Received: 5 May 2025 | Accepted: 6 June 2025

DOI: 10.1002/jpn3.70131

JPGN

INVITED REVIEW

Hepatology

Advances in prognostic biomarkers for biliary atresia: Current insights and future directions

Ahmad Anouti[1] | **Pavithra Sudhakara**[1,2] | **Chelsea Pratt**[1,2] | **Reena Mourya**[1,2] | **Lisa VanWagner**[3] | **Pranavkumar Shivakumar**[1,2] | **Sindhu Pandurangi**[1,2]

[1]Department of Pediatrics, Children's Medical Center Dallas, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[2]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Medical Center Dallas, Dallas, Texas, USA

[3]Department of Medicine and Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence

Pranavkumar Shivakumar, and Sindhu Pandurangi, UT Southwestern Medical Center I Children's Medical Center Dallas, 1935 Medical District Dr, Dallas, TX 75235, USA. Email: pranav.shivakumar@utsouthwestern.edu and sindhu.pandurangi@utsouthwestern.edu

Funding information

NASPGHAN Foundation George Ferry Young Investigator Award

Abstract

Biliary atresia (BA) is a progressive, fibrosing cholangiopathy of infancy characterized by inflammatory obstruction of the bile ducts, ultimately leading to end-stage liver disease if untreated. Early diagnosis and timely surgical intervention via hepatoportoenterostomy (HPE) are critical for improving outcomes; however, prognostication remains challenging due to heterogeneous responses to surgery and variable clinical trajectories. This review provides a comprehensive synthesis of current research on prognostic biomarkers in BA, encompassing clinical indicators, routine laboratory parameters, novel serum biomarkers, histopathologic features, hepatic gene expression profiles, imaging modalities, and both in vitro and computational prognostic modeling systems. While traditional clinical factors, such as age at HPE and postoperative serum bilirubin levels, continue to serve as important predictors of outcome, they lack sufficient discriminatory power for individualized risk stratification. Recent advances have identified emerging biomarkers, including inflammatory cytokines, immune activation markers, and indicators of fibrosis and extracellular matrix remodeling, which show potential in correlating with disease progression and native liver survival. Imaging modalities such as ultrasound elastography have also demonstrated promise in noninvasively assessing liver stiffness and predicting clinical outcomes. Furthermore, the identification of hepatic gene expression signatures and multigene prognostic classifiers offers new avenues for precision risk assessment. However, most of these advancements have not translated into clinical practice due to small sample sizes and limited external validation. Future research efforts must focus on large-scale, multicenter studies to validate findings and establish robust, integrative prognostic models that can inform clinical decision-making and facilitate personalized therapeutic strategies in BA.

KEYWORDS

biliary atresia, biomarker, prediction, prognosis

1 | INTRODUCTION

Biliary atresia (BA) is a neonatal fibrosing cholangiopathy that progresses to cirrhosis and liver failure if left untreated.[1] Early diagnosis and timely surgical intervention via hepatoportoenterostomy (HPE) can improve clinical outcomes.[2] Approximately 50% of BA patients will require liver transplantation (LT) by age two.[3] Beyond infancy, native liver survival in BA following HPE into young

adulthood ranges from 23% to 44%, with the majority undergoing LT by 21 years of age.[4–8]

Due to wide variation in clinical trajectories, ranging from rapid progression toward LT in infancy to decades of native liver survival, clinicians need reliable tools that can predict an individual patient's disease course. Accurate prognostication can guide the timing of transplant referral, intensity of surveillance, and future selection for emerging disease-modifying trials. There are currently no widely accepted or consistently applied measures for predicting post-HPE prognosis.[4] Beyond standard laboratory values, several investigative tools, including imaging techniques, histopathological assessments, novel serum biomarkers, and hepatic gene expression profiling, have been explored to improve prognostic accuracy (Figure 1). This review aims to provide a comprehensive and updated overview of the current landscape of prognostic biomarkers in BA, highlighting emerging tools that may enhance future risk stratification and inform clinical decision-making.

What is Known

- Early bilirubin clearance after hepatoportoenterostomy and younger age at surgery have been main prognostic benchmarks for biliary atresia.
- Imaging, histology and single-analyte serum tests have been studied, yet no universally accepted risk-stratification tool exists.

