Journal of Cystic Fibrosis 22 (2023) 248–255

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Long-term follow-up and liver outcomes in children with cystic fibrosis and nodular liver on ultrasound in a multi-center study☆,☆☆

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☆☆ Source of Funding: Supported by the Cystic Fibrosis Foundation (NARKEW17AB0 to M.N.) and the National Institutes of Health NIDDK U01 DK062453 to M.N. and NIDDK U24 DK062456 to Dr. John Magee and Dr Wen Ye.

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https://doi.org/10.1016/j.jcf.2022.07.017

ARTICLE INFO

Article history:
Received 10 March 2022
Revised 30 June 2022
Accepted 29 July 2022
Available online 16 August 2022

Keywords:
Cirrhosis
Cystic fibrosis liver disease
Ultrasound

abbreviations: CF, cystic fibrosis
PUSH, prediction by ultrasound of the risk of hepatic cirrhosis
NOD, nodular
VCTE, vibration controlled transient elastography
NL, normal
LSM, liver stiffness measurement
CFRD, cystic-fibrosis-related diabetes
CFTR, cystic fibrosis transmembrane regulator
US, ultrasound
CAP, continuous attenuation parameter
AST, aminotransferase
ALT, alanine aminotransferase
GGT, gamma-glutamyl transferase
APRI, aspartate aminotransferase to platelet ratio index
PELD, pediatric end-stage liver disease
FIB4, fibrosis index based on four factors
INR, international normalized ratio
WBC, white blood cell count
FEV1, forced expiratory volume in one second
FVC, forced vital capacity
IGT, impaired glucose tolerance

ABSTRACT

Background: Nodular liver (NOD) in cystic fibrosis (CF) suggests advanced CF liver disease (aCFLD); little is known about progression of liver disease (LD) after detection of sonographic NOD.
Methods: Clinical, laboratory, and ultrasound (US) data from Prediction by Ultrasound of the Risk of Hepatic Cirrhosis in CFLD Study participants with NOD at screening or follow-up were compared with normal (NL). Linear mixed effects models were used for risk factors for LD progression and Kaplan-Meier estimator for time-to-event.
Results: 54 children with NOD (22 screening, 32 follow-up) and 112 NL were evaluated. Baseline (BL) and trajectory of forced expiratory volume, forced vital capacity, height/BMI z-scores were similar in NOD vs NL. Platelets were lower in NOD at BL (250 vs 331×10^3/microL; $p < 0.001$) and decreased by 8600/year vs 2500 in NL. Mean AST to Platelet Ratio Index (1.1 vs 0.4; $p < 0.001$), Fibrosis-4 Index (0.4 vs 0.2, $p < 0.001$), and spleen size z-score (SSZ) [1.5 vs 0.02; $p < 0.001$] were higher in NOD at BL; SSZ increased by 0.5 unit/year in NOD vs 0.1 unit/year in NL. Median liver stiffness (LSM) by transient elastography was higher in NOD (8.2 kPa, IQR 6–11.8) vs NL (5.3, 4.2–7, $p < 0.0001$). Over 6.3 years follow-up (1.3–10.3), 6 NOD had esophageal varices (cumulative incidence in 10 years: 20%; 95% CI: 0.0%, 40.0%), 2 had variceal bleeding, and 2 underwent liver transplantation; none had ascites or hepatic encephalopathy. No NL experienced liver-related events.
Conclusions: NOD developed clinically evident portal hypertension faster than NL without worse growth or lung disease.

1. Introduction

Cystic fibrosis (CF) is one of the most common inherited disorders, affecting about 1/4000 births in the U.S. [1]. While the highest morbidity in CF is due to pulmonary disease, the pancreas, intestine, and liver are major gastrointestinal organs affected. The majority of patients with CF have elevated aminotransferases during their lifetime [2]; gallstones and hepatic steatosis occur frequently [3]. Nodularity of the liver with or without portal hypertension is recognized as advanced CF liver disease (aCFLD) and occurs in 5–10% of children with CF by age 10, due to biliary cirrhosis, obliterative portal venopathy, or nodular regenerative hyperplasia [4–6]. Clinical manifestations vary, ranging from minor biochemical or imaging abnormalities to dramatic clinical events such as variceal hemorrhage [3,6–9].

