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Elevated Serum Bile Acids Predict Poor Liver Outcomes in Children With Alagille Syndrome: Results From the GALA Study Group

Carla Fiorella Murillo Perez[1] | Shannon M. Vandriel[1] | Emmanuel M. Gonzales[2] | Jian-She Wang[3] | Li-Ting Li[3] | Huiyu She[3] | Irena Jankowska[4] | Piotr Czubkowski[4] | Dorota Gliwicz-Miedzińska[4] | Emmanuel Jacquemin[4] | Jérôme Bouligand[5] | Lorenzo D'Antiga[6,7] | Emanuele Nicastro[6] | Björn Fischler[8] | Henrik Arnell[9] | Susan M. Siew[10] | Michael Stormon[10] | Kathleen M. Loomes[11] | David A. Piccoli[11] | Elizabeth B. Rand[11] | James E. Squires[12] | Saul J. Karpen[13,14] | Rene Romero[13] | Mureo Kasahara[15] | Zerrin Önal[16] | Étienne Sokal[17] | Tanguy Demaret[17] | Sabina Wiecek[18] | Florence Lacaille[19] | Dominique Debray[20] | Winita Hardikar[21] | Sahana Shankar[22] | Pamela L. Valentino[23] | Shikha S. Sundaram[24] | Noelle H. Ebel[25] | Jeffrey A. Feinstein[26] | Orith Waisbourd-Zinman[27] | Henry C. Lin[28] | Nathalie Rock[29] | Henkjan J. Verkade[30] | M. Kyle Jensen[31] | Catalina Jaramillo[31] | Kyung Mo Kim[32] | Seak Hee Oh[32] | Jernej Brecemiclj[33] | Seema Alam[34] | Giuseppe Indolfi[35] | Niviann Blondet[23] | Rima Fawaz[36] | Silvia Nastasio[37] | Pier Luigi Calvo[38] | Gabriella Nebbia[39] | Cigdem Arikan[40] | Catherine Larson-Nath[41] | Andréanne N. Zizzo[42] | Thomas Damgaard Sandahl[43] | Christos Tzivinikos[44] | Nehal M. El-Koofy[45] | Mohamed A. Elmonem[46] | Amal A. Aqul[47] | Wikrom Karnsakul[48] | Pinar Bulut[49] | Nanda Kerkar[50,51] | Victorien M. Wolters[52] | Amin J. Roberts[53] | Helen M. Evans[53] | Maria Camila Sanchez[54] | Maria Lorena Cavalieri[54] | Deirdre A. Kelly[55] | Jane Hartley[55] | Way Seah Lee[56] | Christina Hajinicolaou[57] | Chatmanee Lertudomphonwanit[58] | Ryan T. Fischer[59] | Jesus Quintero Bernabeu[60,61] | Ruben E. Quiros-Tejeira[62] | Cristina Targa Ferreira[63] | Elisa Carvalho[64] | John Eshun[65] | Aglaia Zellos[66] | Antal Dezsőfi[67] | Raquel Borges Pinto[68] | Kathleen Schwarz[69] | Maria Rogalidou[70] | Jennifer Garcia[71] | María Legarda Tamara[72] | Marisa Beretta[73] | Quais Mujawar[74] | Ermelinda Santos-Silva[75,76] | Cristina Molera Busoms[77] | Eberhard Lurz[78] | Cristina Gonçalves[79,80] | Carolina Jimenez-Rivera[81] | Jesus M. Banales[82] | Richard J. Thompson[83] | Bettina E. Hansen[84,85] | Binita M. Kamath[1,11] | The Global ALagille Alliance (GALA) Study Group

Correspondence: Binita M. Kamath (kamathb@chop.edu)

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ABSTRACT

Background and Aim: Alagille syndrome (ALGS) is a rare disorder characterised by cholestasis and extrahepatic manifestations. Given the current era of ileal bile acid transporter (IBAT) inhibitor therapies that reduce serum bile acid (SBA) levels, we evaluated whether SBA predicts liver disease outcomes in ALGS.

Methods: Patients were ascertained from the **G**lobal **AL**agille **A**lliance (GALA) cohort. A prognostic threshold of SBA 102 μmol/L was assessed as a time-dependent covariate in Cox regression analyses for native liver survival (NLS) and event-free survival (EFS), while adjusting for total bilirubin (TB) levels.

For affiliations refer to page 9.

Results: 570 GALA patients were included (348 [61%] male). There was a moderate positive correlation between SBA and TB (Pearson correlation = 0.47, $p < 0.001$). SBA below 102 μmol/L was a significant predictor of outcomes (NLS: HR = 3.78, 95% CI 2.39–5.99, $p < 0.001$; EFS: HR = 3.44, 95% CI 2.35–5.04, $p < 0.001$). SBA remained a significant predictor for improved EFS after adjusting for TB clearance at 1 year (TB < 2 mg/dL; HR = 2.00, 95% CI 1.10–3.65, $p = 0.02$). Median SBA in the first year of life above 102 μmol/L, predicted lower NLS (67.2% vs. 83.5% at 7 years $p = 0.05$) and EFS (63.4% vs. 80.9% at 7 years, $p = 0.02$).

Conclusion: Lower SBA in children with ALGS liver disease predicts improved NLS and EFS. SBA is also associated with NLS in children with ALGS who clear their bilirubin, that is, those with anicteric cholestasis. Although the patients studied here did not receive IBAT inhibition, these data suggest that lowering SBA may improve important clinical outcomes.

1 | Introduction

Alagille syndrome (ALGS) is an inherited cholestatic liver disorder characterised by paucity of the intrahepatic bile ducts, and a myriad of extrahepatic manifestations. In cholangiopathies like ALGS, the structural integrity of the hepatobiliary tree is compromised, leading to pathologic intrahepatic bile acid accumulation and associated pruritus. Standard medical therapies for cholestasis-associated pruritus include ursodeoxycholic acid (UDCA), cholestyramine, and rifampin, though they are rarely completely effective. Surgical biliary diversion (SBD) has demonstrated limited efficacy in ameliorating symptoms and improving liver biochemistry in ALGS [1]. In recent years, a paradigm shift has occurred due to the availability of ileal bile acid transporter (IBAT) inhibitor therapies, which have been shown to be effective at reducing serum bile acids (SBA) and improving pruritus in children with ALGS [2, 3].

Despite the known elevation of SBA in ALGS, the natural trajectory of these levels and their association with long-term clinical outcomes has not been elucidated. Serum levels of total bilirubin (TB) have been previously established as a predictor of hepatic clinical outcomes, with a median bilirubin of 5–10 mg/dL between 6 and 12 months of age being associated with an increased risk of liver transplantation (LT) or death [4]. The NAPPED Study Group demonstrated that a post-SBD SBA level < 102 μmol/L was associated with prolonged native liver survival (NLS) after SBD in bile salt export pump (BSEP) deficiency [5]. This prognostic threshold may also be predictive in other cholestatic liver diseases, including ALGS.