What is New

- Early studies suggest novel serum biomarkers including serum bile acids, inflammatory cytokines, markers of fibrosis/extracellular matrix remodeling may improve risk prediction.
- Multi-gene hepatic signatures suggest that inflammatory versus fibrotic subtypes track with biliary atresia (BA) prognosis.
- Shear-wave elastography measurements both pre and post hepatoportoenterostomy hold prognostic value.
- Pilot integrative models (clinical + imaging + omics) show encouraging discrimination.

2 | CLINICAL FEATURES AND STANDARD LABORATORY TESTS

Early diagnosis and the timing of HPE are widely recognized as critical predictors of prognosis in BA in large scale studies.[2,9,10] Favorable surgical outcomes are associated with HPE performed before 45–60 days of life. In fact, a recent systematic review and meta-analysis of 564 BA patients demonstrated that HPE performed before 30 days of age is associated with a substantial increase in native liver survival at 5, 10, and even 20 years postoperatively.[2]

A study conducted by the Childhood Liver Disease Research Network (ChiLDReN) found a total serum bilirubin level < 2 mg/dL at 3 months post-HPE was predictive of transplant-free survival at 2 years (86% TB < 2 mg/dL vs. 20% TB > 2 mg/dL).[11] Other studies similarly show a clear difference in 2 year transplant-free survival between children with total serum bilirubin < 2 mg/dL and those with total bilirubin > 6 mg/dL (84% vs. 16%).[12] However, normalization of serum bilirubin levels following HPE does not consistently predict favorable long-term clinical outcomes. Among infants who achieve bilirubin normalization, a substantial proportion continue to experience complications, including splenomegaly (71%), thrombocytopenia (45%), and ascites (18%).[11] Notably, 18% of these infants still require liver transplantation within the first 2 years of life, despite initial biochemical improvement.[11]

The prognostic value of gamma-glutamyl transferase (GGT) has also been investigated as a potential biomarker. Ihn et al. reported that GGT levels > 550 IU/L at 5 months post-HPE were associated with worse outcomes, even in the absence of jaundice (hazard ratio [HR]: 1.74; 95% CI: 1.40–2.87).[13] In another study, Shankar et al. found that low GGT levels (< 200 IU/L) at the time of presentation were associated with poorer prognosis compared to patients presenting with higher GGT levels.[14] Similarly, Sun et al. demonstrated that the 2-year native liver survival rate was significantly lower in patients with GGT levels ≤ 300 IU/L compared to those with GGT > 300 IU/L (HR: 1.80; 95% CI: 1.38–2.33).[15] Thus, both low and persistently high GGT levels may have prognostic implications in BA, depending on the clinical context and timing of measurement.

In addition to individual laboratory values, the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) has been explored as a prognostic tool in BA, particularly for assessing hepatic fibrosis.[16] Variability in thresholds has been noted across studies. Grieve et al. reported that an APRI > 1.22 had 75% sensitivity and 84% specificity for cirrhosis in BA, while APRI > 3.0 was associated with persistent jaundice and the need for liver transplantation. Muntean et al. observed that patients in the highest APRI quartile had a significantly lower 5-year native liver survival (34%) compared to those in the lowest quartile (54%).[17] Suominen et al. identified an APRI > 1.34 as predictive of increased transplant risk and APRI correlated with histological portal fibrosis and CD34-positive microvessels in the centrizonal

