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ORIGINAL ARTICLE

Hepatology

The effect of elexacaftor–tezacaftor–ivacaftor on liver stiffness in children with cystic fibrosis

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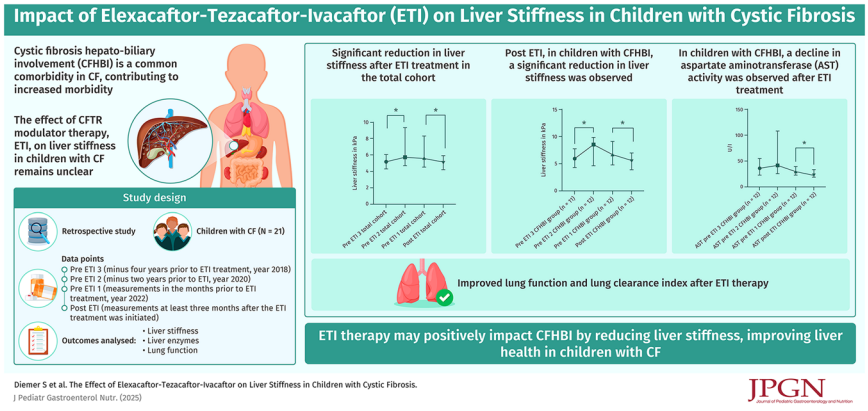
Abstract

Objectives: Cystic fibrosis hepato-biliary involvement (CFHBI) is a common comorbidity in patients with CF and is associated with increased morbidity and mortality. The effect of the new and highly potent CF transmembrane conductance regulator modulator therapy, elexacaftor–tezacaftor–ivacaftor (ETI), on CFHBI, is still unclear. This study aimed to investigate the impact of ETI on liver stiffness in children with CF, as measured using two-dimensional (2D) shear wave elastography (SWE).

Methods: Twenty-one children with CF were included in this retrospective study at the CF centre, Skåne University Hospital, Lund, Sweden. Twelve children of our cohort had CFHBI; none had advanced CF liver disease. 2D SWE data from annual assessments, clinical data and liver enzymes were analysed.

Results: We found a significant reduction in liver stiffness after starting treatment with ETI in the total cohort. This reduction in liver stiffness could even be seen in children with CFHBI. Liver enzymes were within the normal range in both pre- and post-ETI therapy in the total cohort. In children with CFHBI, a decline in aspartate aminotransferase activity was observed after ETI was initiated. Lung function and lung clearance index improved significantly after ETI treatment commenced.

Conclusion: ETI treatment could positively affect CFHBI in children with CF, as demonstrated by reduced liver stiffness during treatment.



KEYWORDS
CFTR modulator, cystic fibrosis hepato-biliary involvement, cystic fibrosis liver disease, elastography

1 | INTRODUCTION

Cystic fibrosis (CF) is the most common inherited disease in the white population and is mainly known as a life-threatening lung disease. CF is caused by biallelic pathogenic variants in the CF transmembrane conductance regulator (CFTR) gene encoding the CFTR ion channel.[1] This channel is located at the apical membrane of epithelial cells in many different exocrine glands—mainly the respiratory system, the digestive system, the proximal tubules of the kidney and the salivary glands, leading to widespread symptoms whence deficient. While a vicious cycle of mucus obstruction and chronic infections/inflammation leads to CF lung disease, early dysfunction of the biliary ducts can lead to CF hepato-biliary involvement (CFHBI).[2]

CFHBI develops sequentially from biliary obstruction to periportal fibrosis, focal biliary cirrhosis and finally to advanced CF liver disease (aCFLD).[3,4] CFHBI can presented by a broad spectrum of findings like hepatomegaly, steatosis, elevated liver enzymes, focal biliary cirrhosis or abnormalities in abdominal ultrasound and even already in the neonates as cholestasis.[5] aCFLD is characterised by having one or more of the following findings: nodular liver, advanced fibrosis (F4), multilobular cirrhosis with or without portal hypertension, or noncirrhotic portal hypertension.[6] This recent nomenclature, CFHBI and aCFLD, published in 2024, aims to simplify the classification of the broad spectrum of liver disease in CF.[7]

According to the CF Foundation, CFHBI and aCFLD were the cause of death in 4.5% of the people with CF (pwCF) who succumbed in the United States in 2023. They are associated with minimal function variant genotypes, a history of meconium ileus, CF-related diabetes, malnutrition, and male sex.[8-10] CFHBI plays an important role in both children and adults, with an increasing incidence during childhood.[5,9,11] Therefore, early childhood screening is important, and in the new consensus recommendation of annual screening starting at the year of CF diagnosis is suggested, including physical examination and liver lab tests; abdominal ultrasound should be performed every second year from the age of 3.[6]

Recently, shear wave elastography (SWE) has been described as a noninvasive and rapid method for assessing CFHBI.[12] It measures liver stiffness, which is closely related to liver fibrosis and is a validated instrument for staging fibrosis in other patient groups with chronic liver disease.[13] SWE has proved to be an effective assessment tool for regular follow-ups and early-stage CFHBI diagnosis in adults and children.[14-16]

What is Known

- Cystic fibrosis hepato-biliary involvement (CFHBI) is a common and severe comorbidity in people with CF (pwCF).
- CFHBI should be screened for already in early childhood.
- The effect of the highly potent CF transmembrane conductance regulator modulator therapy, elexacaftor–tezacaftor–ivacaftor (ETI), on CFHBI, is unclear.