This investigation aimed to characterize the trajectory of SBA in a real-world cohort of children with ALGS ascertained from the **G**lobal **AL**agille **A**lliance (GALA) Study. Specifically, this analysis sought to determine whether SBAs are associated with liver disease outcomes. Given that TB is an established predictor in children with ALGS, the prognostic value of SBA was assessed in the context of TB. We hypothesized that SBA levels can independently and in conjunction with TB predict long-term hepatic outcomes. Furthermore, we hypothesized that higher levels of SBAs would be inversely correlated with platelet count as a marker of clinically evident portal hypertension (CEPH).

2 | Methods

2.1 | Study Population

Patients were ascertained from the GALA Study Group, an international cohort of patients with ALGS from 92 centres and 36 countries. Eligibility for inclusion in the GALA cohort was defined as patients with clinically and/or genetically confirmed ALGS diagnosis according to established clinical criteria born between January 1997 and August 2019, or patients with genetically confirmed ALGS born prior to January 1997. The characteristics of this cohort have been previously described [1].

For this analysis, patients were included if they presented with neonatal cholestasis and had at least one SBA measurement during eligible follow-up, defined as the time period prior to Kasai, trial enrollment, or 18 years of age, whichever came first, after which patient data were not evaluated. Patients were excluded if there was an unknown date for key clinical events such as death, enrollment in a clinical trial for an IBAT inhibitor, SBD, or Kasai procedure. The study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the ethics committee at each participating centre.

2.2 | Data Collection

Data were collected retrospectively by each participating center and uploaded directly onto REDCap (Research Electronic Data Capture). Analyses for this study were conducted with data obtained as of February 2023.

Neonatal cholestasis was defined as having at least one of the following in the first 3 months of life: (1) direct/conjugated bilirubin (CB) greater than 2 mg/dL (34 μmol/L); (2) SBA or GGT greater than three times the upper limit of normal; or (3) fat-soluble vitamin deficiency, otherwise unexplainable [2]. Biochemical parameters obtained for this study were SBA, TB, and platelet count. The primary endpoint was native liver survival (NLS) and was calculated from the date of birth until LT, death, or date of last clinical follow-up, whichever came first. Event-free survival (EFS) was a secondary endpoint and was calculated from the date of birth until the first occurrence of the following: SBD, manifestations of portal hypertension (ascites requiring treatment with diuretics, or varices requiring intervention at endoscopy), LT,

Summary

- Alagille syndrome (ALGS) is a rare liver disease where high bile acid levels in the blood may lead to worse outcomes.
- In a study of 570 children, those with lower bile acid levels (below 102 μmol/L) had better long-term liver health and fewer serious complications.
- Although none received new bile acid-lowering treatments such as IBAT inhibitors, the findings suggest that reducing bile acids could help improve outcomes in ALGS.

death, or date of last clinical follow-up. Time to platelet count $<150\times10^9$/L was considered another secondary endpoint as an indirect measure of CEPH [6]. Event-free survival with platelet count $<150\times10^9$/L was calculated from the date of birth until the first occurrence of the following: SBD, manifestations of portal hypertension (ascites requiring treatment with diuretics, or varices requiring intervention at endoscopy), LT, death, platelet count $<150\times10^9$/L, or date of last clinical follow-up. Patients were censored at the time of Kasai, enrollment in a clinical trial for an IBAT inhibitor, or 18 years of age, whichever came first when calculating all the endpoints.

UDCA use was collected during follow-up visits and was subsequently used to dictate whether patients ever received UDCA or if they had documented UDCA use within the first 6 months of life. Due to inconsistently reported UDCA use from one site, this centre was excluded when describing the proportions of UDCA use in this cohort ($n=204$ patients excluded).

2.3 | Statistical Analysis

Demographic and clinical characteristics are presented as count (percentage) for categorical data and median (25–75th percentiles) for continuous data. Data that were not normally distributed were log-transformed (natural log) for the analyses. The correlation between SBA and TB was assessed with a scatter plot and Pearson correlation coefficient. Trends in SBA and TB over time from birth and from the date of last follow-up (reverse time) were assessed with a scatter plot and stratified by clinical outcome. NLS and EFS were estimated with Kaplan–Meier curves and between-group comparisons were tested with the log-rank test. NLS, EFS, time to platelet count $<150\times10^9$/L, and event-free survival with platelet count $<150\times10^9$/L were also estimated with a time-dependent Cox proportional hazards regression (hazard ratio [HR] with 95% CI) to utilise all repeated measurements of SBA data available. To determine if there was an optimal threshold for SBA as a prognostic dichotomous variable, within a range that can be attained with available therapies, a grid search of SBA thresholds between 50 and 200 μmol/L by steps of 10 μmol/L as time-dependent covariate was conducted comparing the negative log likelihoods of the Cox regressions. The potential identified threshold will be used in further analyses. In addition the prognostic value of the SBA threshold of 102 μmol/L, previously established in PFIC, was assessed as a time-dependent covariate in the Cox regression [5], and also the SBA threshold of 200 μmol/L which has previously been identified as a threshold of clinical response to maralixibat in ALGS [7].

The median of serial SBA values from the first year of life was used to stratify patients according to the identified optimal SBA threshold, and evaluate the association with NLS, EFS, and platelet count $<150\times10^9$/L, and event-free survival with platelet count $<150\times10^9$/L. Given that bilirubin is an established predictor of clinical outcome, the time-dependent Cox regression analyses included TB clearance as a confounding factor in multivariable analysis, defined as bilirubin <2 mg/dL at 1 year (±6 months). A sensitivity analysis using a bilirubin threshold of <1 mg/dL for TB clearance was also conducted. Multiple sensitivity analyses were performed to account for the differences in frequency of SBA measurements between patients. All Cox regression analyses included geographical region (Africa, Asia, Europe, Middle East, North America, and Oceania (Australia and New Zealand)) as a stratum. All analyses were two- sided and $p<0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY).

3 | Results

3.1 | Study Population

After applying the inclusion and exclusion criteria, the study included a total of 570 patients with ≥1 SBA measurement from the GALA cohort (Figure 1). The patient population was predominantly male (61%), and the median year of birth was 2012 (IQR 2007–2015). Most patients were from Asia (38%) and Europe (35%), with data collected from 45 centres in 22 countries (Table 1).

