

# New Algorithm for the Integration of Ultrasound Into Cystic Fibrosis Liver Disease Screening

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See “Integrating Clinical Ultrasound Into Screening for Cystic Fibrosis Liver Disease: Approach With Caution and Optimism” by Narkewicz on page 394.

## ABSTRACT

**Objectives:** Liver nodularity occurs across the spectrum of cystic fibrosis liver disease (CFLD), from regenerative nodules to cirrhosis, and can occur without liver enzyme abnormalities. Our aims were to determine if incorporating abdominal ultrasound (US) with annual laboratory testing improves the detection of CFLD and establish CF-specific thresholds for liver screening labs.

**Methods:** CF patients at least 6 years old who were exocrine pancreatic-insufficient had an US with Doppler and shear wave elastography. Patients were divided into Normal, Echogenic, or Nodular groups, based on US findings. Results were compared with aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets, AST to platelet ratio index (APRI), Fibrosis 4 (FIB-4), and gamma-glutamyl transferase (GGT) to platelet ratio (GPR). Receiver operator curve, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cut-off with Youden Index were calculated.

**Results:** From 82 patients, incorporation of US identified more nodular livers than using labs alone. The Nodular group had significantly greater median AST (44), ALT (48), GGT (46), APRI (0.619), FIB-4 (0.286), GPR (1.431). Optimal cut-offs to detect liver nodularity in CF were AST >33, ALT >45, GGT >21, Platelets <230, APRI >0.367, FIB-4 >0.222, GPR >0.682. Using GGT, APRI, and GPR, we generated an algorithm to direct the use of US in CFLD screening.

**Conclusions:** Using modified serum lab thresholds, addition of liver fibrosis indices, and/or abdominal US can increase detection of liver nodularity in CF. A combination of GGT, GPR, and APRI can help direct which CF children should undergo US evaluation. These tools may improve earlier identification of fibrosis and/or cirrhosis in CF patients.

**Key Words:** cystic fibrosis, liver disease, liver function tests, ultrasound

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## What Is Known

- Cystic fibrosis-related liver cirrhosis contributes to gastrointestinal complications of pediatric cystic fibrosis patients.
- Liver function tests have poor specificity for detection of liver disease in cystic fibrosis.
- Grayscale ultrasound is commonly used to assess the liver, however, how to effectively integrate it into a screening program remains unclear.

## What Is New

- We have established cystic fibrosis-specific thresholds for liver function tests that increase sensitivity and specificity for detection of liver nodularity in cystic fibrosis.
- We have demonstrated that improved liver disease screening program detection can be accomplished through the use of liver fibrosis indices.
- We developed an algorithm integrating liver function tests and fibrosis indices that guides when to perform an ultrasound.

Cystic fibrosis (CF)-related liver cirrhosis is the third leading cause of mortality in CF after pulmonary and transplant complications. Focal biliary fibrosis/cirrhosis may occur in up to 50% of CF patients (1,2), with multilobular cirrhosis in a smaller percentage of individuals (7%) (3). This process originates in childhood, with the highest incidence of cirrhosis during or before adolescence (4). Complications of cirrhosis and portal hypertension contribute to significant morbidity including, but not limited to, fat malabsorption, fat-soluble vitamin deficiency, gastrointestinal bleeding from varices, and splenomegaly with associated hematologic abnormalities.

The CF Foundation and European counterparts have recommended annual screening for liver involvement (4,5). CF Foundation guidelines recommend annual liver and spleen examination,

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and measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), and bilirubin (5). Lack of cystic fibrosis transmembrane conductance regulator (CFTR) expression in hepatocytes, coupled with transient elevations from infections, results in poor specificity of AST/ALT for CF liver disease (CFLD). GGT may be a more specific marker (6), but AST/ALT remain the most widely used tests for liver screening. Due to this poor specificity, the CF Foundation recommends further workup for thresholds of  $>1.5\times$  upper limit of normal (ULN) (5). Research has shown the capability of abdominal ultrasound (US) to improve the identification of liver involvement in CF, but little “real-world” data exists for the routine use of US in CF liver-screening programs.

To improve identification of liver fibrosis and cirrhosis in our pediatric CF patients before the onset of cirrhosis-associated complications, we performed a quality improvement initiative integrating abdominal grayscale US with Doppler with annual laboratory testing. We provide evidence for the “real-world” utility of integrating US examination into pediatric CF liver-screening protocols and CF-specific laboratory and liver fibrosis index thresholds for the determination of sonographic evaluation. These tools may improve the earlier detection of liver fibrosis or cirrhosis in CF, improve identification of cirrhosis-associated complications, and allow for the study of interventional therapies.