The Prediction by Ultrasound of the Risk of Hepatic Cirrhosis (PUSH) (NCT01144507) study evaluated whether sonographic liver heterogeneity in children with CF, 3–12 years of age at entry, would predict the development of nodular liver (NOD), presumed to reflect aCFLD. Baseline data from that study revealed unsuspected NOD in 3.3% of these young children with CF and an association with CF-related diabetes (CFRD) [10]. We have previously shown that a heterogeneous liver US pattern identified children with a 9-fold increased risk for developing NOD or aCFLD compared to NL [11]. The goals of the present study were to describe the clinical characteristics of children with NOD compared to normal (NL), to explore long-term clinical outcomes, and to examine CFRD as a risk factor for progression of aCFLD in children with NOD. The rationale for studying NOD was to develop an early, non-invasive, and useful indicator of children at risk for developing aCFLD.

2. Materials and methods

2.1. Study population and data sources

Between January 12, 2010 and October 17, 2013, 725 children with CF 3–12 years of age underwent screening ultrasound (US) at the baseline visit of the PUSH study. Inclusion and exclusion criteria for the PUSH study have been described but include (1) diagnosis of CF determined by a sweat chloride of more than 60 mEq/L or two disease-causing CFTR genetic mutations with evidence of end-organ involvement; (2) enrollment in either the Cystic Fibrosis Foundation or Toronto CF registry; (3) diagnosis of pancreatic insufficiency based on fecal elastase or type of CFTR mutation; and (4) no known cirrhosis or portal hypertension or short bowel syndrome. Ultrasound grades were classified by liver parenchymal patterns as normal (NL), heterogeneous (HTG), homogeneously hyperechoic (HMG), or nodular (NOD) [10].

Classification was based on consensus grade of three protocol trained study radiologists blinded to the readings of the other radiologists. Among the 722 participants with consensus grades at the PUSH baseline visit, 249 eligible patients (125 NL, 62 HTG, 38 HMG, and 24 NOD) entered the 9-year prospective longitudinal study. For the duration of the study, participants underwent annual follow-up, including physical examination, laboratory and biospecimen collection, and quality of life surveys. Research US was performed at years 2, 4, 6, and 8 or 9 of follow-up. Detailed methodology of the PUSH study has been previously reported [10,11].

For this study, we evaluated PUSH participants with a US grade of NOD at baseline or any follow-up US visit. PUSH participants with a US grade of NL at baseline and who remained NL throughout the study were used as a control comparison group.

Demographics, physical exam, and laboratory measurements were collected in PUSH, with additional CF-relevant clinical and historical data including pulmonary function, lung transplant, CFRD, and impaired glucose tolerance (IGT) status recorded from the United States CF Foundation Patient Registry (CFFPR) for study participants (105 NL and 49 NOD) enrolled at the ten study sites in the United States [12]. Between March 8, 2017 and December 31, 2018, the Longitudinal Assessment of Transient Elastography in Cystic Fibrosis (ELASTIC) (NCT03001388) study enrolled a subset of participants from PUSH to collect vibration-controlled transient elastography (VCTE) data [13].

2.2. Outcomes

Liver-related events recorded on case report forms included bleeding, documented varices in children who underwent endoscopy as part of routine clinical care, ascites, encephalopathy, and liver transplantation. Changes in liver-related lab measurements (albumin, platelet count, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transferase [GGT], AST to platelet ratio index [APRI: AST/upper limit of normal of AST)/platelet count] [14], fibrosis index based on 4 factors [FIB4; age $\times$ AST)/ (platelet count $\times$ $\sqrt{}$ALT] [14], total bilirubin, white blood cell count [WBC]), and spleen size measured on US as the longest craniocaudal dimension and expressed as a spleen-size-for-age z-score (SSZ) using age-specific normal ranges were recorded [15]. CF-specific pulmonary and nutritional outcomes, including predicted forced expiratory volume in one second (FEV1), forced vital capacity (FVC), Pseudomonas positivity, height z-score, BMI z-score, anthropometrics (right mid-upper arm circumference z-score, right triceps skinfold thickness z-score, subscapular skinfold thickness z-score), CFRD status, lung transplant, and all-cause mortality were also analyzed. CFRD was coded by three categories: normal, impaired glucose tolerance (IGT), and CFRD. For this analysis, this variable was dichotomized to CFRD vs IGT or normal. The PUSH study also collected data for participants prescribed CFTR modulators since November 2015.

2.3. Definition of study baseline

Baseline variables for participants with NOD and NL US pattern at screening were collected from the PUSH baseline clinical visit. For NOD participants later identified during follow-up PUSH visits, lab measurements, Pseudomonas positivity, height z-score, BMI z-score, anthropometrics, FEV1, and FVC within a year of the first NOD US represented their baseline values.