SBA availability in this cohort was broad and ranged from 1 SBA measurement to 34 measurements per patient. There were 359 (63%) patients with at least two values, 290 (51%) with at least three, 247 (43%) with at least four, and 208 (37%) with at least five measurements. The timing of SBA measurement was according to standard of care at each participating centre and was variable

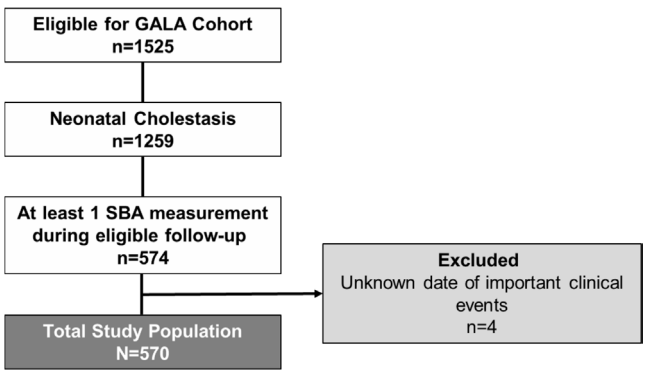

FIGURE 1 | Flowchart of patients included in the study population. Eligible follow-up is defined as the time period prior to Kasai, trial enrollment, and 18 years of age. Kasai, surgical biliary diversion, trial enrollment and death were considered important clinical events.

TABLE 1 | Demographic characteristics of children with Alagille syndrome (ALGS) in study population.

	***n* = 570**
Biological sex, *n* (%)	
Male	348 (61.1)
Female	222 (38.9)
Year of birth	2012 (2007–2015)
UDCA use (ever)	293/366 (80.1)
Country/region	
Africa	1 (0.2)
Asia	218 (38.2)
Europe	201 (35.3)
Middle East	15 (2.6)
North America	111 (19.5)
Oceania (Australia and New Zealand)	24 (4.2)

Abbreviation: UDCA, ursodeoxycholic acid.

per patient. Multiple sensitivity analyses to account for the frequency of measurements did not change the results. The median of all SBA measurements ($n = 2629$) for the total cohort at any age was 140 μmol/L (Q1–Q4 72–241) (Figure S1). Most SBA measurements were from the first 2 years of life ($n = 1497/2629$, 57%), as was the first SBA measurement per patient ($n = 438/570$, 77%). The median SBA for the first 2 years of life was 147 μmol/L (Q1–Q4 85–240).

In this cohort, nine patients (1.6%) had a Kasai procedure, and 14 patients (2.5%) were enrolled in a clinical trial for an IBAT inhibitor during follow-up, at which time they were censored. In those who had a Kasai procedure during follow-up, there were a total of 12 SBA measurements (all within the first 90 days), for whom the median SBA was 106 μmol/L (Q1–Q4 60–153). While their follow-up data were only included up until the point of the procedure, their pre-Kasai SBA levels did not deviate from SBA in the first 90 days of the remainder of the cohort (121 μmol/L, Q1–Q4 83–161) and were thus included in the analysis. A sensitivity analysis with and without the data from patients with a Kasai did not alter the results.

UDCA use ever was reported in 80% ($n = 293/366$) of patients and in 78% ($n = 267/344$) within the first 6 months of life in those with available UDCA data. In patients who initiated UDCA in the first 6 months, median SBA during the subsequent 12 months (6–18 months) was 164 μmol/L (Q1–Q4 44–269) compared to 137 μmol/L (Q1–Q4 48–261) in those who were not prescribed UDCA ($p = 0.93$) (Figure S2).

3.2 | NLS and EFS

For the primary outcome of NLS, there were a total of 121 events, 96 LT and 25 deaths. For the secondary outcome of EFS, there were 161 events, of which 38 were related to manifestations of portal hypertension (24 were diuretic treatment for ascites and 14 were varices with endoscopic intervention), 28 were SBD, 78 were LT, and 17 were deaths. The NLS rates for the study population at 5, 10, and 18 years were 81.1%, 59.3%, and 53.6%, respectively. EFS rates at 5, 10, and 18 years were 75.0%, 58.7%, and 46.1% (Figure S3).

3.3 | Trends in SBA and TB

The correlation between SBA and TB was assessed with a scatter plot. There was a moderate positive correlation between SBA and TB (Pearson correlation = 0.47, $p < 0.001$) (Figure S4). For SBA trends over time, SBA was elevated and remained elevated in those who subsequently experienced LT or death (Figure 2A). SBA did not increase prior to the outcome (Figure 2B). This contrasts with TB, which decreased from the time of birth, with the greater decline in those patients who did not experience LT or death (Figure 2C). Furthermore, TB markedly increased prior to patients experiencing LT or death (Figure 2D).

3.4 | Prognostic Value of SBA for Liver Disease Outcomes

The grid search of thresholds ranging from 50 to 200 μmol/L demonstrated that 102 μmol/L had the highest negative log likelihood, and therefore a better fit for the model in predicting NLS (Figure S5). There were 27% of patients that remained below a threshold of 102 μmol/L during follow-up.

The association of SBA with liver disease outcomes (platelet count $< 150 \times 10^9$/L, SBD, manifestations of portal hypertension, liver transplant, death) was evaluated with a time-dependent variable for SBA > 102 μmol/L. The median first time to SBA above 102 μmol/L was 0.84 years (95% CI 0.52–1.16) (Figure S6).

In univariate Cox regression analysis, the SBA threshold was a significant predictor of liver disease outcomes, including NLS, EFS, platelet count $< 150 \times 10^9$/L, and EFS with platelet count $< 150 \times 10^9$/L (Table 2). From the time that patients reached an SBA > 102 μmol/L, they had a 3.78-fold increase in risk for NLS (LT and death) ($p < 0.001$); EFS (SBD, manifestations of portal hypertension, LT, and death) a 3.44-fold increase ($p < 0.001$); a 2.68-fold increase for time to platelet count $< 150 \times 10^9$/L ($p < 0.001$); and a 2.94-fold increase for EFS with platelet count $< 150 \times 10^9$ ($p < 0.001$). There was no significant interaction between the SBA threshold and clearance of TB. SBA remained a significant factor for EFS while adjusting for TB clearance at 1 year, defined as TB < 2 mg/dL (Table 3). Similarly, when TB clearance was defined as TB < 1 mg/dL, SBA remained a significant factor for EFS (HR 1.94, 95% CI 1.07–3.51, $p = 0.03$).

A median SBA above 102 μmol/L in the first year was associated with lower NLS (7-year: 67.2% vs. 83.5%, $p = 0.05$), EFS (7-year: 63.4% vs. 80.9%, $p = 0.02$), EFS with platelet count $< 150 \times 10^9$/L (7-year: 58.5% vs. 73.7%, $p = 0.03$) and higher incidence of platelet count $< 150 \times 10^9$/L (7-year: 19.3% vs. 10.1%, $p = 0.03$) (Figure 3).

