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

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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.

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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

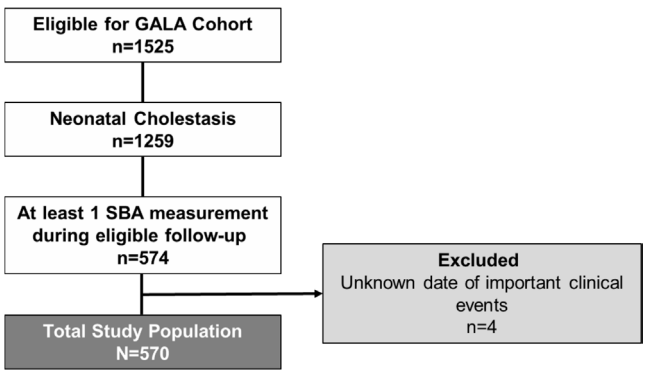

FIGURE 1 | Flowchart of patients included in the study population. Eligible follow-up is defined as the time period prior to Kasai, trial enrollment, and 18 years of age. Kasai, surgical biliary diversion, trial enrollment and death were considered important clinical events.

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).

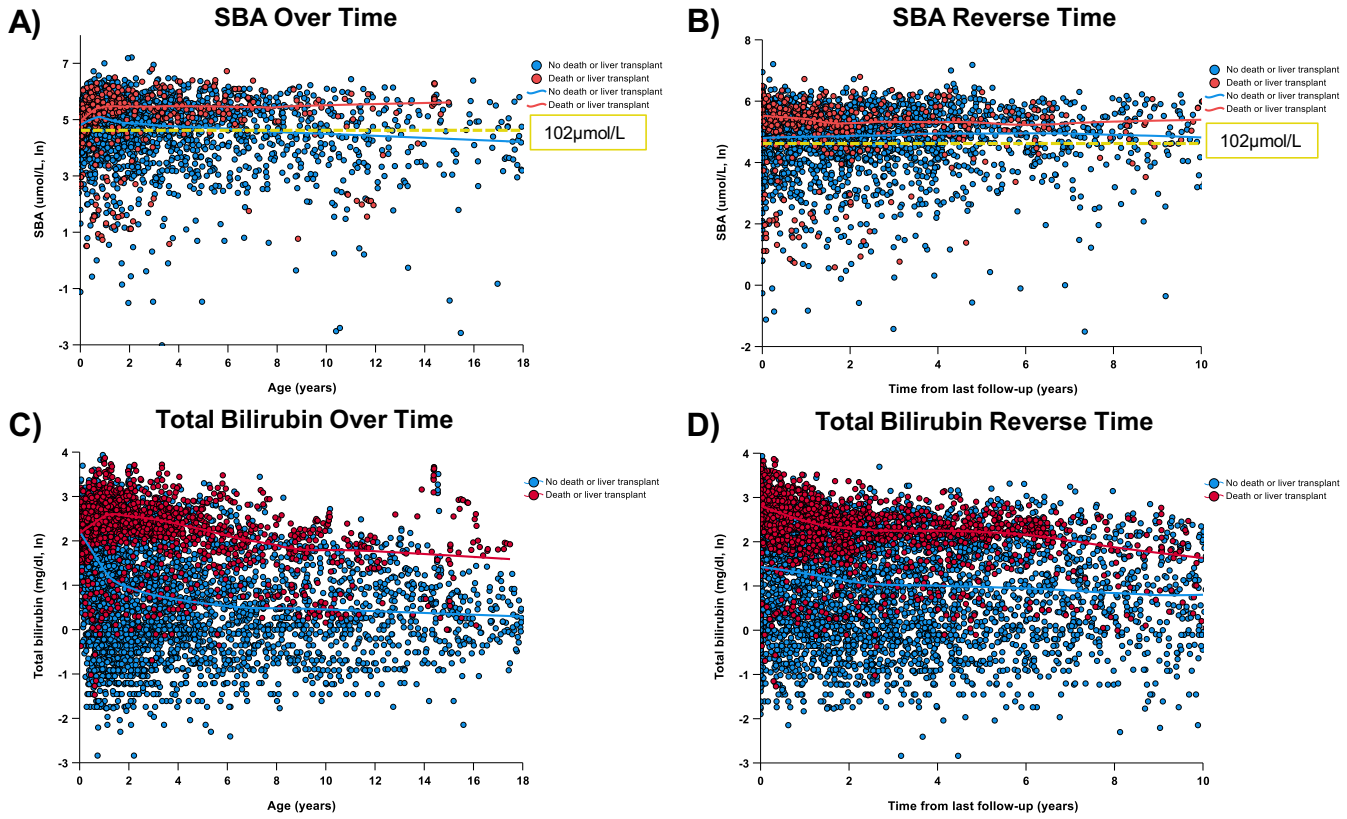

FIGURE 2 | Scatter plot representing trends in (A) serum bile acid (SBA) from birth until last follow-up; (B) SBA in reverse time order where time zero is the value measured at last clinical follow-up; (C) total bilirubin from time of birth; and (D) total bilirubin in reverse time order where time zero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