2.4. Statistical analyses

Clinical, laboratory, US, and VCTE data from PUSH participants at the time NOD was identified were compared to baseline visit data from participants with NL for the duration of the study. T-test or Wilcoxon test were used to test differences in continuous variables, and Chi-squared test or Fisher's exact test were used to test difference in categorical variables between the two groups. Linear mixed effects models were used to study changes in lab measurements, spleen-size-for-age z-score, pulmonary function, BMI z-score, height z-score, and anthropometrics over time. The cumulative event rate of diagnosis of first varices from first NOD US pattern was estimated using the Kaplan-Meier estimator. To compare CFRD incidence in NOD vs NL, the log-rank test to compare Kaplan-Meier curves for the event of CFRD diagnosis was used. As the recommended age for CFRD screening in children with CF is 10 years, CFRD status beginning at that age was used as the starting time point for this survival analysis. All analyses were performed using SAS 9.4 (Cary, NC), and p-value <0.05 was considered to be statistically significant.

3. Results

3.1. Study population

Among the 722 children with CF and consensus US at their PUSH screening US visit, 24 were identified as NOD and entered the PUSH longitudinal study together with 125 eligible NL, 62 HTG, and 38 HMG (Fig. 1). Two of the 24 children who were identified as NOD at screening US visit were lost to follow-up after the initial NOD US. Among the three groups of children with non-NOD patterns at screening visit, 6 NL, 23 HTG, and 3 HMG subsequently developed NOD at follow-up; 15 participants demonstrated NOD at year 2, 13 at year 4, and 4 at year 6. Among the 125 NL followed, 112 remained NL at all follow-up visits and served as the comparison group. Altogether, 54 NOD and 112 NL were included in this analysis. Demographics of the different cohorts are shown in Table 1; age of NOD at the time of first NOD US was significantly older than that of the NLs (mean 10.9 vs 8.4 years, $p < 0.0001$). Adjusting for age did not change the conclusions of baseline or longitudinal analyses below (data not shown). The median (min, max) follow-up for the NODs and NLs were 5.7 (0.5, 10.4) and 7.7 (2.0, 9.9) years, respectively. NOD at baseline vs NOD at followup (Table S1) were very similar except for age and WBC.

3.2. Liver related events

Platelet (mean 250k vs 331k/microL) and WBC (mean 7.8 vs 9.2k/microL) counts were significantly lower in NOD at baseline, but still within normal clinical range (Table 1). Total bilirubin, AST, ALT and GGT were significantly higher in NOD at baseline. Albumin levels at baseline were similar. APRI (mean 1.1 vs 0.4) and FIB4 (mean 0.4 vs. 0.2) were significantly higher in the NOD group compared to the NL group at baseline

Platelet count declined at a rate of 8,600/year (95% CI: 4,300–13,000) in NOD, significantly more rapidly than in NL (2,500/year, 95%CI: -0-5000; p=0.018) (Fig. 2). The change over time in AST, ALT, and GGT were similar between the NOD and NL. There were no differences in change of albumin over time between the two groups. APRI increased more rapidly by 0.07/year (95% CI: 0.03–0.10) in the NOD group compared to the NL group ($p < 0.0001$); FIB4 increased by 0.05/year (95% CI: 0.03–0.06) more rapidly in the NOD group ($p < 0.0001$).

Table 1 summarizes selected sonographic variables. Mean sonographic spleen length was 11 cm in NOD vs 8.9 in NL; spleen size for age adjusted z-scores was also larger in NOD (mean 1.5) compared to NL (0.02). While spleen size z-score increased significantly over time in both groups, the increase in NOD was more rapid (Fig. 2; 0.5 unit/year in NOD vs 0.1 unit/year in NL; $p < 0.0001$). Initial liver stiffness measurement (LSM) was available for 38 NOD and 65 NL participants during the PUSH study follow-up. Initial liver stiffness measurement (LSM) was significantly higher in NOD (8.2 kPA) vs NL (5.8 kPa); mean CAP (continuous attenuation parameter) scores were similar between NOD and NL.

While no participant demonstrated clinically significant ascites or encephalopathy, 6 NOD participants were found to have esophageal varices; 2 of the 6 experienced variceal bleeding at 11.1 and 12.9 years of age, respectively (5.6 and 8.7 years after the identification of NOD) (Table 2). From first identification of NOD, the cumulative incidence rate at 10 years for detecting esophageal varices was 20% (96% CI: 00.0%, 40.0%) (Fig. S1). Among the 6 NOD