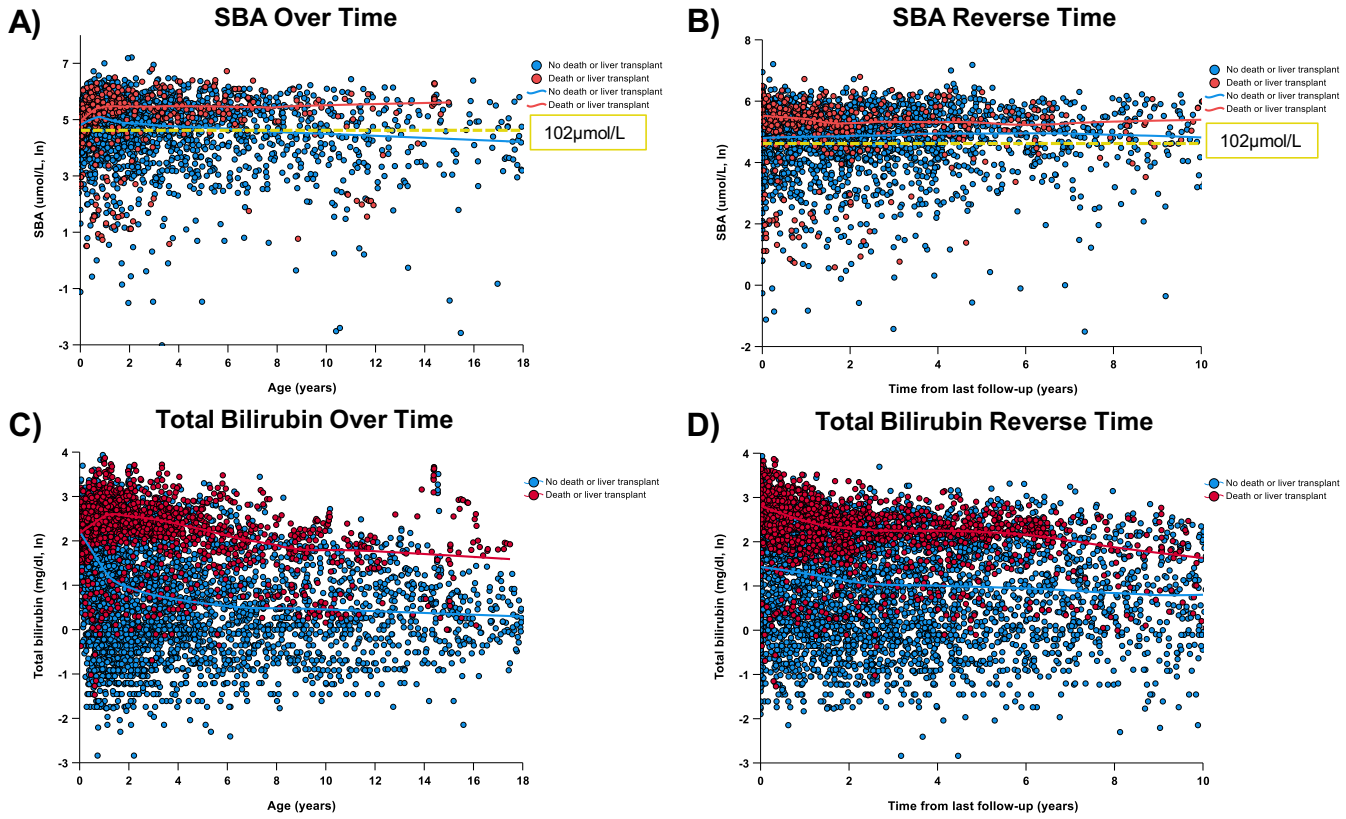

FIGURE 2 | Scatter plot representing trends in (A) serum bile acid (SBA) from birth until last follow-up; (B) SBA in reverse time order where time zero is the value measured at last clinical follow-up; (C) total bilirubin from time of birth; and (D) total bilirubin in reverse time order where time zero is the value measured at last clinical follow-up.

TABLE 2 | Univariate Cox regression of SBA > 102 µmol/L as a time-dependent variable with liver disease outcomes.

Outcome	HR (95% CI)	*p*
Native liver survival	3.78 (2.39–5.99)	< 0.001
Event-free survival	3.44 (2.35–5.04)	< 0.001
Time to first platelet count $< 150 \times 10^9$/L[a]	2.68 (1.74–4.13)	< 0.001
Event-free survival with time to first platelet count $< 150 \times 10^9$/L	2.94 (2.14–4.03)	< 0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; SBA, serum bile acid.
[a]Platelet count was used as an indicator of clinically evident portal hypertension.

Similar results were observed when an SBA threshold of 200 µmol/L was assessed (Tables S1 and S2). The association of platelet count $< 150 \times 10^9$/L as a time-dependent variable with NLS was validated (HR 6.34, 95% CI 4.24–9.50, $p < 0.001$).

4 | Discussion

This is the first comprehensive study of SBA in ALGS using longitudinal measurements in a large international cohort of patients. As expected, SBA levels in ALGS are markedly elevated particularly in the first 2 years of life (median 147 µmol/L). We studied trends in SBA levels in ALGS patients stratified by liver disease outcome and demonstrated that in those patients destined to undergo LT, SBA levels are elevated and remain elevated over time until LT/death and this trend does not change dynamically over time. Surprisingly, a grid search of SBA levels to identify a prognostic dichotomous threshold in ALGS, identified 102 µmol/L, which has been previously described in PFIC [5]. We now show that this SBA threshold is a significant predictor of liver disease outcomes in ALGS. Specifically, reaching this SBA threshold was associated with an increased risk for clinical manifestations of portal hypertension, SBD, platelet count $< 150 \times 10^9$/L, liver transplant, and death. Most importantly, even in patients with ALGS who clear their jaundice by the age of 1 year, SBA remains a significant predictor of liver disease outcome.

The GALA study has previously shown that TB is a significant predictor of liver disease outcomes [4]. The current analysis demonstrates the value of SBA as a predictor of liver disease outcomes, even in those children with ALGS who clear their jaundice. This phenomenon of anicteric cholestasis is common in ALGS and in these patients TB is not a useful predictor of liver disease progression. Therefore, this analysis adds another biochemical parameter that has clinical utility in the monitoring of these patients. We recommend at least annual SBA measurements in children with ALGS and high bilirubin in order to assess the severity of cholestasis and to assess the potential value of IBAT therapy. We also recommend at least annual SBA measurements in children with ALGS and low-normal bilirubin to assess for anicteric cholestasis, to assess the potential value of

TABLE 3 | Multivariable Cox regression of serum bile acid (SBA) threshold 102 μmol/L as a time-dependent variable and total bilirubin clearance (< 2 mg/dL) at 1 year with liver disease outcomes.