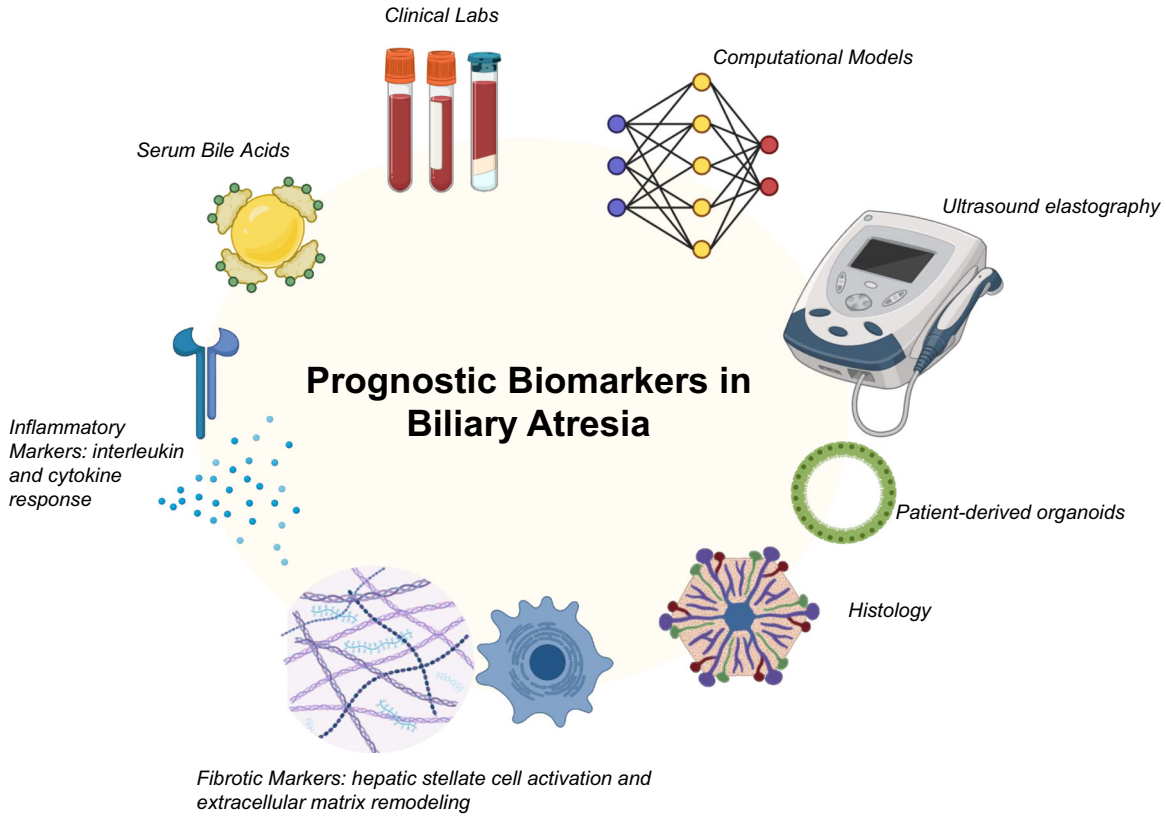

FIGURE 1 Prognostic biomarkers in biliary atresia (BA). Key modalities informing outcome prediction summarized in this review are clinical laboratory values, serum bile acids, inflammatory cytokines and interleukins, fibrosis and extracellular matrix markers, liver histology, cholangiocyte organoid models, ultrasound elastography, and computational modeling. These approaches aim to enhance risk stratification in BA.

region.[18] APRI is a promising noninvasive marker with potential prognostic value in BA.

3 | NOVEL SERUM MARKERS

A growing body of research has focused on identifying novel serum biomarkers with prognostic significance in BA, aiming to complement or surpass traditional clinical indicators (Table 1).

3.1 | Serum bile acids

Despite normalization of total bilirubin following HPE, serum bile acids often remain elevated, indicating incomplete recovery of bile acid excretion. A 2023 ChiLDReN study analyzing serum samples from 137 infants with normalized bilirubin levels at 6 months postoperatively identified a serum bile acid threshold of < 40 μmol/L as predictive of improved liver biochemistries, including higher albumin and platelet counts at 2 years. Infants with bile acids ≤ 40 μmol/L had a 10-year cumulative incidence of liver transplant or death of 8.5% (95% CI: 1.1%–26.1%), compared to 42.9% (95% CI: 28.6%–56.4%) among those > 40 μmol/L.[19]

3.2 | Inflammatory cytokines

Circulating cytokines, IL-8, IL-18, and IL-34, have also been evaluated as potential negative prognostic markers in BA. IL-8 contributes to bile duct injury through neutrophil recruitment and immune activation.[20] Udomsinprasert et al. reported that higher plasma IL-8 levels were associated with significantly reduced survival in BA patients.[21] Similarly, Bessho et al. identified IL-8 and laminin subunit gamma 2 (LAMC2) as part of a BA-specific hepatic gene expression signature, linking IL-8 overexpression with disease progression. In a murine model of BA, disrupting IL-8 signaling reduced bile duct injury and improved survival.[22] Moreover, serum IL-18 has also been found to be significantly associated with increased jaundice and decreased survival time in BA.[23] Honsawek et al. found that higher IL-34 levels were linked to decreased survival and positively correlated with liver stiffness.[24]

TABLE 1 Novel serum prognostic biomarkers in biliary atresia.

