(_1\) decline (p=0.54) or FEV\(_1\) at 6 years of age (p=0.24).

Univariate analysis of potential risk factors for the US finding was performed (Table III). Compared with normal, both heterogeneous subjects and those with cirrhosis were less likely to be diagnosed with CF before 3 months of age, or to have a *Pseudomonas aeruginosa* infection before 2 years of age and were more likely to have used ursodeoxycholic acid at any time in the past (Table III). Subjects with cirrhosis also were more likely than normal to have used macrolide antibiotics at any time in the past (Table III). Compared with normal, homogeneous subjects were more likely to have had meconium ileus and prior reported use of ursodeoxycholic acid (Table III). There were no differences among the groups in the early use (before 2 years of age) of medications including
antifungals, steroids, acid blockers, oral corticosteroids, ursodeoxycholic acid, or macrolide antibiotics or in insurance status (data not shown).

To evaluate the possibility that some of our findings might be confounded by subject age, we performed univariate logistic regression analysis to identify risk factors for any abnormal US (heterogeneous, cirrhosis or homogeneous) adjusting for age at screening US (Table IV). After adjusting for age, early infection with *Pseudomonas aeruginosa* (<2 years of age) (p=0.0007), ursodeoxycholic acid use before US (<0.0001) at any time in the past, and CF-related diabetes/impaired glucose tolerance (p=0.019) were still significantly associated with abnormal. *Pseudomonas aeruginosa* infection before 2 years of age lowered the odds ratio of being in the abnormal group by 60%. Early ursodeoxycholic acid use was associated with a 4 fold increase and having CF-related diabetes or impaired glucose tolerance was associated with a 2 fold increase in the odds of being in the abnormal group. We performed a comparable analysis excluding homogeneous from the abnormal group and found similar results.

**Discussion**

In this prospective study, abnormalities in US patterns are present in 18% of children with pancreatic insufficient CF, which is in agreement with data from Patriquin et al obtained >15 years ago. Although the distribution of US abnormalities in our study is similar, the overall prevalence of heterogeneous US findings in our cohort is higher than that previously reported. Unexpectedly, an US pattern of cirrhosis was found in 3.3% of subjects who had no clinical evidence of liver disease such as portal hypertension (ie, splenomegaly, ascites) or thrombocytopenia. This is consistent with prior reports and suggests that cirrhosis may present early in life. The possibility of detecting CF cirrhosis in its earliest stages, prior to the development of clinical signs or symptoms, has implications for establishing important clinical endpoints that could be tracked when therapeutic drugs become available. The PUSH study illustrates that sonographic echotexture abnormalities are common in CF patients, but their ability to predict clinical outcomes such as the risk for the development of cirrhosis, will only be determined through long term follow up. At study entry, a heterogeneous pattern was demonstrated in 8.9%, and 5.7% had an homogeneous pattern. It is also possible that the US findings will vary over time, with intermittent hepatic injury and repair, or due to as yet to be determined factors. Notably, subjects with an abnormal US were older and more likely to be male in the heterogeneous group than those with a normal pattern. This is consistent with a higher frequency of multilobular cirrhosis in males and further suggests that there indeed may be a progression from heterogeneous to cirrhosis.

A homogeneous echogenic pattern is felt to reflect hepatic steatosis. In the non-CF pediatric population, a homogeneous pattern is most frequently associated with nonalcoholic fatty liver disease (NAFLD) related to obesity. In our subjects, even though there was a higher BMI z-score in those with a homogeneous pattern, only 15% of those in the homogeneous group were overweight (BMI z score >1.5). Thus, in CF the homogeneous pattern is not exclusive to overweight children. CF specific dietary interventions, medications, and nutritional deficiencies such as protein-calorie malnutrition or essential fatty acid and fat soluble vitamin deficiency may influence the development of the...
homogeneous pattern. NAFLD disproportionally affects Hispanic persons, so it was not surprising that nearly 20% of our homogeneous subjects were Hispanic\textsuperscript{14,15}. However, there were no Hispanic subjects in our reported heterogeneous group, despite representation among the other US grades. In light of these findings, it is still not clear if homogeneous is part of the progression of heterogeneous to cirrhosis. Correlation of homogeneous US findings and liver biopsy in patients with CF has not yet been undertaken.