Outcome	Thresholds	HR (95% CI)	*p*
Native liver survival	SBA > 102 μmol/L	1.72 (0.90–3.28)	0.10
	Bilirubin < 2 mg/dL at 1 year	0.13 (0.05–0.29)	**< 0.001**
Event-free survival	SBA > 102 μmol/L	2.04 (1.13–3.71)	**0.019**
	Bilirubin < 2 mg/dL at 1 year	0.14 (0.07–0.29)	**< 0.001**
Time to first platelet count $< 150 \times 10^9$/L[a]	SBA > 102 μmol/L	1.70 (0.80–3.60)	0.17
	Bilirubin < 2 mg/dl at 1 year	0.24 (0.11–0.50)	**< 0.001**
Event-free survival with time to first platelet count $< 150 \times 10^9$/L	SBA > 102 μmol/L	1.64 (0.97–2.79)	0.07
	Bilirubin < 2 mg/dl at 1 year	0.14 (0.08–0.27)	**< 0.001**

Abbreviations: CI, confidence interval; HR, hazard ratio; SBA, serum bile acid.
[a]Platelet count was used as an indicator of clinically evident portal hypertension.
Note: The bolded values are statistically significant.

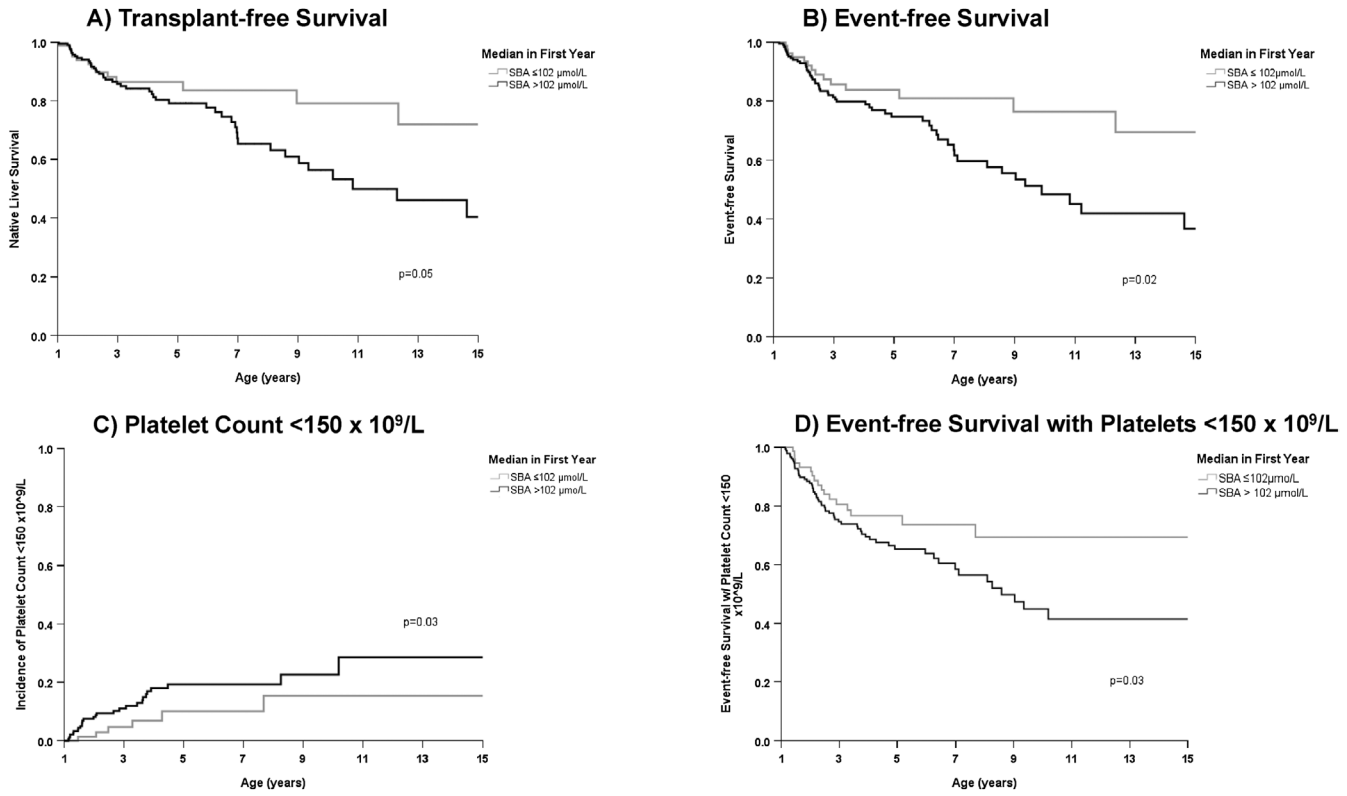

FIGURE 3 | (A) Native liver survival (NLS); (B) event-free survival (EFS); (C) time to first platelet count $< 150 \times 10^9$/L, and (D) event-free survival (EFS) with time to first platelet count 150×10^9/L according to median serum bile acids (SBA) in the first year.

an IBAT therapy and as a predictor of liver disease outcome. The value of SBA as a prognostic marker for liver disease progression in patients with anicteric cholestasis has already been demonstrated in biliary atresia [8]. In this study, children with biliary atresia with normalised bilirubin levels and low serum bile acids (≤ 40 μmol/L) had a significantly lower incidence of liver transplant/death than those in the higher SBA group.

IBAT inhibitors have changed the treatment landscape for ALGS and are currently approved for the treatment of cholestatic pruritus. A recent analysis of clinically important liver-related events in ALGS patients treated in clinical trials with maralixibat and compared to a synthetic aligned cohort selected from GALA, revealed a 70% reduction of events in the maralixibat-treated cohort [5]. Whilst this analysis was statistically significant, the data do not readily explain the underlying mechanism for this reduction. It was not clear if the reduction in events was related to the better treatment of pruritus and associated delay in liver transplantation, or if IBAT inhibition was actually impacting liver disease biology and altering the natural history. The current study indicates that lower SBA levels are associated with improved NLS. If SBA are related to pruritus severity, then

this finding of improved NLS could again be related to pruritus; however the association of higher SBA with lower platelet counts and ascites and gastrointestinal bleeding, suggests a connection between SBA and the development of portal hypertension. Therefore, in addition to treating cholestatic pruritus, IBAT inhibitors may also be ameliorating liver disease progression in ALGS, presumably by depletion of intrahepatic bile acids. It should be noted, however that in the current analysis no patients actually received IBAT inhibitors and therefore the data represent a natural history association between lower SBA and good hepatic outcomes, and not response to an intervention.

There are a few limitations to this analysis. The retrospective nature and the variability of SBA levels are worth mentioning, though these are partially overcome by the large study cohort and the substantial number of SBA measurements included in the analysis. It would have been ideal to have other biomarkers of portal hypertension available such as spleen size and elastography measurements to better evaluate the association of SBA levels with markers of hepatic fibrosis. Finally, as expected, UDCA use is common practice in this population of patients and our study was limited by the lack of availability of UDCA dosages to further assess the association between UDCA use and SBA levels. From a mechanistic standpoint it would also be valuable to have bile acid speciation data; however there are no biospecimens available in GALA. Despite these limitations this remains the largest study to date of SBA levels in ALGS and importantly contains longitudinal data to assess dynamic changes over time.