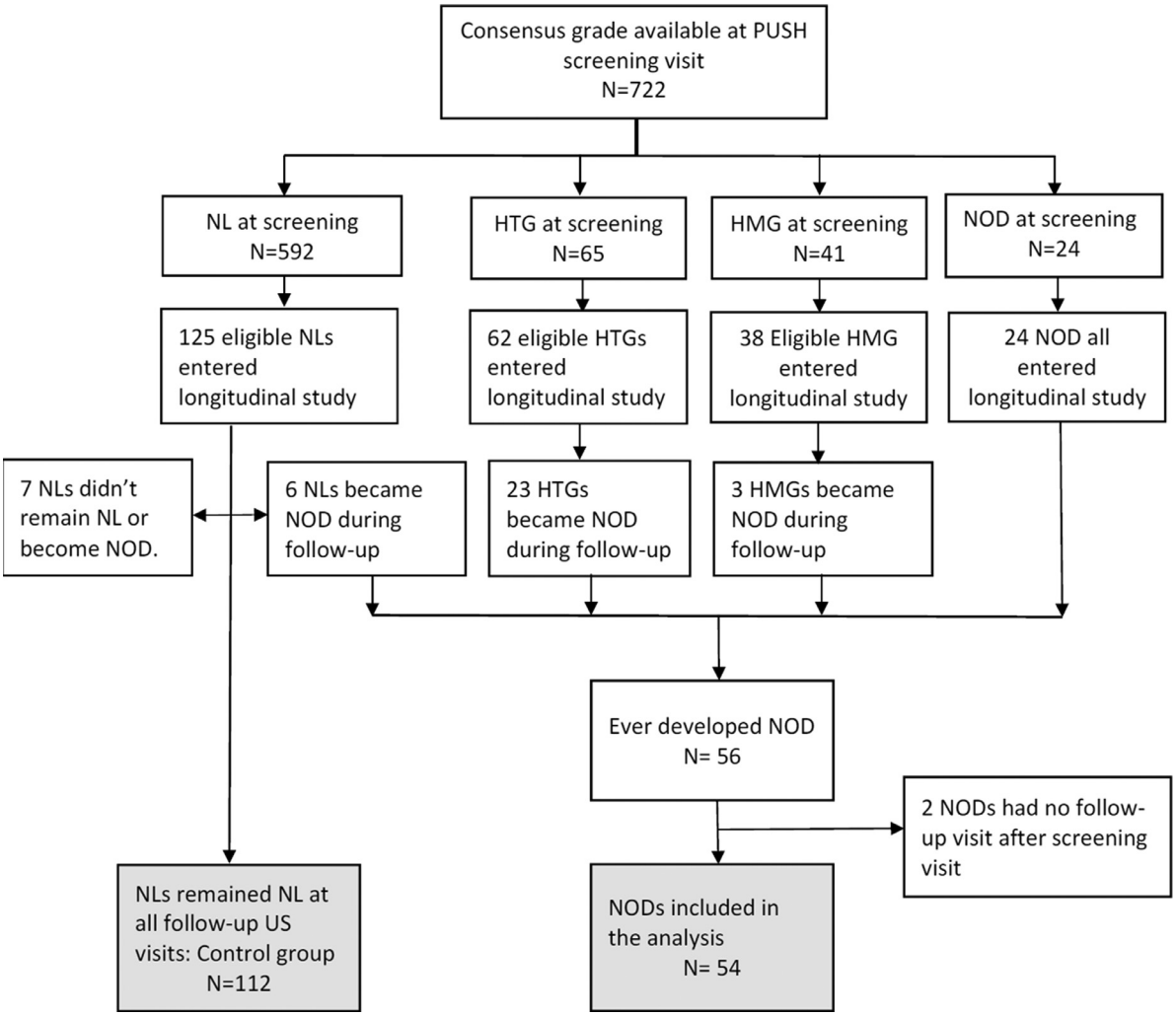

Fig. 1. Study cohort flowchart.

participants who had esophageal varices, 2 underwent liver transplantation at 8.0 (PELD score= 2) and 18.1 (PELD score = -4; MELD score = 9) years of age, respectively. Four of these six participants had NOD at study baseline (one of these underwent liver transplant); the other 2 participants were HTG at baseline and converted to NOD at the year 2 visit (one of these underwent liver transplant). Figs. S2 and S3 present the trajectory of spleen size z-score and platelet count for all NOD participants. The six participants with esophageal varices had more rapid increase in spleen size and steep decrease in platelet count compared to other participants (compared to NOD or NL participants). There were zero liver events recorded among NL.

3.3. Pulmonary, nutritional and diabetes outcomes

The rate of decline in FEV1% predicted was not different between NOD vs NL (1.9%/year vs 1.5%/year, Fig. 2). There was also no difference in rate of decline in FVC% predicted between NOD vs NL. BMI z-score, height z-score, right triceps skinfold thickness z-score, and subscapular skinfold thickness z-score were similar at both baseline and over time NOD and NL (Fig. 2). Right mid-upper arm circumference z-score was similar in NOD vs NL at baseline but decreased slightly more in 10 years in NOD (-0.5 vs. -0.05, p=0.059); this change in NOD was statistically significant (p=0.013).

