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Original Article

Alterations of bile acid composition in children with cystic fibrosis compared to healthy controls

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ABSTRACT

Background: Approximately 20 percent of people with cystic fibrosis (CF) develop cystic fibrosis hepatobiliary involvement (CFHBI). Some show the more severe form advanced cystic fibrosis liver disease (aCFLD). The biliary tree is an important site for cystic fibrosis transmenbrane conductance regulator (CFTR) activity. Despite previous studies the impact of CFTR dysfunction on bile acid homeostasis, the composition of the different bile acids and its impact on hepatobiliary function remains unclear.
Methods: Between November 2020 and July 2022 serum samples from children with CF were collected. Bile acids were analysed by liquid chromatography coupled to tandem mass spectrometry. Serum samples from otherwise healthy patients hospitalised for elective procedures served as controls.
Results: 73 children with CF, and 100 control patients were enrolled. Eight children of the CF cohort were diagnosed with aCFLD. In children with CF ($n = 73$), overall bile acid concentration as well as primary and secondary bile acids were significantly elevated, whereas the ratio of taurine conjugated bile acids was decreased. These alterations were not observed in infants and became more pronounced with age. Furthermore, children with aCFLD ($n = 8$, 11 %) showed significantly increased concentrations of secondary bile acids as well as lithocholic, glycolithocholic, deoxycholic and glycodeoxycholic acid.
Conclusions: Our data show that bile acid composition is altered in children with CF. This difference is evident from preschool age onward. Moreover, different bile acid compositions are detected in children with and without aCFLD. These changes appear to aggravate with age, which could indicate an age-dependent increase in hepatobiliary impairment.

1. Introduction

Cystic fibrosis (CF) is the most common monogenetic disorder in the Caucasian population [1]. Although the last decades have seen remarkable improvements, the disease still limits survival and quality of life [2]. Following improvements in pulmonary status, extra pulmonary complications become more apparent.

Cystic fibrosis hepatobiliary involvement (CFHBI) develops in the first two decades of life, usually in childhood before puberty [3]. Approximately 20 percent [1,4] of people with CF (pwCF) develop hepatobiliary involvement. The progression is often slow and patients are asymptomatic. However, some forms of CFHBI known as advanced cystic fibrosis liver disease (aCFLD) develop faster and show a broad spectrum of hepatic alterations, including hepatobiliary involvement (e.g. focal biliary cirrhosis), obliterative portal venopathy and steatosis [5,6]. CFHBI, and especially aCFLD, is a significant contributor to the mortality and morbidity, and it is the third leading cause of death in cystic fibrosis [1,4]. To differentiate CFHBI from aCFLD, parameters such as liver stiffness, liver size and elevated liver enzymes are being used [5].

As the cystic fibrosis transmembrane conductance regulator (CFTR) gene is highly expressed in the apical membrane of cholangiocytes in intra- and extrahepatic epithelia and in the gallbladder, the biliary tree is an important site for CFTR activity [3,7–9]. Previous studies reported

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several mechanisms by which the dysfunction of CFTR contributes to hepatobiliary damage. The "bicarbonate umbrella" hypothesis emphasizes the importance of CFTR function in preserving a healthy bicarbonate balance [10,11]. Fiorotto et al. described an increased vulnerability to bacterial endotoxins due to a loss of CFTR function in a mouse model [12]. This may result in heightened sensitivity to inflammation from intestinal bacterial products [3,12,13]. However, the pathophysiology of CFHBI is not yet fully understood [1].

Bile acids go through different stages in their synthesis, from which arises a differentiation in primary and secondary bile acids. Furthermore, a conjugation with either taurine or glycine can occur. Bile acids take an essential part in the digestive process of fatty acids. As the biliary tree is mainly impacted, the composition of different bile acids in the bile and the blood via the enterohepatic circulation may differ. Some authors have described an increased loss of bile acids in the faeces in pwCF [14–16]. A study in adults with cystic fibrosis revealed an increase in serum bile acids in comparison to healthy controls [17]. On the other hand, Strandvik et al. reported normal biliary lipid metabolism in a small cohort of well-nourished and well-controlled adult pwCF compared to controls [18]. Furthermore, a study conducted in CF mice showed defects in gallbladder emptying, which disrupted enterohepatic circulation and led to a decrease in secondary toxic bile acids that entered the liver [19]. However, the bile acid composition (BAC) in paediatric pwCF with end stage liver disease was found to differ from that observed in other paediatric patients with end stage liver disease due to different underlying causes [20]. Therefore, the impact of CFTR function on bile acid homeostasis, and its impact on hepatobiliary impairment, remains ambiguous. The objective of our study was to investigate the serum bile acid composition in children diagnosed with CF compared to a control group and their potential correlation to aCFLD.