Taken together, the data presented here reveal that SBA is a biomarker of liver disease severity in ALGS, and lower SBA levels are associated with improved markers of liver disease severity (platelet count) and LT/death. These data provide a practical tool for clinicians caring for patients with ALGS, especially those who clear their hyperbilirubinemia. Furthermore, this study supports the notion of initiating treatment with IBAT inhibitors in ALGS for cholestasis treatment and not reserving this therapy for symptomatic pruritus only. Indeed, the EMA has approved IBAT inhibitors for the treatment of cholestasis in PFIC (not pruritus alone) based on data similar to those presented here for BSEP deficiency. The current analysis sheds light on the role of SBAs in the pathogenesis of liver disease progression in ALGS and provides a rationale for targeting bile acids as a therapeutic strategy.

Author Contributions

Carla Fiorella Murillo Perez: participated in the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Shannon M. Vandriel:** participated in the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jian-She Wang:** participated in the study concept and design, data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Li-Ting Li:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Huiyu She:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Irena Jankowska:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Piotr Czubkowski:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Dorota Gliwicz-Miedzińska:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Emmanuel M. Gonzales:** participated in the study concept and design, data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Emmanuel Jacquemin:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jérôme Bouligand:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Lorenzo D'Antiga:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Emanuele Nicastro:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Björn Fischler:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Henrik Arnell:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Susan M. Siew:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Michael Stormon:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Kathleen M. Loomes:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **David A. Piccoli:** participated in the study concept and design, data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Elizabeth B. Rand:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **James E. Squires:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Saul J. Karpen:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Rene Romero:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Mureo Kasahara:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Zerrin Önal:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Étienne Sokal:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Tanguy Demaret:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Sabina Wiecek:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Florence Lacaille:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Dominique Debray:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Winita Hardikar:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Sahana Shankar:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Pamela L. Valentino:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Shikha S. Sundaram:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Noelle H. Ebel:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jeffrey A.**

Feinstein: data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Orith Waisbourd-Zinman:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Henry C. Lin:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Nathalie Rock:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Henkjan J. Verkade:** participated in the study concept and design, data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **M. Kyle Jensen:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Catalina Jaramillo:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Kyung Mo Kim:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Seak Hee Oh:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jernej Brecemiclj:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Seema Alam:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Giuseppe Indolfi:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Niviann Blondet:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Rima Fawaz:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Silvia Nastasio:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Pier Luigi Calvo:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Gabriella Nebbia:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Cigdem Arikan:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Catherine Larson-Nath:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Andréanne N. Zizzo:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Thomas Damgaard Sandahl:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Christos Tzivinikos:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Nehal M. El-Koofy:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Mohamed A. Elmonem:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Amal A. Aqul:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Wikrom Karnsakul:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Pinar Bulut:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Nanda Kerkar:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Victorien M. Wolters:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Amin J. Roberts:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Helen M. Evans:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Maria Camila Sanchez:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Maria Lorena Cavalieri:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Deirdre A. Kelly:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jane Hartley:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Way Seah Lee:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Christina Hajinicolaou:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Chatmanee Lertudomphonwanit:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Ryan T. Fischer:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jesus Quintero Bernabeu:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Ruben E. Quiros-Tejeira:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Cristina Targa Ferreira:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Elisa Carvalho:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **John Eshun:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Aglaia Zellos:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Antal Dezsőfi:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Raquel Borges Pinto:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Kathleen Schwarz:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Maria Rogalidou:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jennifer Garcia:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **María Legarda Tamara:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Marisa Beretta:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Quais Mujawar:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Ermelinda Santos-Silva:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Cristina Molera Busoms:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Eberhard Lurz:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Cristina Gonçalves:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Carolina Jimenez-Rivera:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Jesus M. Banales:** data acquisition, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Richard J. Thompson:** participated in the study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Bettina E. Hansen:** participated in the study concept and design, statistical analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. **Binita**

M. Kamath: participated in the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the version to be published, obtaining funding, and overall study supervision.