Prevalence of CFRD at baseline (6.8% in NOD vs. 2.9% in NL) and ever in the course of the study (26.5% in NOD vs 21.9% in NL) were not different between groups. While NOD had significantly more IGT than NL at baseline (26.5% vs 4.9%; $p < 0.0001$), cumulative incidence of CFRD (33.9% vs 46.3%) diagnosis by age 20 did not differ (Fig. 3).

While platelet count decreased and spleen size, FIB-4, and APRI increased significantly over time in NOD, these changes were not significantly different in NOD participants with CFRD (diagnosed before or during the course of the study) and those without (Fig. S4).

During the course of the PUSH study, 31 out of 52 (59.6%) NOD and 70 out of 110 (63.6%) NL subjects received CFTR modulator therapy (p=0.62). No NOD or NL participants underwent lung transplantation (Table 2).

4. Discussion

aCFLD occurs in 5–10% of people with CF [4,5,16,17], and portal hypertension often manifests before liver synthetic function is impaired [3]. aCFLD may include cirrhosis as well as non-cirrhotic portal venopathy [4,18]. In comparison to children with CF and normal ultrasound in this unique longitudinal study, we found that the presence of NOD can be an early predictor of advanced CF liver disease, indicating current or emerging clinically evident portal hypertension [19], but cannot differentiate between cirrhotic or non-cirrhotic causes. While children with NOD have normal synthetic function, they exhibit much larger spleen size and lower

Table 1
Participants Characteristics at Baseline.

Demographics/Features [¶]	NOD (N=54)		NL (N=112)		*p*-value
	N		N		
Male, count (%)	54	33 (61%)	112	55 (49%)	0.15[§]
Age (years), mean (SD)	54	10.9 (3.0)	112	8.4 (3.1)	<.0001[#]
Ethnicity, count (%)					0.28[*]
Hispanic	54	1 (1.9%)	112	7 (6.3%)	
Non-Hispanic		53 (98.15%)		105 (93.7%)	
Race, count (%)					0.72[*]
Asian	54	1 (1.9%)	112	0 (0.00%)	
African American		1 (1.9%)		3 (2.7%)	
Multiracial		0 (0.00%)		2 (1.8%)	
White		52 (96.3%)		106 (94.6%)	
Unknown		0 (0.00%)		1 (0.9%)	
Platelet (10^3/mm^3), mean (SD)	50	252.5 (90.4)	104	331.4 (71.9)	<.0001[€]
APRI, mean (SD)	49	1.1 (0.8)	103	0.4 (0.2)	<.0001[€]
APRI > 1.0 (n, %)	49	20 (42%)	103	0 (0%)	<.0001[*]
APRI > 1.5	49	8 (17%)	103	0 (0%)	<.0001[*]
FIB-4, mean (SD)	48	0.4 (0.2)	99	0.2 (0.1)	<.0001[€]
GGTP (U/L), mean (SD)	46	65 (78)	97	14 (7)	<.0001[#]
median (IQR)		39 (25, 75)		12 (10, 15)	
Albumin (g/dL), mean (SD)	48	4.1 (0.5)	97	4.2 (0.4)	0.29[#]
ALT (U/L), mean (SD)	50	58 (44)	101	29 (12)	<.0001[€]
median (IQR)		41 (32, 71)		27 (20, 35)	
AST (U/L), mean (SD)	50	59 (38)	104	34 (11)	<.0001[€]
median (IQR)		49 (35, 58)		33 (28, 39)	
Total bilirubin (mg/dL), mean (SD) Median (IQR)	43	0.6 (0.5)	84	0.4 (0.3)	0.013[#]
		0.4 (0.3, 0.7)		0.4 (0.2, 0.5)	
WBC (10^3/mL), mean (SD)	50	7.8 (2.7)	105	9.2 (3.5)	0.0092[€]
FEV1% predicted, mean (SD)	51	92.1 (16.3)	89	92.9 (14.9)	0.78[€]
BMI z-score[†], mean (SD)	43	-0.37 (0.39)	77	-0.39 (0.39)	0.74[€]
Height z-score[†], mean (SD)	43	-0.28 (0.72)	77	-0.22 (0.73)	0.69[€]
Right triceps skinfold thickness z-score[‡], mean (SD)	38	-0.37 (0.73)	68	-0.34 (0.71)	0.85[€]
Subscapular skinfold thickness z-score[*], mean (SD)	34	-0.52 (0.43)	67	-0.51 (0.41)	0.93[€]
Right mid arm circumference z-score[*], mean (SD)	37	-0.49 (0.66)	63	-0.50 (0.71)	0.84[#]
Spleen Size (cm), mean (SD)	54	11.0 (2.2)	112	8.9 (1.5)	<.0001[#]
Spleen Size z-score, mean (SD)	54	1.5 (2.1)	112	0.02 (1.2)	<.0001[€]
VCTE LSM (kPa), n	38	8.2 (6, 11.8)	65	5.3 (4.2, 7.0)	<.0001[#]
median (IQR)					
VCTE CAP, n	25	228 (53)	36	230 (55)	0.91[€]
mean (SD)					
CF related diabetes at baseline, count (%)	49		105		<.0001[§]
Normal glucose tolerance		23 (46.9%)		97 (92.4%)	
Impaired glucose tolerance		13 (26.5%)		5 (4.8%)	
CFRD		3 (6.8%)		3 (2.9%)	