Marker	Key characteristics	Clinical relevance	Prognostic utility and significant findings
Total serum bile acids (TBA)[19]	Reflects bile acid metabolism and congestion.	Elevated even with normal total bilirubin levels, indicating ongoing congestion.	TBA > 40 μmol/L at 6 months post-HPE associated with worse outcomes, advanced liver disease.
Cytokines (IL-8[20–22], IL-18[23], IL-34[24], IL-12p40[25])	Soluble polypeptides involved in immune responses.	Elevated in BA patients compared to healthy controls.	Elevated IL-8, IL-18, and IL-34 associated with worse outcomes (jaundice, fibrosis, hepatic dysfunction). Elevated IL-12p40 predicts 3-month jaundice-free survival (81% PPV, 83% NPV), fourfold increased 3-year survival with native liver.
Matrix metalloproteinase-7 (MMP-7)[26]	Matrix metalloproteinase involved in tissue remodeling.	Diagnostic marker for BA differentiation from other cholestatic diseases.	Elevated levels associated with non-function post-HPE, increased risk of poor outcomes. MMP-7 at 6 week and 3 months post HPE predict survival with native liver at 2 years (AUC 0.796, CI 0.707–0.867 and AUC 0.861, CI:0.781–0.920, respectively)
Cartilage oligomeric matrix protein (COMP)[27]	Tissue remodeling mediated in part by cartilage oligomeric matrix protein.	Correlated with hepatic fibrosis in BA.	Higher COMP levels associated with poor survival outcomes, particularly in patients with advanced fibrosis.
Clusterin (CLU)[28]	Extracellular chaperone linked to fibrosis and liver dysfunction.	Lower levels in BA patients with poor outcomes.	Reduced CLU linked to poor survival rates post-HPE (AUC 0.85, sensitivity 81.5%, specificity 73.5%).
Fibroblast growth factor (FGF-19)[29]	Fibroblast growth factor linked to bile acid regulation.	Increased serum levels associated with poor KPE outcomes.	FGF-19 < 109 pg/mL predicts native liver survival (HR 4.31, CI: 1.90–9.74) and correlates with primary bile acid levels.
Mac-2 binding protein glycan isomer (M2BPGi)[30]	Glycosylation-modified protein, reflects liver fibrosis.	Elevated in BA patients with advanced liver fibrosis.	M2BPGi predicts advanced fibrosis (≥F3) and correlates with liver stiffness and fibrosis stages. Cutoff of 1.84 COI predicts cirrhosis (AUC 0.93, sensitivity 91%, specificity 96%).

Abbreviations: AUC, area under the curve; BA, biliary atresia; CI, confidence interval; HPE, hepatoportoenterostomy; HR, hazard ratio; IL, interleukin.

Conversely, IL-12p40 has been identified as a favorable prognostic marker. Preoperative serum IL-12p40 levels ≥ 33 pg/mL predicted jaundice-free status at 3 months post-HPE with positive and negative predictive values of 81% and 83.3%, respectively. Higher IL-12p40 levels were also associated with a fourfold increase in 3-year native liver survival.[25] Furthermore, a recent ChiLDReN study identified elevated serum granulocyte-macrophage colony-stimulating factor (GM-CSF) as a positive prognostic biomarker in predicting successful biliary drainage post-HPE, driven by GM-CSF's role in modulating polarization of macrophages.[31]

3.3 | Markers of extracellular matrix (ECM) remodeling/fibrosis

Circulating markers of ECM remodeling and fibrosis have been increasingly studied for their prognostic utility in BA, as they may reflect underlying hepatic disease progression. Matrix metalloproteinase-7 (MMP-7), a key regulator of ECM turnover, has been established as a highly sensitive diagnostic biomarker for BA.[32–38] Beyond diagnosis, both baseline and post-HPE serum levels of MMP-7 have been linked to reduced biliary drainage and accelerated fibrosis progression in a single center study, supporting its prognostic relevance.[26,39]