2. Methods

2.1. Study design and ethical approval

Prior to performing the study, ethical approval was obtained from the institutional review board (Ethics Committee of the University of Regensburg, #18-969-101). All patients or/and their legal guardians gave informed consent before enrolment. The study was performed in accordance with the declaration of Helsinki. CF was diagnosed according to published guidelines [21]. Patients were recruited between November 2020 and July 2022.

2.2. CF group

Eighty paediatric pwCF (49 male, 30 female, 1 gender diverse) between the ages of 0 and 17 years (median age: 7.00 years) were enrolled in the study, and samples were collected during routine outpatient visits from 73 of them (43 male, 29 female, 1 gender diverse; median age: 7.50 years). Detailed clinical data of the CF study population, e.g. genotype, underlying aCFLD in relation to the pwCF enrolled in the German CF registry is provided in **Supplement Table 1**.

2.3. Control group

Serum samples from 100 patients (59 male, 41 female) between the age of 0 to 17 years (median age: 7.00 years) served as a control group. The serum samples were obtained as surplus of routine blood samples collected during hospital stay for minor illnesses or small interventions. Patients with diseases that potentially interfere with bile acid homeostasis (e.g. gastroenteritis, known hepatic impairment or inflammatory bowel diseases) were excluded from the analysis.

2.4. Assessment of hepatobiliary involvement

The presence and severity of hepatobiliary involvement were determined by established clinical (Potter Score: hepatomegaly, splenomegaly, GPT, gamma-GT) and ultrasound (Williams Score: hepatic parenchyma, liver edge, periportal fibrosis) scoring systems (**Supplement Table 2**) [22,23].

An aCFLD was defined according to recently published recommendations [5]. The symptoms present in our study cohort are presented in Table 1.

2.5. Bile acid analysis

The blood samples were immediately centrifuged, and the serum was stored at −80 degrees Celsius until the bile acids were measured. Serum bile acids were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) as described previously by Scherer et al. [24] and Krautbauer et al. [25]. Except for hyodeoxycholic acid (HDCA) species, quantification was based on matching stable isotope labelled internal standards for all reported bile acids. Bile acids are presented as median and upper and lower quartile in μmol/l.

Bile acid profiles are presented as individual bile acids, either in their primary or secondary form or as conjugates (taurine- and glycine-conjugates). Furthermore, we formed sums of the individual bile acids (primary and secondary, unconjugated and conjugated, taurine- or glycine-conjugated bile acids) in order to distinguish at which point in the bile acid synthesis the differences occurred and in which way the physiological conjugation with the metabolites glycine and taurine is affected. In addition, ursodeoxycholic acid (UDCA) as well as UDCA-conjugates, taurine-conjugated ursodeoxycholic acid (TUDCA) and glycine-conjugated ursodeoxycholic acid (GUDCA), were subtracted from the total amounts since many pwCF were substituted with UDCA and this would have confounded the results. As result, we present the "corrected" sums for total bile acids (total BA), primary bile acids (primary BA), secondary bile acids (secondary BA), conjugated bile acids (conjugated BA), unconjugated bile acids (unconjugated BA), taurine-conjugated bile acids (taurine BA) and glycine-conjugated bile acids (glycine BA).

The bile acids included in each sum are described in **Supplement Table 3**.

To further compare the BAC, ratios were formed between the corrected sums of taurine-conjugated/total BA, glycine-conjugated/total BA, taurine-conjugated/glycine-conjugated BA, taurine-conjugated/unconjugated BA, unconjugated/conjugated BA and primary/secondary BA.

Following the classification by the German CF registry, patients in both groups (CF and control group) were classified according to their age in the groups "infant" (0 to 1 year old), "preschool child" (1–5 years old), "school child" (6–11 years old) and "adolescent" (12–17 years old) [26].