## MATERIALS AND METHODS

### Human Subjects

An abdominal grayscale US with Doppler and acoustic radiation force impulse (ARFI) shear wave elastography was added to annual laboratory testing for CF patients who were at least 6 years old and exocrine pancreatic-insufficient as a quality improvement initiative within the Stanford Children’s CF Center. Additionally, US evaluation was performed for any CF patients with physician concerns for liver involvement (e.g. elevations in liver enzymes, thrombocytopenia, abnormal physical exam). The Stanford Institutional Board Review determined that the retrospective review of laboratory and US reports did not meet criteria for human subject research. Data was examined in consecutive patients from November 2015 to October 2017. Some individuals underwent repeat US examination, based on physician discretion, however, only initial US exams were used for analysis to eliminate sampling bias.

### Data Acquisition

US exams were performed using a Siemens S3000 ultrasound machine. To determine the real-world utility of US, studies were performed by ultrasonographer technicians and read by pediatric radiologists at Lucile Packard Children’s Hospital at Stanford, according to standard clinical care. Results were categorized into 3 groups, based on their gray scale liver echotexture (Normal, Echogenic, or Nodular). “Normal” were homogenous appearing without increased echogenicity; “Echogenic” had increased parenchymal echotexture or periportal echogenicity (in a heterogeneous or homogeneous pattern); “Nodular” required parenchymal or capsular nodularity. All Nodular ultrasounds were reviewed by a senior pediatric radiologist with specific expertise in ultrasonography (RAB) to ensure accuracy for analysis. All other US were read by the pediatric radiologist on service (often with a resident/fellow). Acoustic radiation force impulse (ARFI) shear wave elastography (SWE) was performed through a right intercostal approach, taking measurements 2 to 4 cm deep in Segment VIII. Acquisitions were obtained in 3 modes: 6 mHz in VTQ (Virtual Touch Quantification), 9 mHz in VTQ, and 9 MHz in VTIQ (Virtual Touch Tissue Imaging

Quantification). At least 5 to 10 separate measurements were obtained with each mode. The median shear wave velocity for each of the 3 acquisition modes, and the average median across all 3 modes was calculated. Serum AST, ALT, GGT, and platelets were obtained per routine clinical care, and were retrospectively analyzed, using labs closest to the time of US. “CALPER” upper limits of normal (ULN) values for AST, ALT, and GGT by sex and age were used for analysis and are listed in Supplemental Digital Content Table 1 (Supplemental Digital Content, <http://links.lww.com/MPG/B666>) (7,8). Lower limit of normal for platelets was  $150 \times 10^3/\mu\text{L}$ .

### Statistics

Median  $\pm$  standard deviation (SD) were calculated. Box and whisker plots with median, upper and lower quartiles, highest and lowest observations, and outliers were generated with SigmaPlot 11. ROC, AUROC, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cut-off by Youden Index were calculated using easyROC (9). To calculate sensitivity and specificity in parallel or series, sensitivity and specificity values were inputted into EpiTools (10). Accuracy was determined using MedCalc. Significance was determined using unpaired Student *t*-test and designated at *P* values  $<0.05$ .