What is New

- In this retrospective study of children with CF, a significant decrease in liver stiffness after the initiation of ETI treatment was observed.
- Even in children with CFHBI, a decline in liver stiffness after ETI initiation was seen.
- In a sub-analysis, a transient increase in liver stiffness in children with CF who started lumacaftor/ivacaftor treatment in 2018/2019 was found.

In the era of CFTR modulator therapy, improved lung function, decreased sweat chloride, improved nutritional status and reduced morbidity and mortality have been reported.[17] However, one of the most common side effects of CFTR modulators is the elevation of liver enzymes. The effect of CFTR modulator therapy on liver stiffness and CFHBI remains unclear.[18-20] In Sweden, CFTR modulator therapy with lumacaftor–ivacaftor was approved in late 2018. The triple modulator elexacaftor–tezacaftor–ivacaftor (ETI) treatment was approved in November 2022.

This study aimed to examine the effects of ETI on liver stiffness measured using two-dimensional (2D) SWE.

2 | METHODS

2.1 | Study population

This study was performed retrospectively at the paediatric CF centre at Skåne University Hospital. Children with CF (CwCF) with a typical clinical presentation of CF and biallelic disease-causing variants in the *CFTR* gene, who started ETI treatment during 2022/2023 and had been subjected to screening for CFHBI using 2D

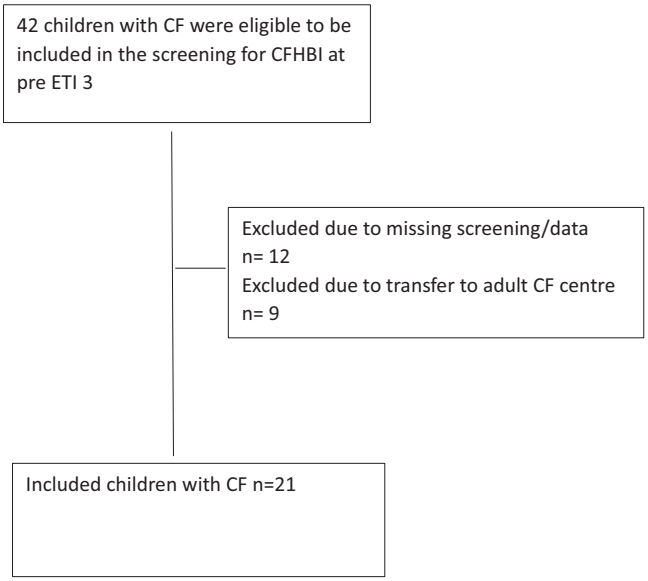


FIGURE 1 Flowchart patient inclusion. CF, cystic fibrosis; CFHBI, cystic fibrosis hepato-biliary involvement; ETI, elexacaftor–tezacaftor–ivacaftor.

SWE at least every 24 months since 2018 were included in our study. Exclusion criteria were missing screening examinations and organ transplantation (Figure 1).

Four 2D SWE measurements were included in our study; measurement points were defined as pre-ETI 3 (minus 4 years before ETI treatment, year 2018), pre-ETI 2 (minus 2 years before ETI, year 2020), pre-ETI 1 (measurements in the months before ETI treatment, year 2022) and post-ETI (measurements at least 3 months after the ETI treatment was initiated, year 2023). The pre-ETI 1 and post-ETI 2D SWE measurements were performed within 24 months (median 17 months), and the participants had been on ETI treatment for at least 3 months when the post-ETI measurement was performed (median 10 months).

Trained radiologists performed all 2D SWE measurements at the medical imaging department at Skåne University Hospital, Lund, Sweden.

2.2 | Data collection

Clinical data were collected from the annual review results registered in the Swedish CF registry and from the participants' medical records (ultrasound, 2D SWE and liver biopsy data). Data from the examination day of the annual review included demographic data, *CFTR* gene variants, standard deviation (SD) of body mass index, bacterial colonisation and lung function test results.

Clinical data regarding the subgroup analysis with CwCF on lumacaftor–ivacaftor were taken at the time point pre-ETI 3, pre-ETI 2 and pre-ETI 1.