Other matrix-related proteins further support the link between ECM remodeling and clinical outcomes. Udomsinprasert et al. reported that elevated circulating levels of cartilage oligomeric matrix protein (COMP) were associated with advanced hepatic fibrosis and poorer survival in BA patients.[27] In a subsequent study, the same group identified significantly lower serum levels of clusterin (CLU), an extracellular chaperone involved in tissue remodeling, in BA patients with jaundice, advanced fibrosis, and decreased survival post-HPE (AUC = 0.85; sensitivity 81.5%, specificity 73.5%).[28] Nyholm et al. evaluated fibroblast growth factor 19 (FGF19),

another ECM-associated molecule, and found serum FGF19 levels < 109 pg/mL were predictive of reduced native liver survival (HR: 4.31, 95% CI 1.90–9.74).[29] Additionally, serum Mac-2 binding protein glycan isomer (M2BPGi), is a marker produced by hepatic stellate cells and previously validated in chronic hepatitis B and C and metabolic associated steatotic liver disease.[40] Ueno et al. demonstrated that M2BPGi levels significantly correlated with hepatic fibrosis severity in BA, predicting cirrhosis with high accuracy (AUC 0.93, sensitivity and specificity of 91% and 96%, respectively).[30] These outcomes support the use of ECM remodeling markers as noninvasive BA fibrosis monitoring and long-term prediction tools.

4 | HISTOLOGY

In continuity with molecular serum-based biomarkers, liver histopathological features at the time of BA diagnosis have also been studied for their prognostic value. Histologic scoring systems in BA typically assess the degree of hepatic inflammation, fibrosis, and ductal proliferation. Regardless of age, the data strongly indicate that severe fibrosis at the KP results in a poor outcome.[41] Xu et al. developed a BA-specific histologic staging system focused on fibrosis severity, which was found to be strongly associated with native liver survival.[42] Patients classified as Stage 3 or 4 had significantly worse prognoses, with 83.3% of stage 4 patients dying or requiring liver transplantation.[42] However,

TABLE 2 Hepatic gene expression in biliary atresia.

Marker	Key characteristics	Clinical relevance	Prognostic utility and significant findings
Sonic Hedgehog (SHH)[44]	Morphogen gene crucial in regulating cell differentiation, proliferation, and patterning during development	Elevated in BA compared to healthy controls	Associated with decreased jaundice-free survival. Abnormal expression leads to cirrhosis. Reactionary expression of SHH and downstream transcription factors leads to bile duct damage
Secretin receptor (SCTR)[45]	Regulates ductal bile secretion and helps in maintaining biliary homeostasis	Elevated levels associated with poor HPE outcomes	Elevated SCTR levels in BA patients at HPE linked to 34%–54% lower 5-year native liver survival
Alpha smooth muscle actin (α-SMA)[46]	Hepatic stellate activation increases the expression of collagen and alpha smooth muscle actin	Elevated levels in BA. Associated with increased fibrosis, reduced jaundice clearance and lower native liver survival	BA patients with elevated α-SMA expression had decreased native survival (57.1 vs. 92.3% in high vs. low expression groups)
Collagen hybridizing peptide (CHP)[47]	CHP is marker to quantify hepatic fibrosis	Higher CHP levels associated with poor outcome of HPE	Higher CHP levels significantly associated with a 3.6-fold increased risk of LT by age 4, and increased to nearly sevenfold when controlling sex, bilirubin and albumin post HPE
Autotaxin (ATX)[48]	Fibrogenic enzyme produced by lysophosphatidic acid	Elevated in BA patients with fibrosis	Correlates with severe liver stiffness (β: 0.012) and positively correlates with Metavir fibrosis stage in BA ($r = 0.79$)
m6A and THY1[49]	Proteins involved in extracellular matrix organization and hepatic stellate cell activation	Elevated levels in BA patients compared to controls	Correlates with worse increased fibrosis and poor prognosis
Signal transducer and activator of Transcription 3 (STAT-3)[50]	Mediates cell signaling from cytokines and growth factors	Decreased expression linked to biliary epithelial cell damage	Reduced expression of STAT3 in BA patients lead to increased production of the CXCL1, contributing to biliary epithelial cell damage.
Ki67[51]	Marker for cellular proliferation	High Ki67 area proportion is a significant predictor of poor prognosis	Ki67 area proportion ≥0.77% significantly predicted worse outcomes (HR: 9.29, 95% CI 3.47–24.91).
Interleukin 17A (IL-17A)[52]	Drives intrahepatic bile duct injury in BA	High levels of IL-17A+ cells in the liver are associated with increased macrophage infiltration	IL-17A+ cells were prevalent in the portal triads in BA subjects and progressive disease

Abbreviations: BA, biliary atresia; HPE, hepatoportoenterostomy.

other studies suggest that histologic features beyond fibrosis may offer superior prognostic utility. The extent of biliary proliferation, assessed by cytokeratin 7 staining, was independently associated in one study with reduced 1-year native liver survival and was the most significant predictor of outcome, surpassing both patient age and fibrosis stage.[43]

4.1 | Hepatic gene expression

While histological analysis provides important information on liver injury and fibrosis, emerging data on hepatic gene expression is offering deeper insights into the molecular underpinnings of BA and its prognostic implications (Table 2).