This study allowed us to investigate potential clinical and historical factors associated with an abnormal US. Previously suggested factors for liver involvement in CF including meconium ileus, undernutrition, and worse FEV\textsubscript{1} were not found to be associated with abnormal US patterns in our study\textsuperscript{3,6,7}. The age-controlled univariate analysis demonstrated that ursodeoxycholic acid use and CF-related diabetes or impaired glucose tolerance were associated with a higher frequency of an abnormal US, and that early Pseudomonas infection (<2 years of age) was associated with a higher frequency of normal US.

Our data show an association of abnormal US with ursodeoxycholic acid even after controlling for age. More subjects with an abnormal US were identified as having non-cirrhotic liver disease in the CF registry a priori, likely secondary to documentation of elevated liver transaminases. As such, this association could be indicative of therapy for clinically suspected liver disease in the absence of detectable portal hypertension and not imply causality. Although high-dose ursodeoxycholic acid has been associated with increased morbidity, including mortality and cancer in adults with primary sclerosing cholangitis\textsuperscript{16,17}, we are not aware of prior studies that suggest that ursodeoxycholic acid may induce US abnormalities in children with CF. Our data, however, neither confirm nor exclude this possibility and we believe this deserves further study.

Our finding of an association between CF-related diabetes or impaired glucose tolerance and an abnormal US that is independent of age is noteworthy. An association with CF-related diabetes and progressive liver disease has been previously reported\textsuperscript{18}. Our data did not reveal any increased incidence of CF-related diabetes or impaired glucose tolerance in the homogeneous group. Thus, even though CF-related diabetes may be a marker of more severe CFTR dysfunction it may also be a marker of other insulin associated mechanisms, distinct from that of NAFLD, that impact liver disease.

Although this association could in part be related to the older age of the subjects and more frequent glycemic testing performed in this group, this trend remained after controlling for age. Most of the subjects tested for glucose metabolism were over 10 years of age, consistent with clinical guidelines\textsuperscript{19}. Thus, even though this association should be regarded with caution as the number of subjects diagnosed with either CF-related diabetes or impaired glucose tolerance is small, there may be a higher overall prevalence of CF-related diabetes and impaired glucose tolerance than reported in this study.

Meconium ileus has historically been considered a risk factor for CF related liver disease (CFLD). However, a recent large, single-center analysis of 401 CF infants over a 25-year period and other studies have found no difference in the percentage of patients with meconium ileus who developed CFLD compared with those without liver disease\textsuperscript{20-22}. Our
results suggest that a history of meconium ileus increases risk for a homogeneous US pattern.

The significant association of early infection and colonization with Pseudomonas after controlling for age is the most provocative finding of this study. Many more subjects in the normal group were infected with Pseudomonas compared with the abnormal group. This may indicate a modifier gene(s) effect similar to the recent work by Li et al demonstrating an association between the meconium ileus modifier polymorphism SLC6A14 and early Pseudomonas infection. This protective association could also be a marker of alteration in the gut or respiratory microbiome related to antibiotic exposure or reduction of systemic inflammation due to the early treatment of Pseudomonas infection. Changes in both the microbiome and systemic inflammation have been associated with NAFLD and other liver diseases. It could also mean that this set of patients may have a less vigorous immune response leading to early Pseudomonas colonization but decreased immune mediated liver inflammatory injury. This phenomenon may also be secondary to early identification of Pseudomonas infection leading to closer follow up or other unrecognized intervention that leads to a protective effect.

Other imaging technologies, notably transient elastography, which measures liver stiffness, has been shown to correlate with advanced fibrosis in pediatric liver diseases, including CFLD but its utility in early fibrosis is unproven.