Clinical data regarding the subgroup CFHBI were taken at time points pre-ETI 1 and post-ETI. The recently published definition of CFHBI was used to define the patients with CFHBI.[7]

Leeds criteria were used to define chronic colonisation with *Pseudomonas aeruginosa*.[21]

Lung function tests were performed at the time of the annual review. Forced expiratory volume in 1 s per cent of predicted (FEV1pp) was measured using the Global Lung Function Initiative equation.[22]

The lung clearance index (LCI) was calculated using multiple breath washouts with Exhalyzer®D (Ecomedics, version 3.3.1) with three consecutive measurements in nitrogen washout mode, representing inhomogeneous ventilation.[23]

Annual laboratory screening for CFHBI comprises alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT). Normal range was defined according to Skåne University Hospital, Lund, Sweden, laboratory reference values ALT (female 8.92–44.91 U/L, male 8.92–65.87 U/L), AST (female 2–18 years 13.17–35.93 U/L, male 2–18 years 15.57–40.72 U/L), GGT (female 6 months to 40 years 8.98–44.91 U/L and male 6 months to 40 years 8.98–65.87 U/L).[24] Liver ultrasound with measurements of liver stiffness by using 2D SWE (Canon/Toshiba Aplio i70) was also performed as part of the annual CFHBI screening. The liver enzymes were measured at the pre-ETI time points at the annual review; the SWE was usually performed at the half-year checkup due to many other clinical examinations at the annual review. At the post-ETI time point, the liver enzyme tests were taken in nine children on the same day as the liver stiffness measurements with 2D SWE; in 12 patients, the samples were taken 2.5 months (median) from the 2D SWE. The children were on ETI at least 3 months before the post-ETI blood samples were drawn.

2.3 | Statistical analysis

Statistical analyses were performed using the GraphPad Prism 10.0.2 software (GraphPad Software). Descriptive statistics and the Wilcoxon matched-pairs signed rank test were used for pre-ETI and post-ETI analyses and are presented as non-parametric median and interquartile range (IQR) values. The level of significance was set at ≤0.05.

3 | RESULTS

3.1 | Cohort characteristics

Twenty-one children and adolescents were eligible for inclusion in the study (Figure 1). Patient characteristics pre-ETI 1 and post-ETI are shown in Table 1.

TABLE 1 Patient characteristics at pre-ETI 1 and post-ETI.

Demographic and clinical data	Pre-ETI 1 total cohort ($n = 21$)	Pre-ETI 1 lumacaftor–ivacaftor ($n = 12$)	Pre-ETI 1 CFHBI ($n = 12$)	Post-ETI total cohort ($n = 21$)
Age in years median (IQR)	14 (13–16)	14.5 (12.5–16)	14 (12.3–15.8)	16 (14–18)
BMI SD (kg/m^2) median (IQR)	0.2 (–0.6 to 0.6)	0.4 (–0.6 to 1.2)	0.3 (–1.2 to 0.5)	0.3 (–0.8 to 1.1)
FEV1pp median (IQR)	85.6 (73.8–97.9)	89.7 (68.8–106)	85.4 (72.9–98)	94.9 (85.1–105.1)
Lung clearance index median (IQR)	7.4 (6.7–9.2)	7.3 (6.4–9.1)	7.4 (6.8–9.1)	6.6 (6.4–7.0)
Chronic colonisation of *Pseudomonas aeruginosa*, *n* (%)	3 (14%)	0 (0%)	1 (8%)	0 (0%)
Pancreatic insufficiency, *n* (%)	21 (100%)	12 (100%)	12 (100%)	21 (100%)
Treatment with ursodeoxycholic acid, *n* (%)	7 (33%)	4 (33%)	7 (58%)	6 (29%)
Treatment with lumacaftor–ivacaftor, *n* (%)	12 (57%)	12 (100%)	7 (58%)	0 (0%)

Abbreviation: BMI, body mass index; ETI, elexacaftor–tezacaftor–ivacaftor; FEV1pp, forced expiratory volume in 1 s per cent of predicted; IQR, interquartile range; SD, standard deviation.

The study group consisted of 11 females (52%); 14 (66%) were homozygous for the F508del variant, and all had pancreatic insufficiency. At pre-ETI 1, 12 patients (57%) were classified as having CFHBI either by signs of CFHBI in the abdominal ultrasound, persisting elevation of liver enzymes, elevated liver stiffness or signs of CFHBI in liver biopsy. None of the patients fulfilled the criteria of aCFLD. Seven children (33%) had ongoing treatment with ursodeoxycholic acid (Table 1) with a median treatment duration of 5.5 years (IQR: 3.9–14.6 years). Ursodeoxycholic acid treatment was initiated in case of persistently abnormal liver function tests and pathological ultrasonography. In two cases, the treatment was started due to neonatal cholestasis.

Treatment with lumacaftor–ivacaftor was approved in late 2018. At the time point pre-ETI 1, 12 patients (57%) were on lumacaftor–ivacaftor treatment.

As described previously,[17] ETI resulted in a clear improvement in lung function of the total cohort, demonstrated by a significant increase in FEV1pp and a significant reduction in LCI (Table 1).

In pre-ETI 3, only 20 CwCF participated in the SWE screening; therefore, we analysed only the data from 20 CwCF in the longitudinal analysis during pre-ETI 3, pre-ETI 2 and pre-ETI 1.