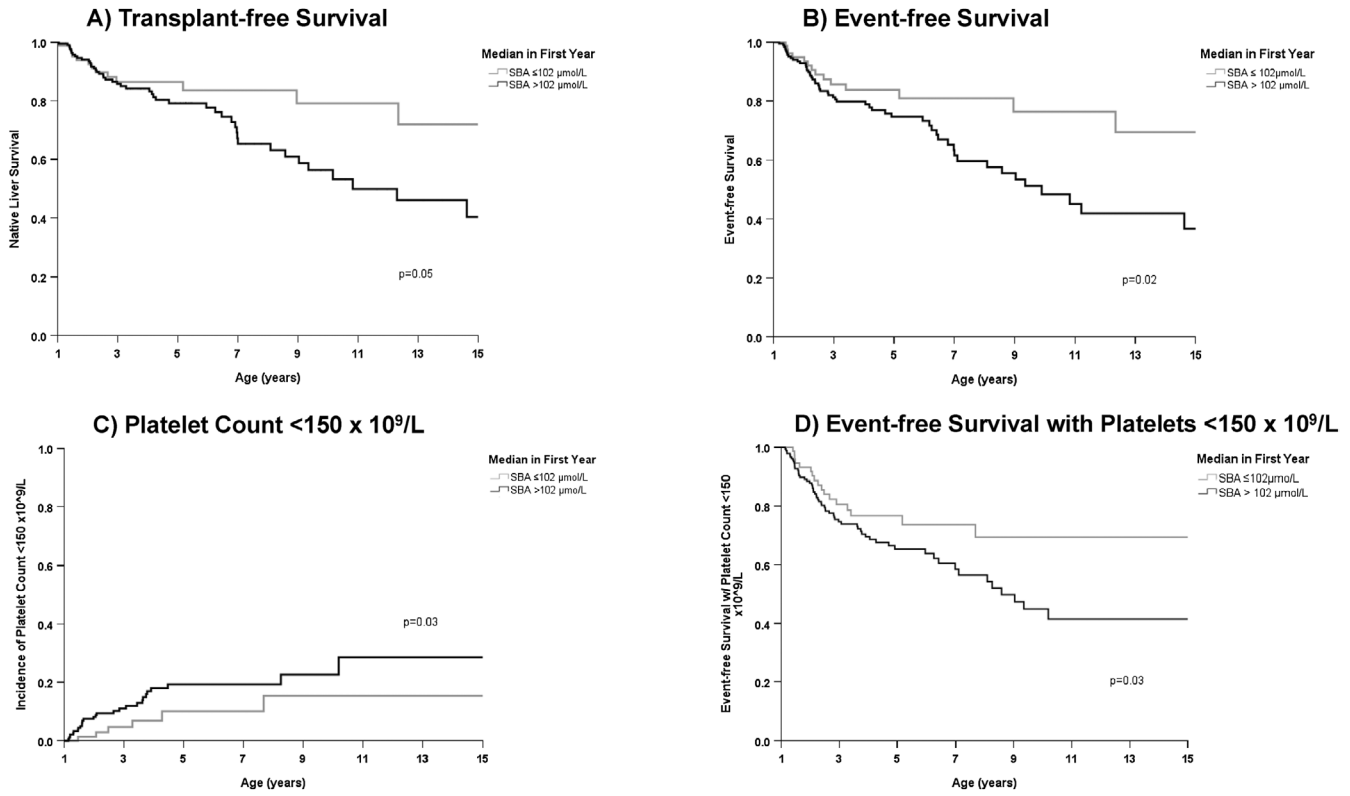

FIGURE 3 | (A) Native liver survival (NLS); (B) event-free survival (EFS); (C) time to first platelet count $< 150 \times 10^9$/L, and (D) event-free survival (EFS) with time to first platelet count 150×10^9/L according to median serum bile acids (SBA) in the first year.

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.

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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. 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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.