Affiliations

[1]Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children and the University of Toronto, Toronto, Canada | [2]Pediatric Hepatology and Liver Transplantation Unit, National Reference Centre for Rare Pediatric Liver Diseases, FILFOIE, ERN RARE LIVER, Bicêtre Hospital, AP-HP, Université Paris-Saclay, Le Kremlin-Bicêtre, and Inserm U1193, Hepatinov, University of Paris-Saclay, Orsay, France | [3]Children's Hospital of Fudan University, The Center for Pediatric Liver Diseases, Shanghai, China | [4]Department of Gastroenterology, Hepatology, Nutrition Disturbances and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland | [5]Service de Génétique Moléculaire, Pharmacogénétique et Hormonologie, Hôpitaux Universitaires Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Centre Hospitalier Universitaire de Bicêtre, Le Kremlin-Bicêtre, France | [6]Ospedale Papa Giovanni XXIII, Pediatric Hepatology, Gastroenterology and Transplantation, Bergamo, Italy | [7]Department of Medicine and Surgery, University of Milano, Milan, Italy | [8]Department of Paediatric Gastroenterology, Hepatology and Nutrition, Astrid Lindgren Children's Hospital, Karolinska University Hospital and CLINTEC, Karolinska Institutet, Stockholm, Sweden | [9]Department of Paediatric Gastroenterology, Hepatology and Nutrition, Astrid Lindgren Children's Hospital, Karolinska University Hospital and Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden | [10]Department of Gastroenterology, The Children's Hospital at Westmead, Sydney, Australia | [11]Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia and the University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA | [12]Division of Pediatric Gastroenterology and Hepatology, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA | [13]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Healthcare of Atlanta and Emory University School of Medicine, Atlanta, Georgia, USA | [14]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health at Virginia Commonwealth University, Richmond, Virginia, USA | [15]Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan | [16]Pediatric Gastroenterology, Hepatology and Nutrition Department, Istanbul University Istanbul Medical Faculty, Istanbul, Turkey | [17]Cliniques Universitaires Saint-Luc, Service De Gastroentérologie and Hépatologie Pédiatrique, Brussels, Belgium | [18]Department of Pediatrics, Medical University of Silesia, Katowice, Poland | [19]Pediatric Gastroenterology-Nutrition and Hepatology Units, Necker-Enfants Malades Hospital, University of Paris, Paris, France | [20]Pediatric Liver Unit, National Reference Centre for Rare Pediatric Liver Diseases (Biliary Atresia and Genetic Cholestasis), FILFOIE, ERN RARE LIVER, Necker-Enfants Malades Hospital, University of Paris, Paris, France | [21]Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Australia | [22]Mazumdar Shaw Medical Center, Narayana Health, Bangalore, India | [23]Gastroenterology and Hepatology Division, Department of Pediatrics, University of Washington, Seattle Children's Hospital, Seattle, Washington, USA | [24]Section of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics and the Digestive Health Institute, Children's Hospital of Colorado and University of Colorado School of Medicine, Aurora, Colorado, USA | [25]Division of Gastroenterology, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California, USA | [26]Department of Pediatrics (Cardiology), Stanford University School of Medicine, Lucile Packard Children's Hospital, Palo Alto, California, USA | [27]Schneider Children's Medical Center of Israel, Institute of Gastroenterology, Nutrition and Liver Diseases, Petah Tikva, Israel | [28]Division of Pediatric Gastroenterology, Department of Pediatrics, Oregon Health and Science University, Portland, Oregon, USA | [29]Division of Pediatric Specialties, Department of Pediatrics, Gynecology, and Obstetrics, Swiss Pediatric Liver Center, University Hospitals Geneva and University of Geneva, Geneva, Switzerland | [30]Department of Pediatrics, Center for Liver, Digestive, and Metabolic Diseases, University Medical Center Groningen, Groningen, the Netherlands | [31]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Primary Children's Hospital, University of Utah, Salt Lake City, Utah, USA | [32]Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Republic of Korea | [33]Pediatric Gastroenterology, Hepatology and Nutrition, and Department of Pediatrics, Faculty of Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia | [34]Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India | [35]Meyer Children's University Hospital IRCCS, Florence, Italy | [36]Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA | [37]Division of Gastroenterology, Hepatology, and Nutritions, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA | [38]Pediatric Gastroenterology Unit, Regina Margherita Children's Hospital, Azienda Ospedaliera-Universitaria Citta' della Salute e della Scienza, Turin, Italy | [39]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Servizio di Epatologia Pediatrica, Milan, Italy | [40]Department of Pediatric Gastroenterology and Organ Transplant, Koc University School of Medicine, Istanbul, Turkey | [41]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis, Minnesota, USA | [42]Division of Paediatric Gastroenterology and Hepatology, Children's Hospital, London Health Sciences Centre, Western University, London, Ontario, Canada | [43]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark | [44]Department of Paediatric Gastroenterology, Al Jalila Children's Specialty Hospital, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE | [45]Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt | [46]Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt | [47]University of Texas Southwestern Medical Center in Dallas and Children's Health, Dallas, Texas, USA | [48]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA | [49]Division of Pediatric Gastroenterology and Hepatology, Phoenix Children's Hospital, Phoenix, Arizona, USA | [50]Massachusetts General Brigham for Children, Boston, Massachusetts, USA | [51]University of Rochester Medical Center, Rochester, New York, USA | [52]Department of Pediatric Gastroenterology, University Medical Center Utrecht, Utrecht, the Netherlands | [53]Department of Paediatric Gastroenterology, Starship Child Health, Auckland, New Zealand | [54]Hospital Italiano Buenos Aires, Pediatric Gastroenterology and Hepatology Division, Buenos Aires, Argentina | [55]Liver Unit, Birmingham Women's and Children's Hospital NHS Trust and University of Birmingham, Birmingham, UK | [56]Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia | [57]Division of Paediatric Gastroenterology, Department of Paediatrics and Child Health, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa | [58]Division of Gastroenterology, Department of Pediatrics, Ramathibodi Hospital Mahidol University, Bangkok, Thailand | [59]Section of Hepatology, Department of Gastroenterology, Children's Mercy Kansas City, Kansas City, Kansas, USA | [60]Pediatric Hepatology and Liver Transplant Department, Hospital Universiatri Vall d'Hebron, Barcelona, Spain | [61]Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute – Donostia University Hospital – University of the Basque Country (UPV/EHU), San Sebastian, Spain | [62]Department of Pediatrics, Children's Hospital and Medical Center and University of Nebraska Medical Center, Omaha, Nebraska, USA | [63]Pediatric Gastroenterology Service, Hospital da Criança Santo Antônio, Universidade Federal de Ciências da Saúde de Porto Alegre, Complexo Hospitalar Santa Casa, Porto Alegre, Rio Grande do Sul, Brazil | [64]Pediatric Gastroenterology Department, Hospital de Base do Distrito Federal, Hospital da Criança de Brasília, Centro Universitário de Brasília, Brasília, Distrito Federal, Brazil | [65]Department of Pediatric Gastroenterology, Le Bonheur Children's Hospital and The

University of Tennessee Health Science Center, Memphis, Tennessee, USA | [66]Mitera Children's Hospital, Athens, Greece | [67]First Department of Paediatrics, Semmelweis University, Budapest, Hungary | [68]Division of Pediatric Gastroenterology, Hospital Criança Conceição, Grupo Hospitalar Conceição, Porto Alegre, Rio Grande do Sul, Brazil | [69]Division of Pediatric Gastroenterology, Rady Children's Hospital San Diego, University of California San Diego, San Diego, California, USA | [70]Division of Gastroenterology and Hepatology, First Department of Paediatrics, University of Athens, "Aghia Sofia" Children's Hospital, Athens, Greece | [71]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Miami Transplant Institute, University of Miami, Miami, Florida, USA | [72]Paediatric Gastroenterology Unit, Cruces University Hospital, Bilbao, Spain | [73]Faculty of Health Sciences, Wits Donald Gordon Medical Centre, University of the Witwatersrand, Johannesburg, South Africa | [74]Section of Pediatric Gastroenterology, Department of Pediatrics, University of Manitoba, Winnipeg, Canada | [75]Centro Hospitalar Universitário de Santo António, Centro Materno-Infantil do Norte Albino Aroso, Porto, Portugal | [76]UCIBIO – Applied Molecular Biosciences Unit, Biochemistry Laboratory, Department of Biological Sciences, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal | [77]Pediatric Gastroenterology Hepatology and Nutrition Unit, Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain | [78]Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, LMU Munich, Munich, Germany | [79]European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hamburg, Germany | [80]Pediatric Gastroenterology/Hepatology Center Lisbon, Lisbon, Portugal | [81]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Eastern Ontario, Ottawa, Canada | [82]Department of Hepatology and Gastroenterology, Biodonostia Health Research Institute – Donostia University Hospital, Universidad del País Vasco (UPV/EHU), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), San Sebastián, Spain | [83]Institute of Liver Studies, King's College London, London, UK | [84]Toronto General Hospital University Health Network, Toronto, Canada | [85]Institute of Health Policy, Management and Evaluation, Toronto, Canada