3.2 | Liver enzymes and ETI

We found a significant reduction in AST with a median of 25.8 IUL (22.2–34.2) pre-ETI 1 compared to AST of 21.6 IU/L (18–28.2) post-ETI ($W = -158$, $n = 21$, $p = 0.0019$) (Figure 2A). However, we found a slight increase in GGT levels after the treatment with ETI (Figure 2C). Pre-ETI 1 GGT median value was 13.8 IU/L (10.8–18), and post-ETI GGT median value was 15 IU/L (13.2–21.6) ($W = 114$, $n = 21$, $p = 0.0317$) (Figure 2C). However, AST and GGT levels were within the normal range pre-ETI 1 and post-ETI.[24]

CwCF with CFHBI showed a significantly elevated AST with a median of 29.64 U/L compared to CwCF without CFHBI, with a median of 23.95 U/L at the time point pre-ETI 1 ($p = 0.0239$). The former group significantly improved in AST post-ETI with a reduction to 21.86 U/L ($W = -54$, $n = 12$, $p = 0.033$) (Figure 2D). There were no significant changes in CwCF with CFHBI in ALT or GGT levels pre-ETI 1 and post-ETI, nor were there significant differences in ALT or GGT levels between CwCF with CFHBI and CwCF without CFHBI at pre-ETI 1 (Figure 2D–F).

3.3 | The effect of ETI on liver stiffness

Comparison of liver stiffness measured by 2D SWE pre-ETI 1 (median: 5.6; IQR: 4.6–8.3) and post-ETI (median: 5.1; IQR: 4.2–5.9) showed that there was a significant reduction in liver stiffness post-ETI in the total cohort ($W = -125$, $n = 21$, $p = 0.0283$) (Figure 3A).

When investigating the long-term development of liver stiffness, we observed a significant increase in liver stiffness between pre-ETI 3 (year 2018) (median: 5.2 kPa; IQR: 4.3–6.1) and pre-ETI 2 (year 2020) (median: 5.6 kPa; IQR: 4.7–8.9) ($W = 139$, $n = 20$, $p = 0.0038$) but there was no significant difference between liver stiffness pre-ETI 3 and pre-ETI 1 or pre-ETI 2 and pre-ETI 1 (Figure 3A).

CwCF with CFHBI presented with an elevated liver stiffness at pre-ETI 1 of 6.8 kPa median (IQR: 4.9–9.2) compared to CwCF without CFHBI 4.9 kPa median (IQR: 3.9–6.3), but this was not a significant difference ($p = 0.0566$). Analysing liver stiffness in CwCF with CFHBI showed a decline to 5.7 kPa median (IQR: 3.9–7.1) during