Our findings demonstrate that the frequency of heterogeneous US abnormalities is higher than previously described, with 3% having unanticipated sonographic cirrhosis. The association between CF-related diabetes and impaired glucose tolerance with abnormal US patterns and the protective effect of early Pseudomonas infection suggest potential mechanisms predisposing to liver disease that merit further study. Although the ultrasound grading system for this study is rigorous, it is descriptive and may not directly correlate with severity of liver disease in CF. We recognize that no histological correlation was available for the imaging patterns that are used in the grading system as liver biopsy was not part of this study. The findings in this study do not yet support routine monitoring with abdominal US, but ongoing clinical follow-up of this large study group will help define the utility of screening abdominal US and the clinical significance of the spectrum of findings in young children with CF as well as the potential role of US in tracking responses to newer therapies.

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Appendix

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Abbreviations

CF cystic fibrosis
US ultrasound
FEV$_1$% predicted forced expiratory volume in 1 second
NAFLD nonalcoholic fatty liver disease
References


Figure.
Violin plot of age distribution by ultrasound finding. NL=normal, HTG=heterogeneously increased echogenicity, HMG=homogeneously increased echogenicity, CIR=cirrhosis. Mean is demonstrated by the white dot and the 25th and 75th percentile by the lower and upper limits of the black bar. The width of the violin shows the relative proportion in each category based on age (y axis).
### Table 1
Demographics and diagnostic history by ultrasound pattern

<table>
<thead>
<tr>
<th>Demographics and Diagnostic History</th>
<th>Ultrasound Results at Screening</th>
<th>p-value £</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NL</td>
<td>HTG</td>
</tr>
<tr>
<td>Number (%)</td>
<td>590 (82.1%)</td>
<td>64 (8.9%)</td>
</tr>
<tr>
<td>Age at ultrasound, mean ±SD †</td>
<td>7.6±2.9</td>
<td>8.5±2.2§</td>
</tr>
<tr>
<td>Female, count (%) †</td>
<td>328 (55.6%)</td>
<td>22 (34.4%)§</td>
</tr>
<tr>
<td>Ethnicity, count (%) §</td>
<td>Non-Hispanic White</td>
<td>509 (86.7%)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic Black</td>
<td>12 (2%)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>47 (8%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>19 (3.2%)</td>
</tr>
<tr>
<td>Genotype, count (%) ‡</td>
<td>ΔF508 homozygous</td>
<td>355 (60.2%)</td>
</tr>
<tr>
<td></td>
<td>ΔF508 heterozygous</td>
<td>181 (30.7%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>54 (9.2%)</td>
</tr>
<tr>
<td>Diagnosis via newborn or prenatal screening, count (%) ‡</td>
<td>135 of 589 (22.9%)</td>
<td>14 of 63 (22.2%)</td>
</tr>
<tr>
<td>Sweat Chloride Value (meq/L), mean ±SD ‡ (n = count)</td>
<td>100.9±13.5 (n=456)</td>
<td>98.7±17.6 (n=44)</td>
</tr>
</tbody>
</table>

US patterns are: Normal (NL), heterogeneous increased echotexture (HTG), homogeneous increased echotexture (HMG) or cirrhosis (CIR)

£ ANOVA or Kruskal-Wallis for continuous variables and Chi-square test or Fisher exact test for categorical variables

† Data obtained from PUSH database

‡ Data obtained from CFF registry database

§ p<0.05 for post-hoc comparison to NL
<table>
<thead>
<tr>
<th>Clinical feature at the time of US findings</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI age adjusted z-score (mean ±SD) £</td>
<td>0.013</td>
</tr>
<tr>
<td>With supplemental feeds (count %) ‡</td>
<td>0.40</td>
</tr>
<tr>
<td>Under nutrition: BMI or height z-score &lt; -1.5 ‡</td>
<td>0.25</td>
</tr>
<tr>
<td>Pseudomonas ever positive (count %) ‡</td>
<td>0.35</td>
</tr>
<tr>
<td>FEV1 % predicted (mean ±SD) ‡</td>
<td>0.32</td>
</tr>
<tr>
<td>FVC % predicted (mean ±SD) ‡</td>
<td>0.59</td>
</tr>
<tr>
<td>PFV1 % predicted (mean ±SD) ‡</td>
<td>0.0087</td>
</tr>
<tr>
<td>CFRD status (count (CFRD) %) ¥</td>
<td>0.0002</td>
</tr>
<tr>
<td>Identified in the registry as non-cirrhotic liver disease (count %) §</td>
<td>0.05</td>
</tr>
</tbody>
</table>