[¶] Median and quartiles were provided for variables with right-skewed distribution.
[†] BMI z-score was based on CDC 2011–2014 reference data.
[‡] Right triceps skinfold thickness z-score was based on CDC 2007–2010 reference data.
[§] Chi-squared test
[#] Wilcoxon test
[*] Fisher's exact test
[€] t-test

Table 2
Events among NOD and NL patients.

Event	NOD (*N* = 54)	NL (*N*=112)
Bleeding complications n (%)	2/54 (3.7%)	0/112 (0.0%)
Documented varices n (%)	6/54 (11.1%)	0/112 (0.0%)
Ascites n (%)	0 (0.0%)	0/112 (0.0%)
Encephalopathy n (%)	0 (0.0%)	0/112 (0.0%)
Liver transplant n (%)	2/54 (3.7%)	0/112 (0.0%)
Lung transplant n (%)	0/54 (0.0%)	0/112 (0.0%)
Death n (%) (note one death in NL group)	0 (0.0%)	1/112 (0.9%)

platelet counts, with more rapid progression of both over 5–10 years. This decline in platelet count among pediatric NOD participants is more rapid than the age associated decline in platelets in healthy children without liver disease [20]. Similarly, the increase in spleen size in NOD participants also outpaces previously document normal increases in spleen size with age. [21] APRI and FIB-4, biomarker indices of fibrosis, are also higher in NOD at baseline and increase at a higher rate. Even prior to any documented liver event, LSM by VCTE among NOD was elevated at 8.2 kPa, echoing the above surrogates of portal hypertension and liver fibrosis.

Interestingly, NOD is not associated with differences in nutritional status compared to NL as assessed by BMI z-score, height z-score, and right triceps skinfold thickness z-score. Perhaps this is because the NOD group was characterized sonographically and before any manifestations of hepatic dysfunction or portal hypertension occurred. FEV_1% predicted is similar in children with NOD vs NL, suggesting little impact of sonographic advanced liver disease on pulmonary function, in contrast to a recent study [17] but consistent with a large international study of 179 patients with severe CFLD and portal hypertension, that also reported no significant decline in CF-specific FEV1 percentiles [22]. This finding that anthropometrics and lung function are not negatively impacted by NOD further highlights the challenges of identifying which children with CF may have early aCFLD.