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Carla Fiorella Murillo Perez: Employee of Gilead; Shannon M. Vandriel: Employee of Mirum Pharmaceuticals Inc.; Jian-She Wang: Consultant for Ipsen Biopharmaceuticals Inc., Mirum Pharmaceuticals Inc., and Qing Bile Therapeutics Inc.; Li-Ting Li: nothing to disclose; Huiyu She: nothing to disclose; Irena Jankowska: nothing to disclose; Piotr Czubkowski: nothing to disclose; Dorota Gliwicz-Miedzińska: nothing to disclose; Emmanuel M. Gonzales: Consultant for: Mirum Pharmaceuticals Inc., Ipsen Biopharmaceuticals Inc; Emmanuel Jacquemin: Consultant for CTRS, Theravia and Vivet Therapeutics, France; Jérôme Bouligand: nothing to disclose; Lorenzo D'Antiga: Consultant for: Mirum Pharmaceuticals Inc., Ipsen Biopharmaceuticals Inc., Alexion, Astra Zeneca, Vivet Therapeutics, Spark, Genespire, Tome, Advanza Pharma; Emanuele Nicastro: nothing to disclose; Björn Fischler: Consultant for Ipsen Biopharmaceuticals Inc.; Henrik Arnell: consultant for Ipsen Biopharmaceuticals Inc., Baxter, Mirum Pharmaceuticals Inc.; Susan Siew: nothing to disclose; Michael Stormon: nothing to disclose; Kathleen M. Loomes: Consultant for Mirum Pharmaceuticals Inc., Ipsen Biopharmaceuticals Inc., and Travere Therapeutics Inc.; David A. Piccoli: nothing to disclose; Elizabeth B. Rand: nothing to disclose; James E. Squires: nothing to disclose; Saul J. Karpen: Consultant for Ipsen Biopharmaceuticals Inc., Mirum Pharmaceuticals Inc.; Rene Romero: nothing to disclose; Mureo Kasahara: nothing to disclose; Zerrin Önal: nothing to disclose; Étienne Sokal: nothing to disclose; Tanguy Demaret: nothing to disclose; Sabina Wiecek: nothing to disclose; Florence Lacaille: Consultant for Alexion; Dominique Debray: nothing to disclose; Winita Hardikar: Consultant for Ipsen, Advanz Pharma; Sahana Shankar: nothing to disclose; Pamela L. Valentino: nothing to disclose; Shikha S. Sundaram: Consultant for Mirum Pharmaceuticals Inc., Ipsen Biopharmaceuticals; Alexander Chaidez: nothing to disclose; Noelle H. Ebel: Consultant for Mirum Pharmaceuticals Inc.; Jeffrey A. Feinstein: nothing to disclose; Orith Waisbourd-Zinman: nothing to disclose; Henry C. Lin: nothing to disclose; Nathalie Rock: Consultant for Mirum Pharmaceuticals Inc.; Henkjan J. Verkade: consultant for Danone/Nutricia Research, Ausnutria BV, Ipsen Biopharmaceuticals Inc., GMP + Orphan, Mirum Pharmaceuticals Inc., Intercept and Vivet; M. Kyle Jensen: nothing to disclose; Catalina Jaramillo: nothing to disclose; Kyung Mo Kim: nothing to disclose; Seak Hee Oh: nothing to disclose; Jernej Brecelj: nothing to disclose; Seema Alam: nothing to disclose; Giuseppe Indolfi: Consultant for Mirum Pharmaceuticals Inc.; Niviann Blondet: nothing to disclose; Rima Fawaz: nothing to disclose; Silvia Nastasio: nothing to disclose; Pier Luigi Calvo: nothing to disclose; Gabriella Nebbia: nothing to disclose; Cigdem Arikan: nothing to disclose; Catherine Larson-Nath: nothing to disclose; Andréanne N. Zizzo: nothing to disclose; Thomas Damgaard Sandahl: nothing to disclose; Christos Tzivinikos: nothing to disclose; Nehal M. El-Koofy: nothing to disclose; Mohamed A. Elmonem: nothing to disclose; Amal A. Aqul: nothing to disclose; Wikrom Karnsakul: nothing to disclose; Pinar Bulut: nothing to disclose; Nanda Kerkar: Advisory Board for Ipsen Biopharmaceuticals Inc. and Mirum Pharmaceuticals Inc.; Victorien M. Wolters: nothing to disclose; Amin J. Roberts: nothing to disclose; Helen M. Evans: nothing to disclose; Maria Camila Sanchez: nothing to disclose; Maria Lorena Cavalieri: nothing to disclose; Deirdre A. Kelly: nothing to disclose; Jane Hartley: nothing to disclose; Way Seah Lee: nothing to disclose; Christina Hajinicolaou: nothing to disclose; Chatmanee Lertudomphonwanit: nothing to disclose; Ryan T. Fischer: Speaker and Consultant for Ipsen Biopharmaceuticals Inc. and Mirum Pharmaceuticals Inc.; Jesus Quintero Bernabeu: nothing to disclose; Ruben E. Quiros-Tejeira: nothing to disclose; Cristina Targa Ferreira: nothing to disclose; Elisa Carvalho: nothing to disclose; John Eshun: nothing to disclose; Aglaia Zellos: nothing to disclose; Antal Dezsőfi: nothing to disclose; Raquel Borges Pinto: nothing to disclose; Kathleen Schwarz: Research grant Ipsen Biopharmaceuticals Inc. and Consultant, Mirum Pharmaceuticals Inc; Maria Rogalidou: nothing to disclose; Jennifer Garcia: nothing to disclose; María Legarda Tamara: nothing to disclose; Marisa Beretta: nothing to disclose; Quais Mujawar: Advisory Board for Alexion Pharma; Ermelinda Santos-Silva: Consultant for Mirum Pharmaceuticals Inc., and Ipsen Biopharmaceuticals Inc; Cristina Molera Busoms: nothing to disclose; Eberhard Lurz: nothing to disclose; Cristina Gonçalves: nothing to disclose; Carolina Jimenez-Rivera: nothing to disclose; Jesus M. Banales: nothing to disclose; Richard J. Thompson: Consultant for Shire, Ipsen Biopharmaceuticals Inc., Mirum Pharmaceuticals Inc., Horizon Pharmaceuticals, Sana Biotechnology, GenerationBio, Retrophin and Qing Bile Therapeutics Inc.; Bettina E. Hansen: Consultant for Mirum Pharmaceuticals Inc., Ipsen Biopharmaceuticals Inc., Chemomab, Calliditas, Intercept, Cyma Bay, unrestricted grants from Cyma bay, Intercept, Mirum Pharmaceuticals Inc., and Ipsen Biopharmaceuticals Inc.; Binita M. Kamath: Consultant for Mirum Pharmaceuticals Inc., Ipsen Biopharmaceuticals Inc., and Audentes Therapeutics, unrestricted educational grants from Mirum Pharmaceuticals Inc., and Ipsen Biopharmaceuticals Inc.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** liv70423-sup-0001-DataS1.docx.