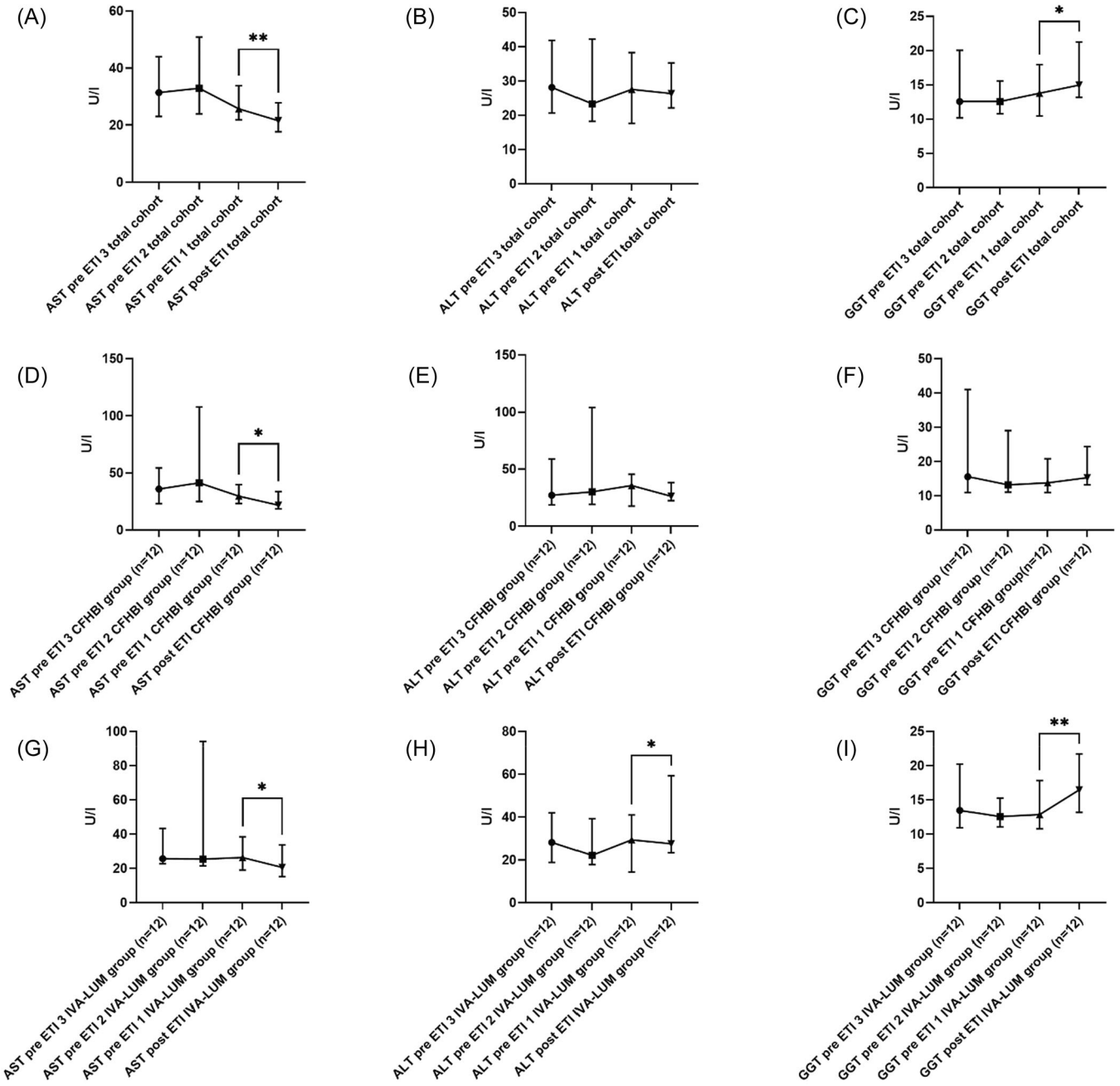


FIGURE 2 Liver enzymes (A–C) Liver enzymes AST, ALT and GGT over time in the total cohort. (D–F) Liver enzymes in patients with CFHBI. (G–I) Liver enzymes in the ivacaftor–lumacaftor treated group. $*p < 0.05$, $**p < 0.01$. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFHBI, cystic fibrosis hepato-biliary involvement; ETI, elexacaftor–tezacaftor–ivacaftor; GGT, γ-glutamyl transferase.

ETI treatment, and this decline was statistically significant ($W = -60$, $n = 12$, $p = 0.0161$) (Figure 3B). In CwCF without CFHBI, liver stiffness only showed a minor decrease from 4.9 kPa median (IQR: 3.9–6.3) pre-ETI 1 to 4.6 kPa median (IQR: 4.3–5.5) post-ETI.

3.4 | The effect of lumacaftor–ivacaftor

At the time point pre-ETI 1, 12 CwCF (57%) were already treated with the CFTR modulator lumacaftor–ivacaftor since late 2018. In a sub-analysis, we wanted to investigate if the treatment with this CFTR modulator influenced liver stiffness, as we observed with the triple CFTR modulator ETI. Liver stiffness before treatment starts with lumacaftor–ivacaftor pre-ETI 3 (measurements during 2018) was 6 kPa median (IQR: 4.4–7.8) and increased during lumacaftor–ivacaftor treatment to pre-ETI 2 (measurements during 2020) 8 kPa median (IQR: 5.1–9.7) in this group ($W = 70$, $n = 12$, $p = 0.0034$) (Figure 3C). However, we could not observe other significant changes in liver stiffness between the other time points (Figure 3C).