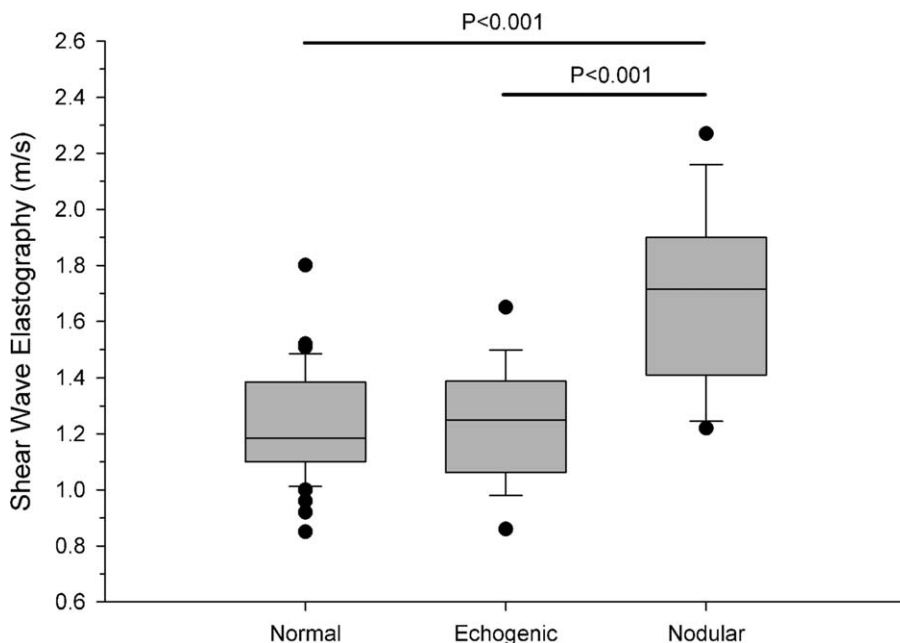
## RESULTS

### Study Cohort

A total of 85 consecutive patients with CF received an abdominal US with 82 patients eligible for analysis. Three CF patients were excluded; 2 for medication-induced elevation of liver enzymes (without evidence of liver fibrosis/cirrhosis) and 1 with heterozygosity for the alpha-1-antitrypsin SERPINA Z allele. The latter was excluded because of the unique contribution of SERPINA Z heterozygosity to hepatocellular damage distinct from CF patients without the SERPINA Z allele (11). Of the 82 patients, 88% (72/82) received an US for the purpose of liver screening (ie, no prior concerns for liver disease), whereas 12% (10/82) had concerns for liver involvement before US exam. Categorizing patients based on echotexture, 52% (43/82) were Normal, 29% (24/82) Echogenic, and 18% (15/82) were Nodular. Patients were 3 to 20 years old (median age  $12 \pm 5$  years old) and 52% were girls. The Nodular group had significantly higher shear wave elastography values than the Normal or Echogenic groups ( $1.72 \pm 0.30$  vs  $1.19 \pm 0.19$  or  $1.25 \pm 0.20$ , respectively,  $P < 0.0001$ ; Fig. 1), indicating increased liver stiffness in the Nodular group. Increased incidence of hepatosplenomegaly and decreased percentage predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) was observed in the Nodular group compared with the Normal or Echogenic groups (Table 1). A sub-analysis found no difference in reported metrics between the Nodular group on ursodiol versus no ursodiol (data not shown). As such, all analyses were performed regardless of ursodiol use.

### Labs from Nodular Group

The Nodular group had significantly elevated median  $\pm$  SD AST ( $44 \pm 22$  vs  $22 \pm 11$  or  $25 \pm 8$ ), ALT ( $48 \pm 46$  vs  $25 \pm 19$  or  $30 \pm 11$ ), GGT ( $46 \pm 46$  vs  $11 \pm 11$  or  $14 \pm 6$ ), and decreased platelets ( $214 \pm 94$  vs  $294 \pm 86$  or  $271 \pm 84$ ) compared with patients in the Normal or Echogenic group, respectively (Fig. 2). Normal and echogenic groups were statistically similar ( $P > 0.05$ ). Optimal laboratory cut-offs (optimal criterion) for AST, ALT, GGT, and platelets were 33 (0.524), 45 (0.496), 21 (0.697), and 230 (0.532) (Fig. 2). Of those within the Nodular group, 67% to 73% of subjects



**FIGURE 1.** Nodular livers have increased shear wave elastography. Box and whisker plots showing the median (line), upper and lower quartiles (box), highest and lowest observations (whiskers), and outliers (circles) were generated with SigmaPlot 11. Significance was determined by comparing Nodular group to Normal or Echogenic groups using Student *t* test.

had laboratory values above the CALIPER ULN. All ROC curves were significantly better than chance in detecting liver nodularity ( $P < 0.01$ ). GGT had the highest AUROC (0.87) to detect liver nodularity in CF children using a value of 21 (Fig. 2E and Supplemental Digital Content Table 2, Supplemental Digital Content, <http://links.lww.com/MPG/B666>). An AST  $>33$  was able to achieve an AUROC  $\geq 0.80$ , whereas an ALT  $>45$  and platelets  $<230$  gave AUROCs of 0.76 to 0.77. Sensitivity for the detection of nodular livers in CF could be improved to 96.5% or 95.6% if a GGT value of  $>21$  was combined with AST  $>33$  or platelets  $<230$  in parallel, respectively. Specificity was optimized at  $>95\%$  if GGT  $>21$  was performed in series with AST  $>33$  (96.5%), ALT  $>45$  (98.2%), or platelets  $<230$  (97.7%).

**TABLE 1.** Clinical and ultrasound characteristics of cystic fibrosis patients studied

	Normal	Echogenic	Nodular
Patients, n	43	24	15
Sex, F/M	23/20	13/11	7/8
Age, years	12 ± 5	15 ± 4	11 ± 4
BMI, %	50.6 ± 22.4	51.1 ± 26.6	47.8 ± 18.5
FEV1, % predicted	89 ± 20	91 ± 19	65 ± 17* <sup>+</sup>
On ursodiol, %	7	13	33
Hepatomegaly, %	12	17	27
Splenomegaly, %	7	17	47
Days between labs and US	30 ± 62	20 ± 27	18 ± 35

Data are expressed as median (± standard deviation [SD]). Hepatosplenomegaly was determined by ultrasound, according to age-specific ranges. BMI = body mass index; F = female; FEV1 = forced expiratory volume in 1 second; M = male; US = ultrasound.