2.6. Statistical analysis

Data processing was conducted using the web-based QNOME-system (www.qnome.de), which is a database system developed for the University Children's Hospital Regensburg (KUNO), to collect and store data by the highest standard (SQL). Data output for analysis was in anonymized form by an encryption algorithm. Changes in the database are tracked with a timestamp and can be assigned to the individual user. Thus, data security according to guideline 2005/28/EG of the

Table 1
Symptoms of included pwCF with aCFLD.

Symptoms	Number of included pwCF
Nodular liver	8
Advanced fibrosis	2
Multilobular fibrosis with/without portal hypertension	0
Noncirrhotic portal hypertension	0

commission (08.04.2005) is ensured.

Statistical analysis was performed by using IBM® SPSS Statistics Software version 31.0. Mann-Whitney-U-Test was performed to test for significant differences.

To further evaluate the relevance of the difference between the CF and the control group, we performed an AUROC analysis.

3. Results

3.1. Differences between CF and control group

In comparison to the control group ($n = 100$), the CF group ($n = 73$) showed significantly higher serum levels of total BA (Fig. 1) ($p < 0.001$), primary BA ($p < 0.001$), secondary BA ($p = 0.003$), unconjugated BA ($p < 0.001$) and conjugated BA ($p = 0.008$) as well as glycine conjugated BA ($p < 0.001$).

Taurine conjugated BA serum levels were significantly ($p < 0.001$) lower in CF compared to the control group. In contrast, glycine conjugated BA levels were significantly higher in CF compared to the control group ($p < 0.001$). (Fig. 2a and b)

In the CF group, the ratio of unconjugated BA compared to conjugated BA was significantly higher than in the control-group ($p = 0.002$).

The ratios of taurine BA/ total BA ($p < 0.001$), taurine BA/unconjugated BA ($p < 0.001$) and taurine BA/glycine BA ($p < 0.001$) were significantly lower in the CF group. The levels of each bile acid are shown in Table 2.

The additional performed AUROC analysis showed AUC-Scores between 0500 and 0771. The taurine-conjugated bile acids (AUC 0658, $p =$ 0000) showed a significant discrimination of pwCF compared to the control group, so did the unconjugated bile acids (AUC 0771, $p =$ 0000). The other sums of bile acids were also able to significantly discriminate between the groups but showed lower AUC-Scores. (**Supplement Table 4**)

3.2. Age-dependent differences

Within the CF group, total BA serum levels decreased significantly with age from infants ($n = 5$) to adolescents ($n = 25$) (Fig. 1) ($p = 0.017$). The same was seen in conjugated BA ($p = 0.023$) and primary BA ($p =$ 0.004).

Compared to the rest of the CF group, median serum taurine BA levels were significantly higher in infants ($n = 5$) ($p = 0.020$).

In the control group, taurine BA serum levels decreased as well from infancy ($n = 6$) to adolescence ($n = 26$) ($p < 0.001$). However, total BA levels were not significantly different between all age-groups in the control-group (Fig. 1).

In the next step we compared the ratios between the CF- and the control group, which showed age dependent differences between the two groups. The ratio taurine BA/total BA were significantly higher in the control group in preschool children (n(CF)=22, n(control)=34) ($p <$ 0.001), school children (n(CF)=18, n(control)=33) ($p < 0.001$) and adolescents (n(CF)=25, n(control)=26) ($p = 0.002$). This was not observed in infants (n(CF)=5, n(control)=6). In addition, the ratio taurine BA/ glycine BA was also higher in the control group compared to the CF group in preschool children ($p < 0.001$), school children ($p <$ 0.001) and adolescents ($p < 0.001$) (**Supplement Figure 1**). Again, no significant difference in this ratio was detected in infants.

3.3. Differences between pwCF with and without aCFLD

Children with CF with diagnosed aCFLD ($n = 8$) showed significantly higher serum levels of secondary bile acids ($p = 0.022$) as well as GLCA ($p = 0.009$), LCA ($p = 0.003$), GDCA ($p = 0.024$) and DCA ($p = 0.026$) compared to those without diagnosed aCFLD ($n = 65$).