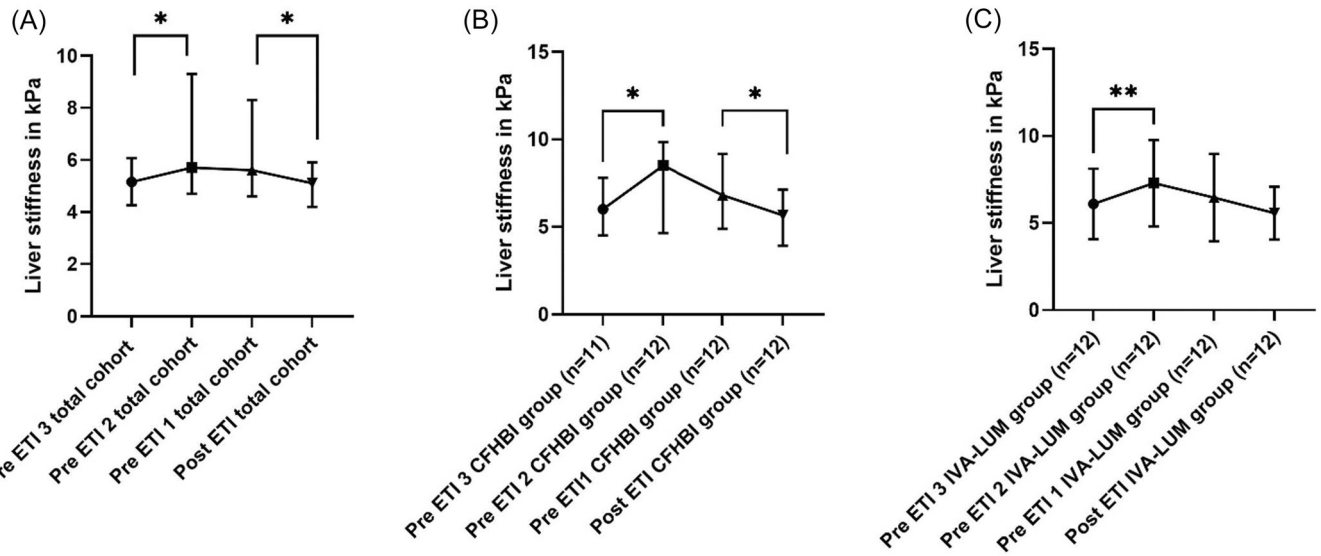


FIGURE 3 Liver stiffness measured by 2D Shear wave elastography. (A) Liver stiffness over time in the total cohort. (B) Liver stiffness over time in patients with CFHBI. (C) Liver stiffness over time in the ivacaftor–lumacaftor-treated group. *$p < 0.05$, **$p < 0.01$. 2D, two-dimensional; CFHBI, cystic fibrosis hepato-biliary involvement; ETI, elexacaftor–tezacaftor–ivacaftor.

Liver enzymes in the subgroup that started ivacaftor–lumacaftor between pre-ETI 3 and post-ETI are shown in Figure 3G–I. There were no significant changes in liver enzymes pre- or post-ivacaftor–lumacaftor treatment (pre-ETI 3 to pre-ETI 2). In this subgroup, we could still see a significant reduction in AST pre-ETI 1 compared to AST post-ETI ($W = -51$, $n = 12$, $p = 0.0444$) as well as a significant reduction in ALT ($W = 52$, $n = 12$, $p = 0.0405$) pre-ETI 1 compared to post-ETI (Figure 2G,H). GGT was significantly increased ($W = 74$, $n = 12$, $p = 0.002$) pre-ETI 1 compared to post-ETI (Figure 2I).

Treatment with lumacaftor–ivacaftor did not show the same beneficial effect on liver stiffness as did ETI treatment.

4 | DISCUSSION

Screening for CFHBI is important because it is a common and serious complication of CF associated with increased morbidity and mortality.[9] In the newly updated screening, evaluation and management guidelines of CFHBI, the measurement of liver stiffness is one of the investigations included for monitoring.[7]

Liver stiffness is measured by elastography, and 2D SWE is an easy and non-invasive screening tool for CFHBI. 2D SWE has been proposed as a follow-up tool for ETI treatment.[25] The lack of standardised reference values for 2D SWE in pwCF complicates the use of single elastography measurements, and this method is probably more valuable for assessments over time.[7,26] In our cohort, we found an overall significant reduction of liver stiffness after at least 3 months of ETI treatment. This reduction of liver stiffness was clearly seen in our 12 CwCF with CFHBI during ETI treatment. CwCF without CFHBI had only small changes in liver stiffness during ETI, but importantly did not lead to an increase in liver stiffness, as was observed during lumacaftor–ivacaftor treatment. This observation that CwCF with CFHBI could improve liver stiffness after ETI treatment is an important beneficial factor. More studies are needed in adult and paediatric CF patients with CFHBI and aCFLD.

In the years before ETI treatment, we found a significant increase in liver stiffness between 2018 and 2020 in the entire cohort. After introducing lumacaftor–ivacaftor treatment in Sweden in 2018, the subgroup of CwCF with lumacaftor–ivacaftor treatment was studied further, and we found that liver stiffness was mostly increased in this group between pre-ETI 3 and pre-ETI 2. A significant increase in liver stiffness after 6 months of lumacaftor–ivacaftor in 31 CwCF aged 6–11 years has been previously reported.[27] Interestingly, we did not find further changes in liver stiffness between the measurement points in pre-ETI 2 and pre-ETI 1 nor between pre-ETI 3 and pre-ETI 1; therefore, this increase between pre- and post-lumacaftor–ivacaftor may be a transient negative effect of lumacaftor–ivacaftor. When analysing liver enzymes in this subgroup, we could not find a negative impact of lumacaftor–ivacaftor on liver function.

Our findings of a clear improvement of liver stiffness in CwCF and CFHBI during ETI treatment is in line with the recently published study by Terlizzi et al.[28] Few studies have focused on the effects of ETI on liver stiffness and CFHBI. Calvo et al. prospectively investigated liver stiffness and liver enzyme development in a single-centre cohort with a starting point before ETI and a follow-up at 1, 3 and 6 months on ETI. Fifty-five individuals with a mean age of 17.7 years (SD 4.9)

were included. A significant overall reduction in mean liver stiffness was found at 6 months, and already after 1 month of ETI, a decline in liver stiffness was observed in those with values ≥5 kPa.[29] Another study in adults showed a significant reduction in liver stiffness during ETI treatment in 14 participants with an elevated liver stiffness >6.8 kPa before ETI, but no change was found in liver enzymes or noninvasive fibrosis indices.[20] Controversially, Schnell et al. reported increased liver stiffness in a prospective study of 20 pwCF (10 aged < 20 and 10 aged >20) after 6 months of ETI.[18] These studies consisted of small cohorts, and more research in larger cohorts is needed.