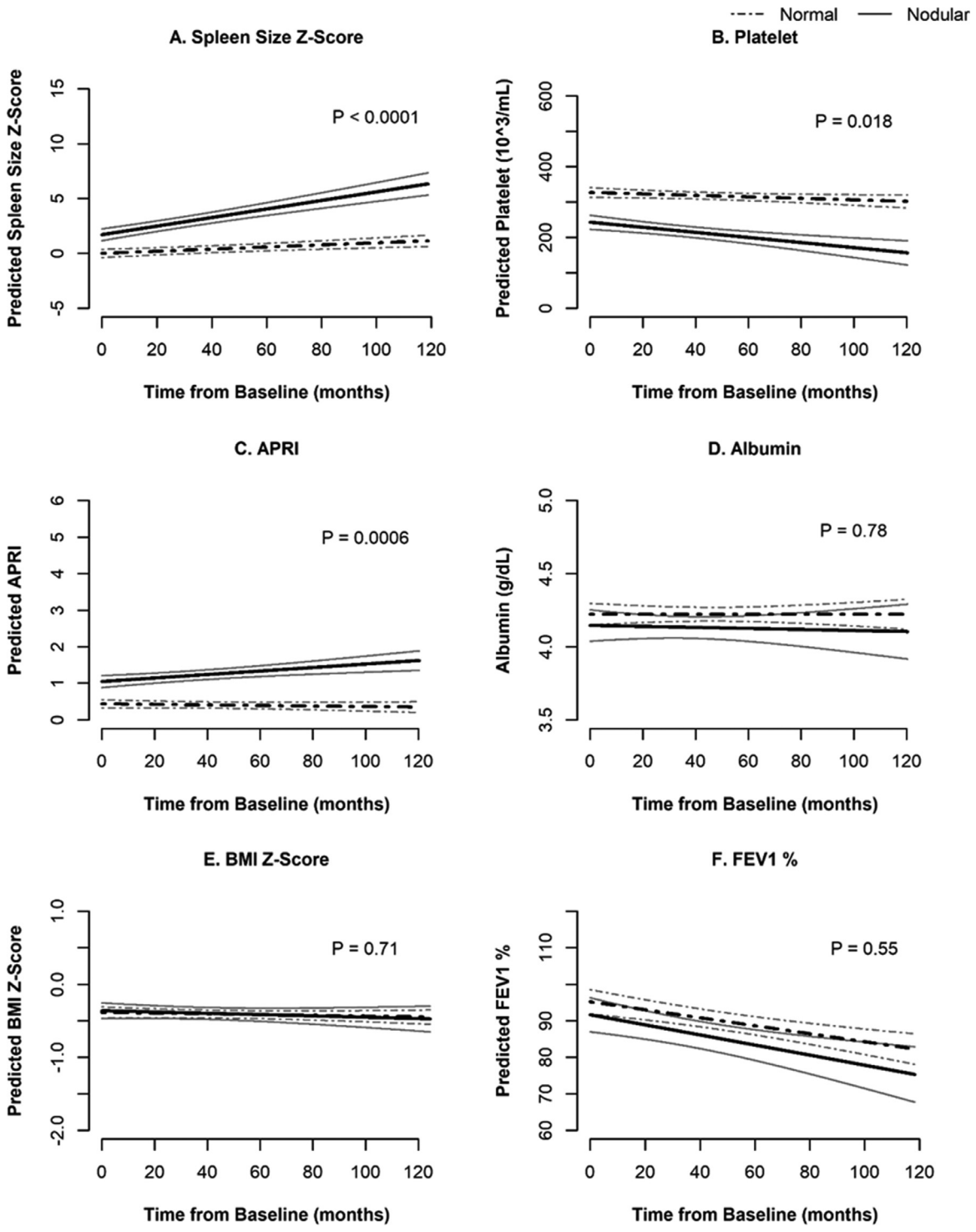

Fig. 2. Disease progression in NOD vs participants with normal US pattern. A, B, C, D, E, and F are estimated mean time trajectories of lab measurements, BMI z-score and predicted FEV1, and their 95% confidence intervals.

At initial identification of NOD, all participants were asymptomatic. Over up to 10 years of follow-up, a small number of participants with NOD developed liver-related events while none with NL experienced these. Varices were reported in over 11% of NOD followed for ≥5 years, and variceal bleeding occurred in 2 participants followed for at least 5 years; the 10-year cumulative incidence rate for detection of esophageal varices was 20% (and the rate is likely higher since routine surveillance endoscopy was not done). Hepatic encephalopathy or clinically significant ascites were not reported in NOD, consistent with preserved liver synthetic function. However, liver transplantation occurred in two participants; the indications for liver transplant were not part of the PUSH database, but PELD scores were low.

CFRD has been reported to occur in association with CF cirrhosis [10,23–25]. Liver disease, defined as portal hypertension, abnormal liver enzymes, or the use of a bile acid (ursodeoxycholic acid or taurine) was previously reported as a risk factor for the development of CFRD in population-based studies [8,25]. In another study,

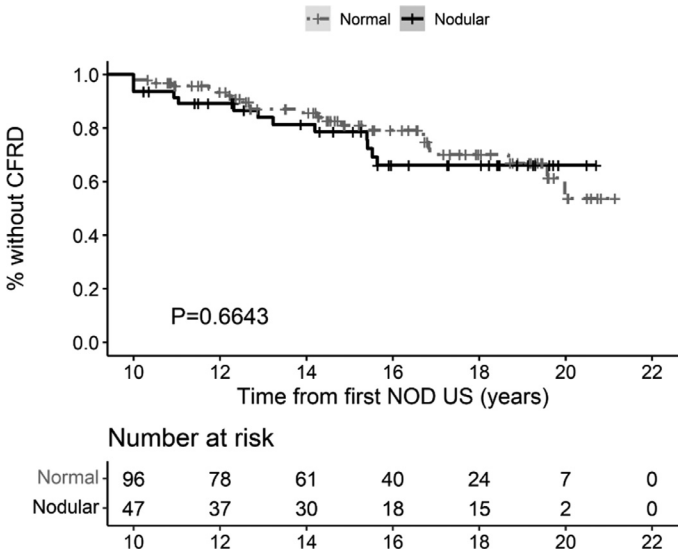

Fig. 3. Kaplan-Meier curves for comparing incidence of CFRD in normal and nodular US groups.