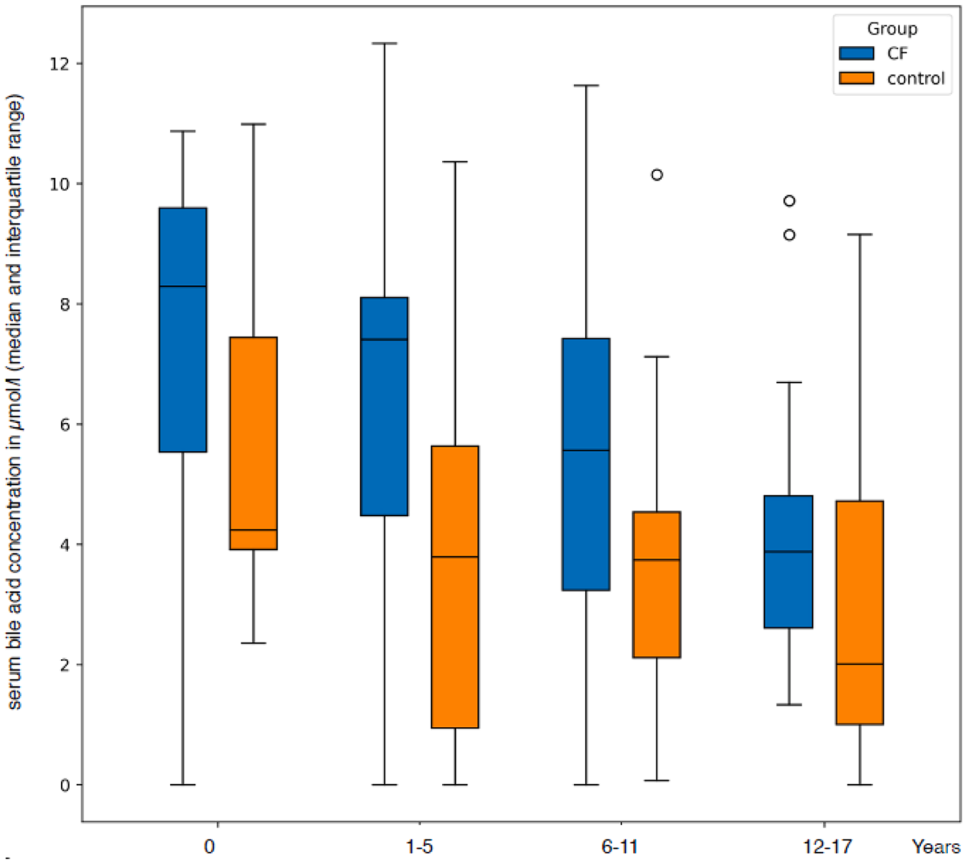

Fig. 1. Total bile acid concentration in CF (blue) and control group (orange) by age groups.