\* $P < 0.05$  versus Normal.

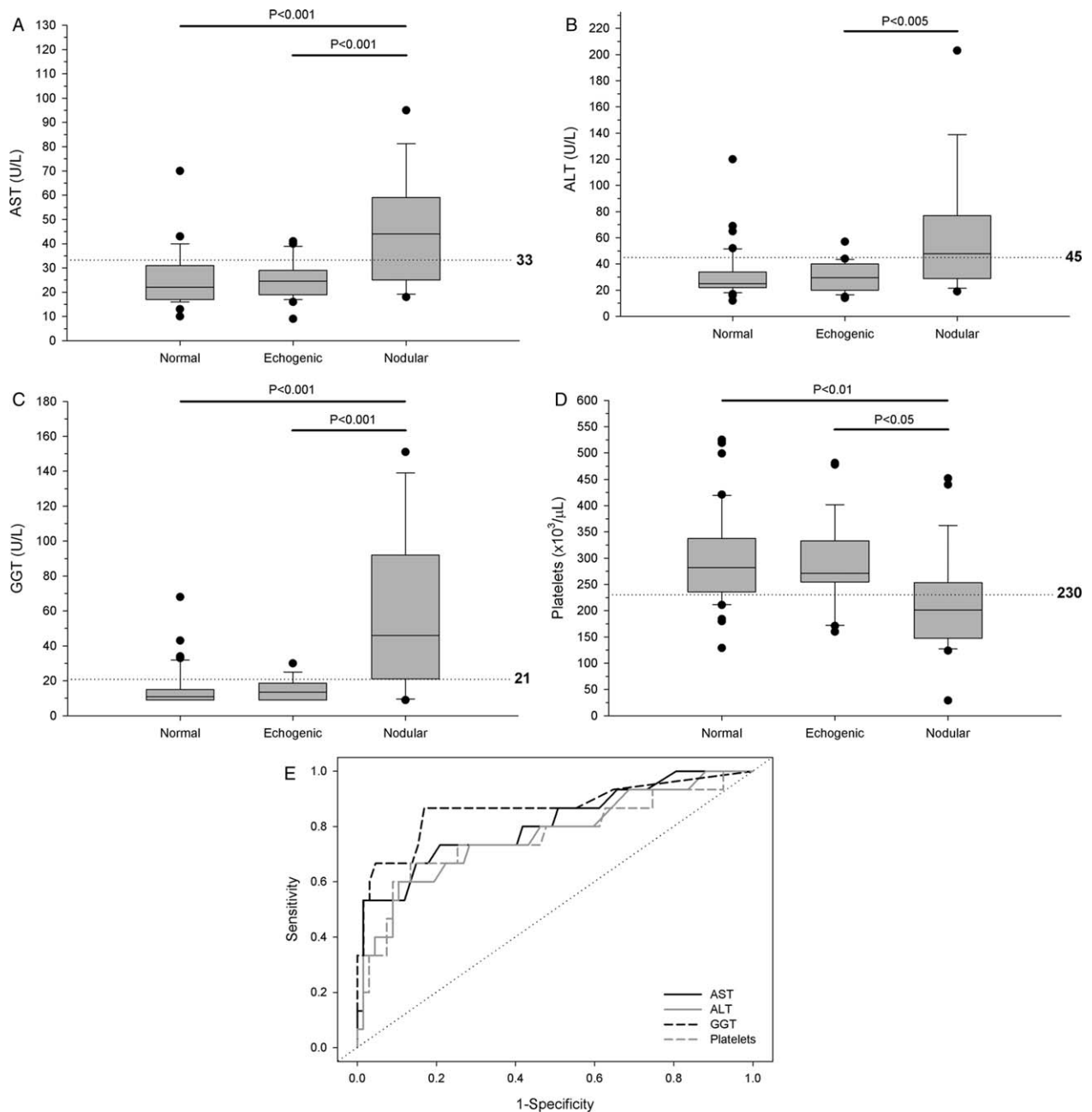
<sup>+</sup> $P < 0.05$  versus Echogenic.