cirrhosis, but not elevation of liver biochemistries, was found to be more common in people with CF who had CFRD [24]. In one recent international study, CFRD was not identified as a clinical feature of severe CFLD with portal hypertension and in another, participants with severe CFLD showed a tendency toward impaired glucose homeostasis with larger studies like this one recommended [26,27]. Cirrhosis was not defined in any of these studies. In our study, which enrolled children prior to recognized liver disease, CFRD was no more common in NOD than NL, and liver disease did not progress more rapidly in children with NOD and CFRD, calling into question whether liver disease and CFRD are really intertwined. However, IGT was more common in NOD, without an increased rate of progression to CFRD; this may be related to insulin resistance in the context of hepatic fibrosis but merits further study.

There are some limitations of this study on the early sonographic diagnosis of CF liver disease. Liver biopsies were not performed in PUSH and thus NOD could not be confirmed as cirrhosis, nodular regenerative hyperplasia, or obliterative portal venopathy. The timeframe captured was early, beginning as early as 3 years of age. While we captured up to 10 years of follow-up in some participants, we recognize that the study period may not fully represent the disease progression more recently documented in adults [8]. There were also some important differences between the groups. NOD participants were older and some NOD were identified later in the study. The exact onset and duration of disease in those with NOD at baseline are unknown. While the NL participants were not matched to NOD for age or other parameters, they were prospectively enrolled during the same time period to serve as healthy CF controls for HTG participants. The number of participants analyzed for CFRD was small and derived from the clinical registry. Thus, it is possible that not all participants were screened for CFRD as recommended [28]. Importantly, because not all participants with evidence of portal hypertension underwent screening endoscopy as standard of care, we likely underestimated the true incidence of varices in NOD. This study was also performed prior to broad use of CFTR modulators.Clearly, the impact of CFTR modulators on liver involvement in CF deserves to be studied.

When the PUSH study began, gray scale US was the most feasible and available imaging modality and TE was in its infancy in pediatrics, [5,29–32]. Today, TE is becoming increasingly available among children's hospitals and is more quantitative, standardized and less subjective than ultrasound in assessing liver fibrosis and fat [13,33–36]. However, US is widely available worldwide, and in addition to detecting heterogeneity and nodularity, it provides important anatomical data about biliary disease, masses, and other manifestations of portal hypertension.

5. Conclusions

NOD is an early marker for advanced liver disease, characterized by preserved synthetic function, nutritional status, and pulmonary function that cannot be distinguished from NL. NOD is associated with increased liver stiffness, spleen size, APRI and FIB-4, as well as a more rapid decline in platelet count, suggesting emerging clinically evident portal hypertension [19]. NOD is not associated with an increased rate of CFRD. Importantly, within a decade of documented nodular US pattern, variceal bleeding and even liver transplantation exclusively occur in NOD but not NL.

Acknowledgements: the investigators thank the children with CF and their families for participating in the study, and the skilled research coordinators and research staff who contributed to the study so much.

Conflicts of Interest: Dr. Molleston received grants from AbbVie, Albireo, Gilead, Mirum/Shire and the Cystic Fibrosis Foundation. Dr. Karnsakul received grants from Albireo, Cystic Fibrosis Foundation, and Gilead. Dr. Freeman receives grant support from the Cystic Fibrosis Foundation, NIH and Travere Therapeutics as well as a consults for AbbVie and Takeda. Dr. Murray received grants from Albireo, Cleveland Clinic, and Gilead. Dr. Leung received grants from AbbVie, Cystic Fibrosis Foundation, Gilead, Merck, and Mirum. Dr. Narkewicz received grants from Cystic Fibrosis Foundation, Gilead, AbbVie and consults for Vertex. Dr. Narkewicz's spouse owns stock in Becton Dickson and Co, Cerner, Johnson & Johnson, Laboratory Corp of America, Merck, PepsiCo, Proctor and Gamble, Stryker, United Health, and Zoetis. Dr. Schwarzenberg received grants from Gilead and the Cystic Fibrosis Foundation, and consults for Abbvie and UpToDate.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.07.017.

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