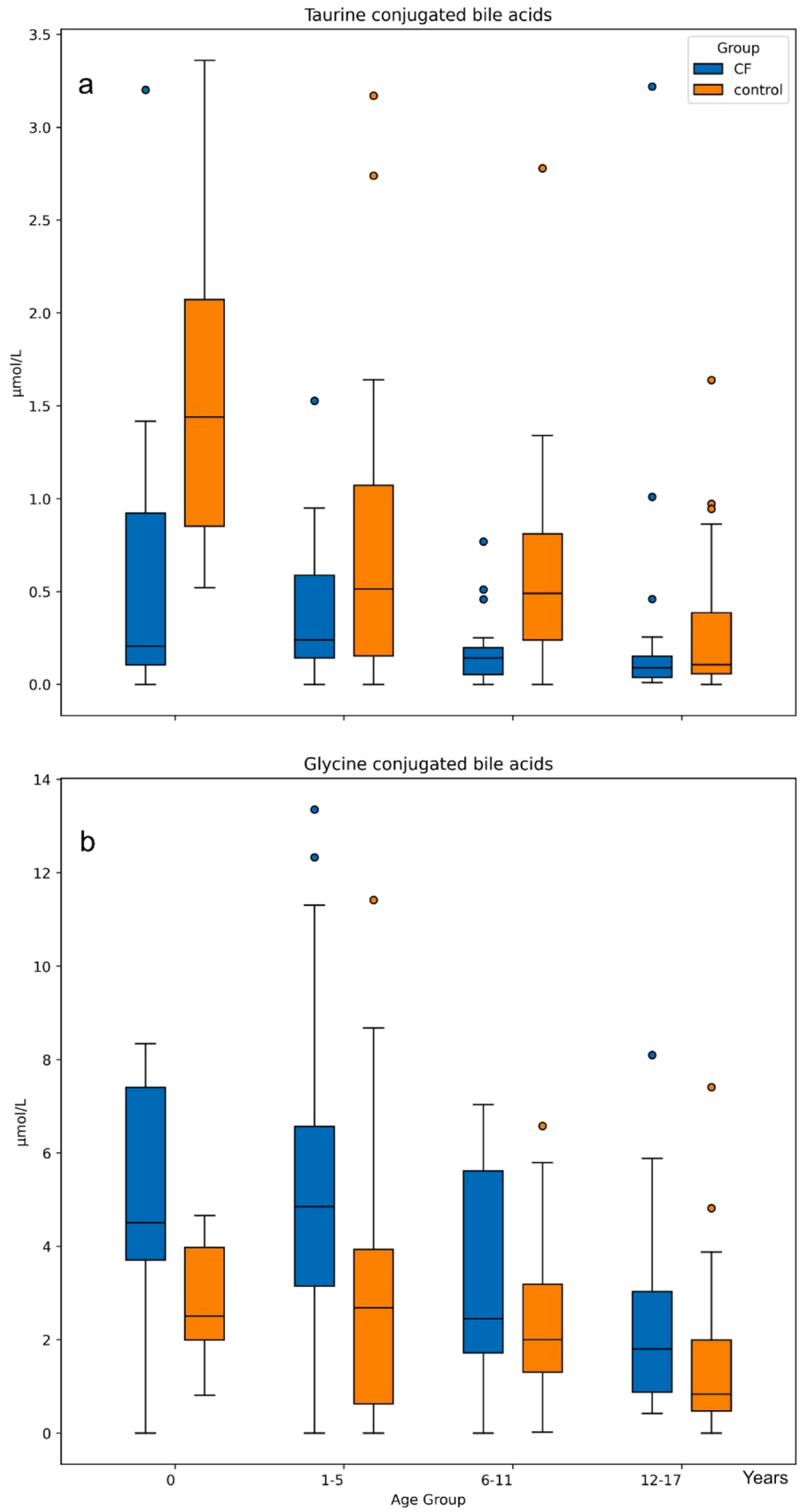

Fig. 2. Taurine- and Glycine conjugated bile acids in CF (blue) and control group (orange) by age groups.

Table 2
Median and interquartile range of bile acids in CF and control group.

	Median and interquartile range		
Bile acid concentration	CF	Control	p-value
GUDCA	**0302 µmol/l (iqr 3.891)**	**0108 µmol/l (iqr 0279)**	**<0.001**
TUDCA	0004 µmol/l (iqr 0040)	0008 µmol/l (iqr 0020)	0.714
UDCA	**0240 µmol/l (iqr 1815)**	**0024 µmol/l (iqr 0040)**	**<0.001**
TCA	**0036 µmol/l (iqr 0089)**	**0078 µmol/l (iqr 0159)**	**0.009**
GCA	**0615 µmol/l (iqr 1068)**	**0367 µmol/l (iqr 0670)**	**0.005**
CA	**0232 µmol/l (iqr 0407)**	**0040 µmol/l (iqr 0084)**	**<0.001**
TCDCA	**0115 µmol/l (iqr 0227)**	**0277 µmol/l (iqr 0603)**	**<0.001**
GCDCA	**2543 µmol/l (iqr 3479)**	**1140 µmol/l (iqr 1797)**	**<0.001**
CDCA	**0643 µmol/l (iqr 0874)**	**0100 µmol/l (iqr 0305)**	**<0.001**
TLCA	**0.00 µmol/l (iqr 0001)**	**0001 µmol/l (iqr 0010)**	**<0.001**
GLCA	0.009 µmol/l (iqr 0029)	0010 µmol/l (iqr 0030)	0.321
LCA	**0010 µmol/l (iqr 0018)**	**0010 µmol/l (iqr 0010)**	**0.031**
HDCA	**0163 µmol/l (iqr 0257)**	**0057 µmol/l (iqr 0091)**	**<0.001**
GHDCA	0.00 µmol/l (iqr 0)	0.00 µmol/l (iqr 0)	0.559
THDCA	0.00 µmol/l (iqr 0)	0.00 µmol/l (iqr 0)	0.990
TDCA	**0000 µmol/l (iqr 0018)**	**0019 µmol/l (iqr 0060)**	**<0.001**
GDCA	0084 µmol/l (iqr 0355)	0090 µmol/l (iqr 0302)	0.456
DCA	0129 µmol/l (iqr 0382)	0060 µmol/l (iqr 0135)	0.129
Sums			
Total BA corrected	**5851 µmol/l (iqr 5800)**	**3665 µmol/l (iqr 3880)**	**<0.001**
Primary BA	**4570 µmol/l (iqr 5490)**	**2710 µmol/l (iqr 3580)**	**<0.001**
Secondary BA	**0826 µmol/l (iqr 1080)**	**0310 µmol/l (iqr 0480)**	**0.003**
Unconjugated BA	**1390 µmol/l (iqr 1710)**	**0360 µmol/l (iqr 0490)**	**<0.001**
Conjugated BA	**3740 µmol/l (iqr 4790)**	**2349 µmol/l (iqr 3440)**	**0.008**
Taurine-conjugated BA	**0165 µmol/l (iqr 0380)**	**0404 µmol/l (iqr 0820)**	**<0.001**
Glycine-conjugated BA	**3510 µmol/l (iqr 4510)**	**1905 µmol/l (iqr 2570)**	**<0.001**
Ratios			
Primary/Secondary BA	6711 (iqr 15.88)	5295 (iqr 13,45)	0.689
Taurine-conjugated/total BA	**0.0344 (iqr 0.04)**	**0.1476 (iqr 0.12)**	**<0.001**
Glycine-conjugated/total BA	0.6769 (iqr 0.30)	0.6444 (iqr 0.27)	0.213
Taurine-conjugated/glycine-conjugated BA	**0.0504 (iqr 0.06)**	**0.2022 (iqr 0.18)**	**<0.001**
Taurine-conjugated/unconjugated BA	**0.1337 (iqr 0.28)**	**0.9583 (iqr 2.33)**	**<0.001**
Unconjugated/conjugated BA	**0.3414 (iqr 0.59)**	**0.1824 (iqr 0.48)**	**0.002**