### Utility of Routine Ultrasound

We next examined how many individuals with nodular livers would have been identified using laboratory tests alone. From within the Nodular group, 87% (13/15) had at least 1 lab value that was  $>1\times$  CALIPER ULN, most of which were  $>1.5\times$  CALIPER ULN (80%, 12/15). AST, ALT, and GGT had similar distributions of patients  $>1\times$  ULN, but GGT had the highest percentage of patients  $>1.5\times$ . With CALIPER normative values, addition of US would have identified an additional 13% to 20% of individuals with nodular livers (Supplemental Digital Content Figure 1, Supplemental Digital Content, <http://links.lww.com/MPG/B666>). Of note, our institutional ULN values were higher than CALIPER values (AST 40–60 U/L, ALT 60 U/L, GGT 60 U/L), and thus internal laboratory testing alone was less effective in identifying nodular livers ( $>1\times$ : 67%,  $>1.5\times$ : 33%). Of those with nodular livers, nearly half of patients (47%) were only identified because of addition of a screening US to their annual testing. As such, using CALIPER ULN values improved the identification of those with nodular livers, given their lower ULN value.

### Liver Fibrosis Indices

Liver fibrosis indices have been developed to aid in the noninvasive determination of liver fibrosis and cirrhosis. The Nodular group had significantly elevated median ± SD AST to platelet ratio index (APRI) ( $0.619 \pm 0.823$  vs  $0.248 \pm 0.111$  or  $0.242 \pm 0.126$ ,  $P < 0.001$ ) and GGT to platelet ratio (GPR) ( $1.431 \pm 1.302$  vs  $0.224 \pm 0.210$  or  $0.262 \pm 0.106$ ,  $P < 0.001$ ) compared to the Normal or Echogenic groups, respectively (Fig. 3). Nodular Fibrosis 4 (FIB-4) values were significantly different than the Normal, but not Echogenic groups ( $0.286 \pm 0.913$  vs  $0.159 \pm 0.097$ ,  $P < 0.05$  vs  $0.213 \pm 0.107$ ,  $P > 0.05$ ) (Fig. 3A–D). There was no statistical difference between the Normal or Echogenic groups ( $P > 0.05$ ). The ideal cut-off (optimal criterion) for APRI, FIB-4, and GPR were 0.367 (0.635), 0.222 (0.523), and 0.682 (0.769), respectively. APRI



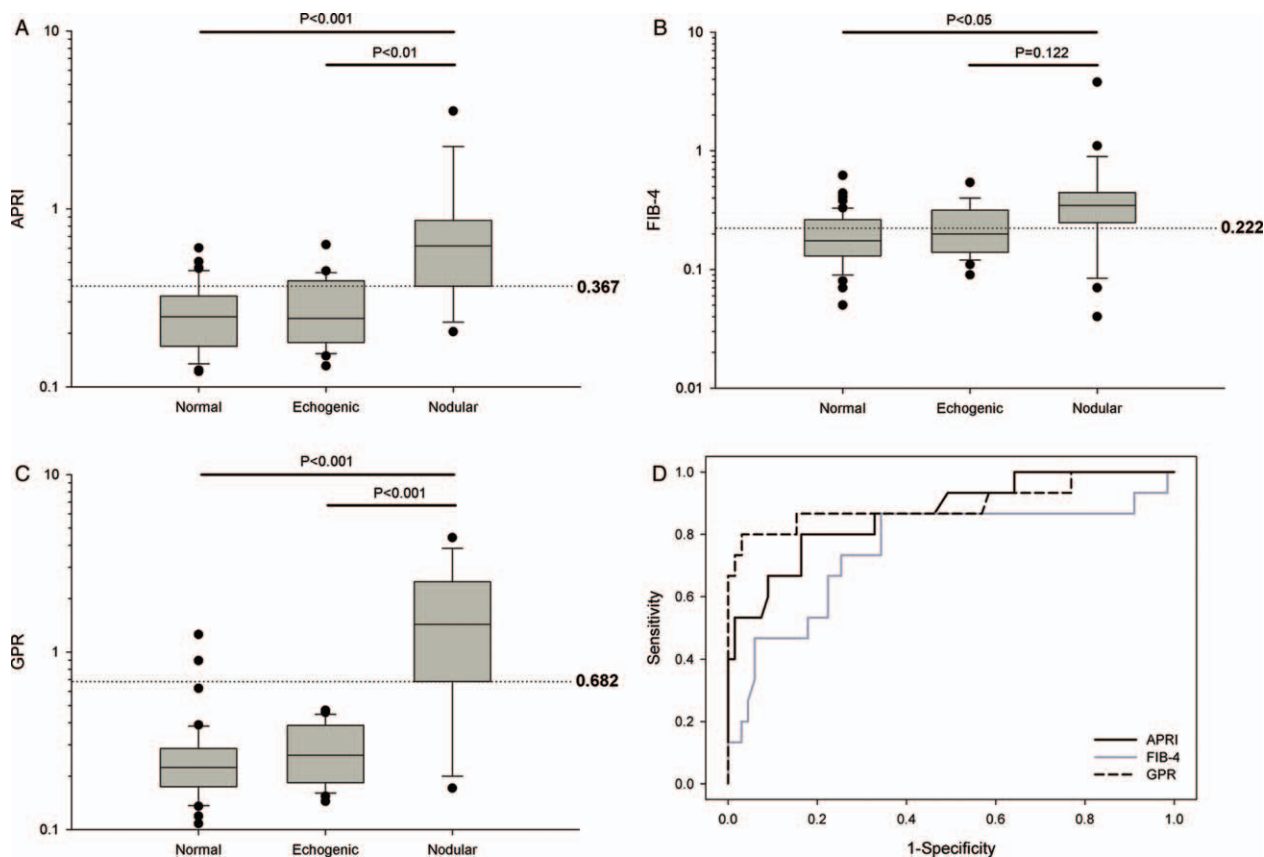
**FIGURE 2.** Elevated AST, ALT, GGT, and decreased platelets in Nodular livers. (A–D) Box and whisker plots showing the median (line), upper and lower quartiles (box), highest and lowest observations (whiskers), and outliers (circles) for AST, ALT, GGT, and platelets were generated with SigmaPlot 11. Significance was determined by comparing Nodular group to Normal or Echogenic groups using Student *t*-test. Dotted line represents optimal cut-off as determined by Youden Index (easyROC). (E) ROC curves generated by easyROC. AUROC values for AST, ALT, GGT, and platelets were 0.81, 0.77, 0.87, and 0.76, respectively.