Liver enzymes have been reported to lack sensitivity and specificity for CFHBI. However, elevated GGT levels have been associated with CFHBI and are suggested as a good marker, together with liver stiffness measurements.[14,30] Elevation of transaminases and bilirubin levels has also been reported as a side effect of ETI.[31] In our study, we found an increase in GGT levels during ETI treatment, but a decrease in AST levels. Interestingly, even in CwCF with CFHBI, we could see a decreased AST level after ETI treatment.

Taking together these findings, we could not see a clear association between the effect of ETI on liver stiffness and liver enzymes. Liver stiffness is probably more a long-term parameter of chronic inflammation, whereas liver enzymes reflect more temporary changes in liver inflammation or obstruction.

ETI is a life-changing treatment for pwCF, and several studies have shown clear improvements in lung function and quality of life.[17] In our single-centre paediatric cohort, we confirmed that lung function and ventilation in the peripheral airways improved significantly with an increase in FEV1pp and a reduction in LCI.

The strength of our study is the paediatric study cohort in the age group where CFLD usually develops. All participants were of school age, showed pancreatic insufficiency, and there was an equal distribution regarding sex. Another strength of the study is that we have already used 2D SWE for some years, the investigators are well-trained in this method, and we have measured points for more than 5 years. The main weakness of our study is its retrospective design and small cohort, mainly due to missing investigations and transitions to the adult CF unit where the 2D SWE surveillance was discontinued. Larger longitudinal studies are needed to define reference values for liver stiffness and the natural course of liver stiffness development in pwCF.

5 | CONCLUSION

This study shows a positive effect on liver stiffness and improvements in lung function in school-aged CwCF after at least 3 months of ETI treatment. Further longitudinal studies on CFHBI during ETI treatment are needed to investigate its long-term effects.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

This study was approved by the local Medical Ethics Committee of Lund (reference number 2018/54). Written informed consent was obtained from all participants aged >15 years or from the guardians of participants aged <15 years.

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REFERENCES

1. Riordan JR, Rommens JM, Kerem BS, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science*. 1989;245(4922):1066-1073. doi:10.1126/science.2475911
2. Oppenheimer EH, Esterly JR. Hepatic changes in young infants with cystic fibrosis: possible relation to focal biliary cirrhosis. *J Pediatr*. 1975;86(5):683-689. doi:10.1016/s0022-3476(75)80351-9
3. Debray D, Narkewicz MR, Bodewes FAJA, et al. Cystic fibrosis-related liver disease. *J Pediatr Gastroenterol Nutr*. 2017;65(4):443-448. doi:10.1097/MPG.0000000000001676
4. Colombo C, Battezzati PM. Liver involvement in cystic fibrosis: primary organ damage or innocent bystander? *J Hepatol*. 2004;41(6):1041-1044. doi:10.1016/j.jhep.2004.10.002
5. Leung DH, Narkewicz MR. Cystic fibrosis-related cirrhosis. *J Cyst Fibros*. 2017;16:S50-S61. doi:10.1016/j.jcf.2017.07.002
6. Sellers ZM, Assis DN, Paranjape SM, et al. Cystic fibrosis screening, evaluation and management of hepatobiliary disease consensus recommendations. *Hepatology*. 2023;79:1220-1238. doi:10.1097/hep.0000000000000646
7. Bodewes FAJA, Freeman AJ, Weymann A, et al. Towards a standardized classification of the hepatobiliary manifestations in cystic fibrosis (CFHBI): a joint ESPGHAN/NASPGHAN position paper. *J Pediatr Gastroenterol Nutr*. 2024;78(1):153-165. doi:10.1097/mpg.0000000000003944
8. Colombo C, Russo MC, Zazzeron L, Romano G. Liver disease in cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2006;43(S1):S49-S55. doi:10.1097/01.mpg.0000226390.02355.52
9. Boëlle PY, Debray D, Guillot L, Clement A, Corvol H. Cystic fibrosis liver disease: outcomes and risk factors in a large cohort of French patients. *Hepatology*. 2019;69(4):1648-1656. doi:10.1002/hep.30148