Legend Table 1: glycine-conjugated ursodeoxycholic acid (GUDCA), taurine-conjugated ursodeoxycholic acid (TUDCA), ursodeoxycholic acid (UDCA), taurine-conjugated cholic acid (TCA), glycine-conjugated cholic acid (GCA), cholic acid (CA), taurine-conjugated chenodeoxycholic acid (TCDCA), glycine-conjugated chenodeoxycholic acid (GCDCA), chenodeoxycholic acid (CDCA), taurine-conjugated lithocholic acid (TLCA), glycine-conjugated lithocholic acid (GLCA), lithocholic acid (LCA), taurine-conjugated hyodeoxycholic acid (THDCA), glycine-conjugated hyodeoxycholic acid (GHDCA), hyodeoxycholic acid (HDCA), taurine-conjugated deoxycholic acid (TDCA), glycine-conjugated deoxycholic acid (GDCA), deoxycholic acid (DCA), Bile acids (BA), interquartile range (iqr).

Children with >4 out of 14 points in the ultrasound score by Williams et al. [23] ($n = 12$), which shows a higher likelihood of aCFLD, had significantly elevated serum levels of secondary BA ($p = 0006$), LCA ($p = 0.004$), GLCA ($p = 0.002$), GDCA ($p = 0033$) and DCA ($p = 0.028$). In patients with >4 out of 9 points in the clinical score by Potter et al. ($n = 7$) [22], which also shows a higher likelihood of aCFLD, those changes in BAC could not be observed.

In the CF-collective, secondary BA were significantly higher in the group of adolescents ($n = 25$) compared to the control group ($n = 26$) ($p = 0.004$). Within the CF group, secondary BA were elevated in adolescents ($p = 0.011$) while in the control group, this trend could not be seen.

LCA, GLCA, GDCA and DCA serum levels were significantly lower in infants in the CF- (LCA: $p = 0.025$; GLCA: $p = 0.017$, GDCA: $p = 0011$; DCA: $p = 0042$) and control group (LCA: $p = 0.015$; GLCA: $p = 0.012$, GDCA: $p = 0009$; DCA: $p = 0003$) compared to the other age groups, in the CF-group all were significantly (LCA: $p < 0.001$; GLCA: $p = 0.005$; GDCA: $p = 0044$; DCA: $p = 0005$) elevated in the adolescence compared to younger children while in the control group only GLCA and DCA were significantly higher in school children (GLCA: $p = 0.001$; DCA: $p = 0.016$) but not in adolescents. (Fig. 4a and b)

All the ratios we calculated were not significantly different between pwCF with and without diagnosed aCFLD.