and GPR exhibited a high AUROC at 0.87 to 0.90 (Fig. 3E and Supplemental Digital Content Table 3, Supplemental Digital Content, <http://links.lww.com/MPG/B666>). FIB-4 >0.222 had the best sensitivity at 86.7%, but GPR had the highest specificity at 96.9%. However, a FIB-4 >0.222, together with GGT >21 in parallel gave a theoretical sensitivity of 98.2%, while using GGT >21 and APRI >0.367 or GPR >682 in series gave a theoretical specificity of approximately 97.2% or 99.5%, respectively.

### Algorithm for Ultrasound Determination

On the basis of these results, we investigated potential algorithms to guide when to do an abdominal US in CF children with exocrine pancreatic insufficiency, using liver nodularity as the outcome variable. Given GGT's high negative predictive value, GGT was the best initial screening test. With their high specificity, using a combination of APRI and GPR as second tier tests maximized identification

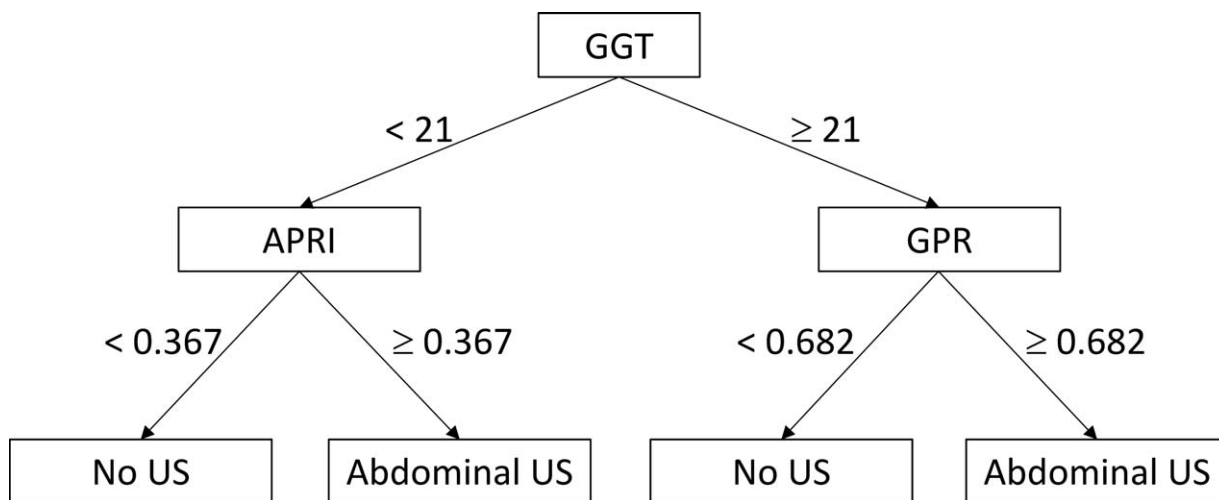




**FIGURE 3.** Liver fibrosis indices in cystic fibrosis Nodular livers. (A–C) Box and whisker plots showing the median (line), upper and lower quartiles (box), highest and lowest observations (whiskers), and outliers (circles) for APRI, FIB-4, and GPR were generated with SigmaPlot 11. Significance was determined by comparing Nodular group to Normal or Echogenic groups using Student *t* test. Dotted line represents optimal cut-off as determined by Youden Index (easyROC). (D) ROC curves generated by easyROC. AUROC values for APRI, FIB-4, and GPR were 0.87, 0.75, and 0.90, respectively.