10. Faro A. *Cystic Fibrosis Foundation Patient Registry 2023 Annual Data Report*. Cystic Fibrosis Foundation; 2024.
11. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. *J Cyst Fibros*. 2011;10: S29-S36. doi:10.1016/S1569-1993(11)60006-4
12. H E, Cr H, S D, Ea E. 2D shear wave elastography, a promising screening tool for cystic fibrosis liver disease, shows a correlation between vitamin D and liver stiffness. *J Cyst Fibros*. 2022;21(5):873-877. doi:10.1016/j.jcf.2022.06.009
13. De Lédinghen V, Le Bail B, Rebouissoux L, et al. Liver stiffness measurement In children using FibroScan: feasibility study and comparison with fibrotest, aspartate transaminase to platelets ratio index, and liver biopsy. *J Pediatr Gastroenterol Nutr*. 2007;45(4):443-450. doi:10.1097/mpg.0b013e31812e56ff
14. Højte C, Jørgensen MH, Jensen F, Katzenstein TL, Skov M. Extended screening for cystic fibrosis-related liver disease including elastographyin children and adolescents. *J Pediatr Gastroenterol Nutr*. 2020;71(5):663-668. doi:10.1097/MPG.0000000000002872
15. Levitte S, Lee LW, Isaacson J, et al. Clinical use of shear-wave elastography for detecting liver fibrosis in children and adolescents with cystic fibrosis. *Pediatr Radiol*. 2021;51(8): 1369-1377. doi:10.1007/s00247-021-05015-w
16. Klotter V, Gunchick C, Siemers E, et al. Assessment of pathologic increase in liver stiffness enables earlier diagnosis of CFLD: results from a prospective longitudinal cohort study. *PLoS One*. 2017;12(6):e0178784. doi:10.1371/journal.pone.0178784
17. Kapouni N, Moustaki M, Douros K, Loukou I. Efficacy and safety of elexacaftor-tezacaftor-ivacaftor in the treatment of cystic fibrosis: a systematic review. *Children*. 2023;10(3):554. doi:10.3390/children10030554
18. Schnell A, Jüngert J, Klett D, et al. Increase of liver stiffness and altered bile acid metabolism after triple CFTR modulator initiation in children and young adults with cystic fibrosis. *Liver Int*. 2023;43(4):878-887. doi:10.1111/liv.15544
19. Levitte S, Fuchs Y, Wise R, Sellers ZM. Effects of CFTR modulators on serum biomarkers of liver fibrosis in children with cystic fibrosis. *Hepatol Commun*. 2023;7(2):e0010. doi:10.1097/hc9.0000000000000010
20. Tewkesbury DH, Scott J, Barry PJ, et al. Effects of elexacaftor/tezacaftor/ivacaftor on liver fibrosis markers in adults with cystic fibrosis. *J Cyst Fibros*. 2024;23(2):349-353. doi:10.1016/j.jcf.2023.09.006
21. Lee TWR, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis patients. *J Cyst Fibros*. 2003;2(1):29-34. doi:10.1016/s1569-1993(02)00141-8
22. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343. doi:10.1183/09031936.00080312
23. Robinson PD, Goldman MD, Gustafsson PM. Inert gas washout: theoretical background and clinical utility In respiratory disease. *Respiration*. 2009;78(3):339-355. doi:10.1159/000225373
24. Skåne Labmedicin. www.analysportalen-labmedicin.skane.se
25. Dana J, Debray D, Beaufrère A, et al. Cystic fibrosis-related liver disease: clinical presentations, diagnostic and monitoring approaches in the era of CFTR modulator therapies. *J Hepatol*. 2022;76(2):420-434. doi:10.1016/j.jhep.2021.09.042
26. Calvopina DA, Noble C, Weis A, et al. Supersonic shear-wave elastography and APRI for the detection and staging of liver disease in pediatric cystic fibrosis. *J Cyst Fibros*. 2020;19(3): 449-454. doi:10.1016/j.jcf.2019.06.017
27. Kanavaki A, Kanavaki I, Zoumpoulis PS, Moustaki M, Douros K, Loukou I. Changes in shear wave elastography after lumacaftor/ivacaftor treatment in children with cystic fibrosis. *Curr Drug Saf*. 2023;18(1):93-96. doi:10.2174/1574886317666220513105114
28. Terlizzi V, Fevola C, Cecchetti M, et al. Effect of elexacaftor-tezacaftor-ivacaftor on liver transient elastography, fibrosis indices and blood tests in children with cystic fibrosis. *J Cyst Fibros*. Forthcoming 2025. doi:10.1016/j.jcf.2024.12.010
29. Calvo PL, Giugliano L, Evangelista A, Bignamini E, Pinon M. Effects of CFTR modulator therapies on liver stiffness and bile flow: a single-centre experience. *J Hepatol*. 2023;79(2): e76-e78. doi:10.1016/j.jhep.2023.02.006
30. Bodewes FAJA, van der Doef HPJ, Houwen RHJ, Verkade HJ. Increase of serum γ-Glutamyltransferase associated with development of cirrhotic cystic fibrosis liver disease. *J Pediatr Gastroenterol Nutr*. 2015;61(1):113-118. doi:10.1097/MPG.0000000000000758
31. Eldredge JA, Oliver MR, Ooi CY. Cystic fibrosis liver disease in the new era of cystic fibrosis transmembrane conductance regulator (CFTR) modulators. *Paediatr Respir Rev*. 2024;50: 54-61. doi:10.1016/j.prrv.2023.12.005

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