3.4. Differences between children with CF with and without CFTR-modulator-therapy

Comparing the children with CF under treatment with a CFTR-modulator ($n = 8$) to those without ($n = 65$), serum levels in GLCA [$p = 0.013$] were significantly lower in the modulator group.

The ratios were not significantly different in these groups.

4. Discussion

This prospective single centre study was performed to highlight two questions: 1) Does BAC of children with CF differ from BAC from healthy controls? 2) Does BAC of children with CF demonstrate differences between patients with or without known aCFLD?

As a first result the present findings confirm previous observations that serum levels of bile acids are different in pwCF [17], which is strengthened by the AUROC analysis that shows a significant differentiation between the CF and the control group.

While the levels of total bile acids, unconjugated and conjugated bile acids as well as glycine-conjugated bile acids are elevated in pwCF, taurine-conjugates were significantly decreased compared to serum levels in our control group. This difference could be observed in all age groups. Interestingly, the ratios we determined showed no difference between the CF and the control group before the end of the first year of life. Significant differences were seen thereafter. A potential explanation of the decreased taurine BA could be an increased faecal taurine loss in pwCF [27].

While age dependent changes of BAC in children without CF were already described by Jahnel et al. [28], to the best of our knowledge this is the first study that systematically analyses the age dependent change of BAC in pwCF and healthy controls.

While the ratios of taurine BA compared to unconjugated BA and of unconjugated BA compared to conjugated BA were different only in preschool and school children, the ratios of taurine BA / total BA and taurine BA / glycine BA were significantly decreased in children with CF from the age of one year onward. This shows that decreased serum levels of taurine conjugated bile acids seem to be a typical alteration in pwCF.

Additionally, there was a decrease with age in total bile acid concentration in the CF-group, while such a tendency could not be seen in the control group. The bile acid ratios we analysed began showing