of true positives and negatives while minimizing false positives and negatives. Retrospectively applying the algorithm in Figure 4 to our patient cohort accurately identified 85% of nodular livers with high sensitivity (93.0%) and negative predictive value (98.2%) (specificity:

83.1%, positive predictive value: 56%). A simpler, more specific version only using GGT and GPR (GGT <21 → no US) was more specific (96.9%), but had decreased sensitivity (80.0%). Given US is noninvasive and relatively inexpensive, we propose that the algorithm



**FIGURE 4.** Proposed screening algorithm to determine when to perform an abdominal ultrasound for liver nodularity in cystic fibrosis patients. The above algorithm represents the best combination of standard liver screening labs and liver fibrosis indices in maximizing the sensitivity, specificity, and accuracy for subsequent identification of liver nodularity by US. GGT values are listed as U/L. US = ultrasound.

in Figure 4 may help determine when to pursue abdominal US for investigation of liver fibrosis/cirrhosis in CF.

## DISCUSSION

Liver cirrhosis is a well-recognized complication of CF. It accounts for the most significant proportion of morbidity and mortality associated with liver involvement in CF. However, there is a wide spectrum of liver pathology in CF, including steatosis (12,13), fibrosis (14), and focal (1,2) or multilobular cirrhosis (3). With 90% of end-stage liver disease occurring in childhood (4), liver cirrhosis is considered a pediatric complication of CF. However, advances in imaging technology now suggest that a large, previously underappreciated, number of adult CF patients may have liver fibrosis (14).

The primary aim of the present study was to determine if addition of abdominal US to a pediatric screening program would improve detection of liver fibrosis and/or cirrhosis in CF. We found that whenever using our internal ULN values, US identified an additional 33% to 67% of nodular livers compared with biochemical markers alone. However, there is increasingly strong evidence that ULN values for liver transaminases used by our center and others may be inappropriately high for children. In fact, when we used validated pediatric-specific normative values, US identified fewer *de novo* cases. It is unclear if our nearly 20% miss rate with newer normative values would continue to be observed with a larger, multicenter study. US is recommended in the CF Foundation and European guidelines if hepatosplenomegaly is identified on examination or there are persistently abnormal liver labs (5,15). Numerous studies over the last 30 years have examined US to detect CF liver pathologies, including the current PUSH (Prediction by Ultrasound of the Risk of Hepatic Cirrhosis in Cystic Fibrosis) study. In the PUSH study, 719 CF children (ages 3–12 years) without known liver cirrhosis underwent abdominal grayscale US with Doppler. From this cohort, 18% of subjects had an US abnormality, with 3.3% having unsuspected cirrhosis (12), similar to a retrospective study in 1- to 18-year-olds (16). In our study, 9.7% (7/72) of those screened without prior clinical concern for liver involvement had liver nodularity on abdominal US. We hypothesize that the lower percentage of nodular patients in the PUSH study is because of their inclusion of a larger number of children ages 3 to 6 years, compared with our own. In the PUSH study, only a small number of patients 3 to 6 years old had evidence of cirrhosis. As such, they predominantly contributed to the denominator in calculating the percentage of patients with cirrhosis (12). We anticipate that we would find an incidence closer to the PUSH study if we performed more ultrasounds on 3 to 6-year-old patients. It remains to be seen if US should be a routine component of liver screening, and if so, what age and interval is recommended. It is unlikely to be cost-effective to perform annual abdominal US on all individuals with CF. Our data presents potential modified biochemical thresholds, that, when coupled with fibrosis indices, could provide adequate sensitivity and specificity for screening, thereby increasing the pretest probability for a positive abdominal US.

The secondary aim of our study was to identify serum biochemical thresholds to improve detection of liver nodularity. The CF Foundation Guidelines recommend annual measurement of AST, ALT, alkaline phosphatase, GGT, and bilirubin for liver screening (5). We did not examine bilirubin in our study, given it is rarely elevated before liver failure in CF. In examining AST, ALT, and GGT, we found that liver nodularity was often present at “sub-normal” values, when using institutional ULN thresholds. However, there is growing recognition that these “normal” values are not appropriate for children (7), and commonly used thresholds are inadequate to detect liver disease in children (17,18). Recently, several US and international studies examining children with

normal body mass indexes (BMIs), no illness, without any hepatotoxic medications have determined age and sex-based percentiles for AST, ALT, and GGT (8,17,19). The effectiveness of laboratory screening to identify liver nodularity in CF improved greatly when we used these lower normative values. As such, we encourage the use of these newer normative liver function test values in CFLD screening programs.