4.1.1 | Markers of hepatobiliary development

The SHH morphogen gene plays a critical role in regulating cellular differentiation, proliferation, and patterning during hepatobiliary development.[53] In BA, reactive upregulation of SHH and its downstream transcriptional targets in response to bile duct injury is associated with decreased jaundice-free survival.[44,53] Protein expression of SHH related factor GLI family zinc finger-2 and epithelial mesenchymal transition related factors were high in BA patients, suggesting the enhancement of SHH signaling pathway in BA cirrhosis.[54]

Similarly, the hepatic secretin receptor (SCTR), which regulates ductal bile secretion and biliary epithelial homeostasis, has shown prognostic relevance. In an analysis of BA liver specimens using real time polymerase chain reaction and immunohistochemistry, Godbole et al. reported that higher SCTR expression at the time of HPE was associated with a 34%–55% reduction in 5-year native liver survival. Furthermore, median SCTR mRNA levels were significantly higher in patients who failed to achieve jaundice clearance post-HPE (75-fold vs. 42-fold). [45,55]

4.1.2 | Markers of fibrosis and extracellular matrix remodeling

Building upon insights from hepatic gene expression, several liver tissue-based markers reflecting fibrosis and ECM remodeling have been investigated for their prognostic significance in BA. Activation of hepatic stellate cells leads to increased expression of collagen and alpha-smooth muscle actin (α-SMA), both key mediators of fibrogenesis.[56] Kerola et al. demonstrated significantly elevated hepatic collagen type I expression in BA patients compared to controls (area fraction: 15.6% vs. 6.8%), along with increased periductal α-SMA expression in 64% of patients, even after successful HPE.[57] Elevated α-SMA levels have been associated in other studies with increased fibrosis, reduced jaundice clearance, and decreased native liver survival.[46,56] Additionally, combined high expression of hepatic glypican-3 and α-SMA was linked to poorer outcomes, with a native liver survival rate of 57.1% compared to 92.3% in those with low expression.[46] In a pilot study by Jaramillo et al., collagen hybridizing peptide (CHP) was used to quantify fibrosis in liver tissue from 21 BA patients. Higher CHP intensity at the time of HPE was associated with a significantly increased risk of liver transplantation within 1 year (50% in the high-CHP group vs. 27% in the low-CHP group).[47] Quantified fibrosis by CHP predicted a 3.6-fold increased risk of transplantation by age 4, which increased to nearly sevenfold after adjusting for sex, bilirubin, and albumin levels at 3 months post-HPE.[47]

In addition to traditional markers, several novel pro-fibrotic factors have recently been identified in BA. Autotaxin, a fibrogenic enzyme produced by lysophosphatidic acid, is significantly elevated in BA and correlates strongly with both severe liver stiffness (β coefficient: 0.012) and Metavir fibrosis stage ($r = 0.79$).[48,58] Similarly N6-methyladenosine (m6A) and thymus cell antigen-1 (THY1), both implicated in extracellular matrix organization and hepatic stellate cell activation, are markedly increased in BA patients relative to controls and linked to poorer overall prognosis.[49]

4.1.3 | Cellular proliferation and immune markers

Beyond ECM remodeling, markers of cellular proliferation and immune activation have emerged as potential prognostic indicators in BA. Signal transducer and activator of transcription 3 (STAT3) plays a central role in mediating signals from cytokines and growth factors.[59] Fu et al. demonstrated that reduced hepatic expression of STAT3 in BA patients led to increased production of the neutrophil chemoattractant CXCL1 and biliary epithelial cell injury. In murine models, STAT3 activation was shown to attenuate inflammation and prolong survival beyond 25 days.[50] The cellular proliferation marker Ki67 has similarly shown prognostic value, as higher expression in BA correlates with poor native liver survival post-HPE. Specifically, a Ki67 area proportion ≥ 0.77% significantly predicted worse outcomes (HR: 9.29, 95% CI 3.47–24.91).[51]