£ ANOVA or Kruskal-Wallis for continuous variables and Chi-square test or Fisher exact test for categorical variables
† Data obtained from PUSH database
‡ Data obtained from CFF registry and Toronto database
¥ Data obtained from CFF registry database only
§ p<0.05 for post-hoc comparison with NL
Table 3

Univariate analysis of potential risk factors for the US finding

<table>
<thead>
<tr>
<th></th>
<th>Ultrasound results at screening</th>
<th></th>
<th></th>
<th></th>
<th>P-value $^£$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal N=590</td>
<td>HTG N=64</td>
<td>HMG N=41</td>
<td>CIRR N=24</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis &lt; 3 months $^$</td>
<td>294 (56.3%) (n=522)</td>
<td>34 (56.7%) (n=60)</td>
<td>21 (60%) (n=35)</td>
<td>5 (25%) $^$ (n=20)</td>
<td>0.046</td>
</tr>
<tr>
<td>Diagnosis symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn or prenatal screening $^$</td>
<td>135 (22.9%) (n=589)</td>
<td>14 (22.2%) (n=63)</td>
<td>5 (12.2%) (n=41)</td>
<td>1 (4.4%) (n=23)</td>
<td>0.079</td>
</tr>
<tr>
<td>Meconium ileus $^$</td>
<td>143 (24.3%) (n=589)</td>
<td>18 (28.6%) (n=63)</td>
<td>17 (41.5%) (n=41)</td>
<td>3 (13%) (n=23)</td>
<td>0.042</td>
</tr>
<tr>
<td>Malnutrition $^¥$</td>
<td>160 (30.7%) (n=522)</td>
<td>21 (35%) (n=60)</td>
<td>13 (37.1%) (n=35)</td>
<td>11 (55%) (n=20)</td>
<td>0.11</td>
</tr>
<tr>
<td>Under nutrition at 1 year (weight-for-height z-score &lt; -1.5 or height z-score &lt; -1.5) $^$</td>
<td>276 (68.5%) (n=403)</td>
<td>32 (71.1%) (n=45)</td>
<td>17 (65.4%) (n=26)</td>
<td>10 (83.3%) (n=12)</td>
<td>0.69</td>
</tr>
<tr>
<td>Under nutrition at 2 year (weight-for-height z-score &lt; -1.5 or height z-score &lt; -1.5) $^$</td>
<td>200 (44%) (n=455)</td>
<td>23 (46.9%) (n=49)</td>
<td>12 (40%) (n=30)</td>
<td>8 (61.5%) (n=13)</td>
<td>0.58</td>
</tr>
<tr>
<td>Medication use before US $^$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urso $^¥$</td>
<td>30 (5.8%) (n=522)</td>
<td>8 (13.3%) $^$ (n=60)</td>
<td>8 (22.9%) $^$ (n=35)</td>
<td>8 (40.0%) $^$ (n=20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Acid blocker $^$</td>
<td>378 (64.2%) (n=589)</td>
<td>47 (74.6%) (n=63)</td>
<td>25 (61%) (n=41)</td>
<td>13 (56.5%) (n=23)</td>
<td>0.30</td>
</tr>
<tr>
<td>Macrolide $^$</td>
<td>169 (28.7%) (n=589)</td>
<td>19 (30.7%) (n=62)</td>
<td>17 (41.5%) (n=41)</td>
<td>12 (52.2%) (n=23)</td>
<td>0.039</td>
</tr>
<tr>
<td>Oral corticosteroids $^$</td>
<td>25 (4.2%) (n=589)</td>
<td>4 (6.5%) (n=62)</td>
<td>1 (2.4%) (n=41)</td>
<td>0 (n=23)</td>
<td>0.69</td>
</tr>
<tr>
<td>Antifungals $^$</td>
<td>8 (1.5%) (n=522)</td>
<td>2 (3.4%) (n=59)</td>
<td>0 (n=35)</td>
<td>0 (n=20)</td>
<td>0.52</td>
</tr>
<tr>
<td>Early Infection history $^$</td>
<td>195 (41.0%) (n=476)</td>
<td>12 (24.5%) $^$ (n=49)</td>
<td>10 (29.4%) (n=34)</td>
<td>2 (13.3%) $^$ (n=15)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Urso=ursodeoxycholic acid