In our study, GGT performed better than AST or ALT in identifying liver nodularity. In CF-related liver cirrhosis, focal biliary cirrhosis may occur before the onset of multilobular cirrhosis. With CFTR expressed in the biliary epithelium, not the hepatocytes, the earliest marker of liver fibrosis is likely to arise from the bile ducts. In a retrospective study of CF patients, Bodewes et al (6) found that a GGT >21 U/L had an AUROC of 0.91 for the development of cirrhosis within 2 years. We found that 21 U/L was the ideal cut-off to differentiate between nodular and non-nodular livers, with an AUROC of 0.87. This was superior to both AST and ALT (0.81 and 0.77, respectively). We also examined platelet counts as an indicator of liver nodularity but found that, alone, it performed the worst. Thrombocytopenia occurs with portal hypertension and, thus, is most often present with advanced cirrhosis. It should be noted, however, that because of chronic systemic inflammation in CF, many CF patients exhibit a relative thrombocytosis; consequently portal hypertension may be present even with “normal” platelet values.

Liver fibrosis indices, such as APRI, FIB-4, and GPR have been investigated as noninvasive markers of chronic liver disease in hepatitis B and C and nonalcoholic fatty liver disease (20–23). Leung et al determined APRI and FIB-4 values for biopsy-associated degrees of liver fibrosis and cirrhosis. They found that an APRI of 0.264 (using AST ULN value of 40 U/L) differentiated between CFLD and CF without liver disease with a sensitivity of 73.1% and specificity of 70.2% (AUROC = 0.75) (24). We found an ideal APRI cut-off of 0.367 to identify nodular livers (AUROC = 0.87–0.90). Given the performance of GGT to detect nodular livers, it is not surprising that GPR also performed well. GPR has most recently been investigated as a fibrosis prediction tool in chronic hepatitis B infection and has been shown to outperform APRI (20). To our knowledge, ours is the first study to examine GPR in CF. Further investigation is necessary to determine the broad utility of GPR. Given our findings, however, we recommend that CF Centers consider using GPR in their CFLD screening programs.

From our analysis, we were able to establish an algorithm utilizing GGT, GPR, and APRI to risk-stratify CF patients for possible liver fibrosis/cirrhosis, helping to determine which patients should undergo US evaluation. Although this algorithm performed with high sensitivity and negative predictive value with our CF Center patients, it is unclear if this algorithm will perform similarly well at other pediatric CF Centers. Likewise, increased numbers of patients are needed to ensure there is not overfitting of the multivariable model. A multi-center study is necessary to determine if this approach will be an effective strategy in utilizing abdominal US to improve the identification of liver disease in CF patients.

## Limitations

Our study has several limitations that must be considered when considering broad application of our findings. First, our data originates from a single pediatric center, resulting in potential geographical bias. Our CF population is made up of diverse ethnic and genetic (CFTR and non-CFTR) backgrounds and may differ from other CF Centers. Given our data only included those up to 20 years old, it is unclear how relevant our data is for adult CFLD screening. We also did not perform screening US in those <6 years old, so we cannot comment on its utility as a screening tool in that

age group. Additionally, our US findings came from a clinical radiology read (most commonly a radiology resident and attending) and from multiple different radiologists. This is in contrast to other research studies where a US is read by a single radiologist or multiple radiologists providing consensus based on strict research criteria. Although this may provide variability in US findings, this strategy provides an analysis using a “real-world” strategy. As such, we feel it provides a useful framework for other CF Centers implementing a clinical liver disease-screening program. Finally, we used sonographic evidence of nodularity, not liver biopsies, as an endpoint for disease. Liver nodularity can represent disorders other than fibrosis/cirrhosis, such as masses, cystic lesions, and hemangiomas, none of which our patients had, or regenerative nodules from portal venopathy rather than fibrosis/cirrhosis. Our elastography data suggests those within our Nodular group have fibrosis and/or cirrhosis, however, we did not perform liver biopsies to validate these findings.

## CONCLUSIONS

Our study supports the real-world use of grayscale US in routine pediatric CFLD screening programs. Through correlations with biochemical markers and fibrosis indices, we have provided a screening algorithm that may more effectively use grayscale US to identify those at risk. Ongoing and future studies integrating US and MR elastography into this algorithm may further improve the identification of early liver fibrosis in CF and also risk stratify individuals who may go on to develop cirrhosis. These strategies may also help ascertain the effectiveness of new CFTR modulators in preventing CF-associated liver fibrosis and/or cirrhosis.

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