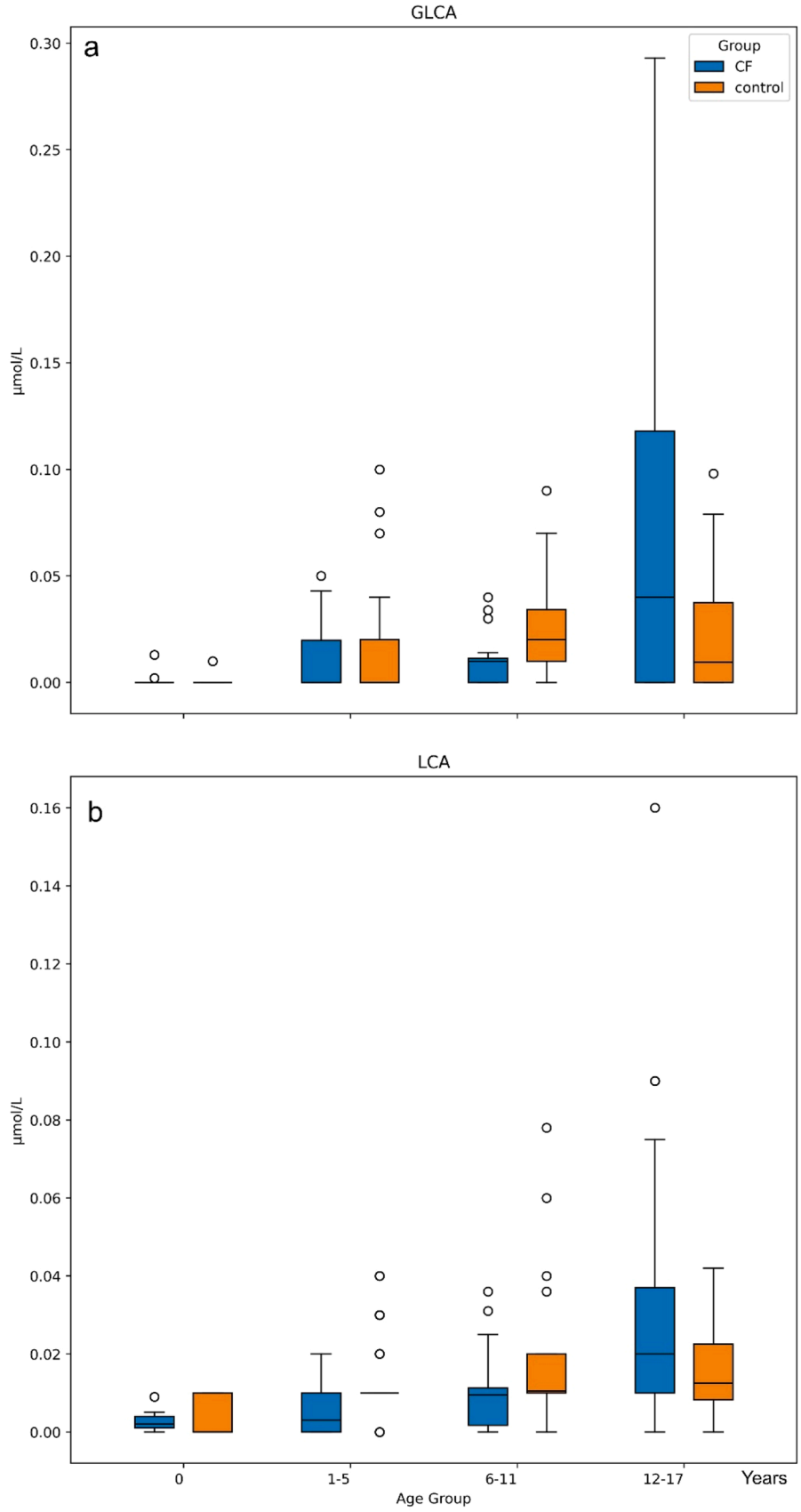

Fig. 4. GLCA and LCA concentration in CF (blue) and control group (orange) by age group.

differences only from the age of 1 year onwards, as infants in both groups had similar bile acid ratios. This could be an indication of an age dependent progression of hepatobiliary involvement in cystic fibrosis.

In both groups, serum taurine levels were descending over the course of the years, which was previously reported in children without CF by Jahnel et al. [28] as a physiologic development as breast milk contains high concentrations of the amino acid taurine.

In comparing the groups of children with CF with and without aCFLD, we observed increased levels of the bile acids LCA, GLCA, DCA and GDCA in the CFLD-group. Those bile acids showed a tendency of increasing concentrations in both groups, but in the aCFLD-group, the increase in the age group from 12 years upwards was significantly higher. This phenomenon could also be seen in the groups with positive Williams-Scores as well as patients with the need of UDCA-substitution (data not shown), as those groups have a high overlap with the group of children with aCFLD. Additionally, we could observe higher levels in secondary bile acids, which could be a direct result of the increase of LCA, GLCA, GDCA and DCA. However, the low number of pwCF and aCFLD ($n = 8$) is a limitation in this subgroup analysis. On the other hand, previous studies also reported an association between cholic acid and aCFLD [29,30], which is in line with our findings.

At the time we conducted the measurements, only 8 (11 %) of the recruited children with CF were treated with a CFTR modulator. In this small group, the bile acid GLCA was significantly lower compared to the rest of the pwCF. As mentioned above, this bile acid is also elevated in pwCF and aCFLD. Therefore, this could indicate a, possibly protective, modification of bile acid homeostasis by this medication. On the other hand an increased liver stiffness was reported in pwCF treated with Elexacaftor/Tezacaftor and Ivacaftor [17]. As this group was too small in our cohort, we are not able to postulate a positive impact of highly effective modulator therapy on CHBI.

A limitation, but also strength, because our data was collected in a very consistent and homogenous manner, of our study is the mono-centric design. Another limitation is the small number of children with aCFLD. On the other hand, to the best of our knowledge this is the first prospective study to compare BAC in children with CF and healthy controls, and the results are in line with other results already reported in the literature. Especially the comparable results in the control group to Jahnel et al. [28] emphasizes the robustness of our measurement. In addition, the high number of children with cystic fibrosis without modulator therapy provides relevant insights in the alteration of BAC in CF particularly with regard to potential long-term effects of CFTR modulators on CFHBI. In addition, we are not able to provide longitudinal data as we measured the bile acids only once in each patient, which is another limitation of our study. Further studies that systematically analyse the longitudinal change of BAC and the impact of pharmaceutical interventions are needed.

Declaration of competing interest

BK: Leadership/Speaker of the working group "Paediatric Liver Transplantation" (pLTx-AG) of the German Society of Paediatric Gastroenterology and Nutrition (GPGE). Secretary of the working group Solid Organ Transplantation in Paediatric Patients (AG OTKJ) of the German Society for Organ Transplantation (DTG). **AK**: Educational Bursary ECFS Congress 2024

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2026.02.006.

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