$^\$ Data obtained from PUSH database

$^£$ ANOVA or Kruskal-Wallis for continuous variables and Chi-square test for categorical variables

$^\$ Data obtained from CFF and Toronto registry database

$^¥$ Data obtained from CFF registry database only
### Table 4

Probability of abnormal US based on clinical characteristics or exposures

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Age at diagnosis &lt; 3 months (Yes vs. No)</strong> ‡</td>
<td>1.068 (0.701, 1.626)</td>
</tr>
<tr>
<td><strong>Diagnosis with new born screening or prenatal (Yes vs. No)</strong> ‡</td>
<td>0.944 (0.545, 1.634)</td>
</tr>
<tr>
<td><strong>Diagnosis with meconium ileus (Yes vs. No)</strong> ‡</td>
<td>1.399 (0.907, 2.159)</td>
</tr>
<tr>
<td><strong>Under nutrition at 2 year (WHZ, &lt; -1.5 or HAZ &lt; -1.5) (Yes vs. No)</strong> ‡</td>
<td>1.137 (0.720, 1.794)</td>
</tr>
<tr>
<td><strong>Medicine use before US</strong> ‡</td>
<td></td>
</tr>
<tr>
<td>Acid blocker (Yes vs. No)</td>
<td>1.017 (0.671, 1.541)</td>
</tr>
<tr>
<td>Macrolides (Yes vs. No)</td>
<td>1.017 (0.656, 1.578)</td>
</tr>
<tr>
<td>Oral corticosteroids (Yes vs. No)</td>
<td>0.701 (0.260, 1.895)</td>
</tr>
<tr>
<td>Antifungals (Yes vs. No)</td>
<td>0.759 (0.157, 3.681)</td>
</tr>
<tr>
<td>URSO (Yes vs. No)</td>
<td>3.694 (2.037, 6.698)</td>
</tr>
<tr>
<td><strong>Early Infection (Pseudomonas in first 2 years) (Yes vs. No)</strong> ‡</td>
<td>0.417 (0.251, 0.692)</td>
</tr>
<tr>
<td><strong>BMI age adjusted z-score at time of US (Yes vs. No)</strong> ‡</td>
<td>1.221 (0.977, 1.526)</td>
</tr>
<tr>
<td><strong>With supplemental feed at time of US (Yes vs. No)</strong> ‡</td>
<td>0.820 (0.526, 1.278)</td>
</tr>
<tr>
<td><strong>CFRD (IGT or CFRD vs. normal) (Yes vs. No)</strong> ‡</td>
<td>2.207 (1.136, 4.285)</td>
</tr>
<tr>
<td><strong>Sweat Chloride Value (meq/l)</strong> ‡</td>
<td>1.245 (0.839, 1.848)</td>
</tr>
<tr>
<td><strong>Sweat Chloride Value (meq/l)</strong> ‡</td>
<td>1.004 (0.987, 1.021)</td>
</tr>
</tbody>
</table>

CFRD=CF related diabetes, IGT=impaired glucose tolerance

‡ Data obtained from CFF registry database

† Data obtained from PUSH database