4.1.4 | Immune activation

In addition to proliferative markers, immune cell polarization and cytokine signaling in the liver

influence disease progression. Nagayabu et al. examined the prognostic role of hepatic macrophage polarization, reporting that a higher ratio of anti-inflammatory, fibrosis-associated M2 macrophages correlated with improved native liver survival and reduced need for liver transplantation within 2 years.[60] Conversely, patients with predominant pro-inflammatory M1 macrophages experienced increased rates of postoperative cholangitis and poorer outcomes.[60] Immune interactions involving dendritic cells, Th17 cells, and macrophages have also been identified as key drivers of intrahepatic bile duct injury in BA. This pathway primes naïve $CD4^+$ T cells to produce IL-17A, which stimulates cholangiocytes to release chemokines such as CCL2, thereby recruiting $CD68^+$ inflammatory macrophages.[52] Specifically, dendritic cells prime naïve CD4 + T cells to produce IL-17A, triggering CCL2 secretion from cholangiocytes, which subsequently recruits inflammatory macrophages and intensifies bile duct injury.[52] In line with these findings, Lages et al. showed prominent IL-17A-positive cell infiltration in the portal triads of BA patients with progressive disease necessitating liver transplantation within 2 years of age.[52]

4.1.5 | Multi-gene signatures

Expanding upon single-gene and pathway-level analyses, recent studies have identified multi-gene expression profiles that enhance prognostic stratification in BA. Luo et al. defined a 14-gene molecular signature, combined with total bilirubin levels 3 months post-HPE, which strongly correlates with survival outcomes at 2 years of age. In the low-survival group, fibrosis-related genes were prominently expressed and associated with a HR of 2.2 for poor outcomes (95% CI: 1.4–3.6). In contrast, high expression of genes involved in glutathione metabolism was linked to improved survival, and treatment with *N*-acetylcysteine in experimental models attenuated liver fibrosis.[61]

Similarly, Moyer et al. identified distinct molecular subtypes in BA based on gene expression patterns. Patients with an inflammatory molecular signature exhibited overexpression of 77 genes primarily associated with immune system activation, including pathways related to T-cell and natural killer (NK) cell function.[62] Clinically, this group was characterized by earlier age at diagnosis and better transplant-free survival, suggesting that the inflammatory signature may represent an earlier, potentially more responsive disease stage. In contrast, a fibrosis-associated signature marked by upregulation of 38 genes involved in extracellular matrix production and tissue remodeling was linked to more advanced disease and poorer outcomes.[62]

4.2 | Imaging tools

In addition to molecular and histological markers, imaging modalities, particularly ultrasound elastography based techniques, have emerged as valuable tools for assessing disease progression and predicting outcomes in BA post-HPE. Shear wave elastography (SWE), a quantitative ultrasound technique, has shown promise in identifying advanced hepatic fibrosis both pre- and postoperatively, with variable cut-offs in different studies. Before HPE, liver stiffness values ≥ 17.5 kPa were predictive of significant fibrosis (F3–F4), with 63.6% sensitivity and 86.4% specificity.[63] Postoperatively, patients with poor outcomes exhibited significantly higher liver stiffness (11.71 kPa) compared to those with good outcomes (6.11 kPa).[64] A study by Yoon et al. demonstrated that a liver SWE cutoff of 10.3 kPa on the day of surgery predicted poor outcomes with 100% sensitivity and 73.9% specificity, while a threshold of 11.4 kPa on postoperative Day 5 provided 75% sensitivity and 73.9% specificity.[63] SWE has also been useful in predicting native liver survival in BA patients following HPE.[65] Patients with liver stiffness ≤ 15.0 kPa had favorable native liver survival, whereas those with stiffness values between 15.0 and 23.1 kPa were at moderate risk of poor outcomes. Notably, liver stiffness > 23.1 kPa was associated with a significantly increased risk of liver failure, with a HR of 4.0 and likelihood of transplantation within 12 months.[65] In another study, Hwang et al. reported that a SWE liver stiffness threshold of 8.7 kPa could effectively distinguish pre-cirrhotic patients from those with compensated or decompensated cirrhosis, with a sensitivity of 81.3% and specificity of 86.7%.[66]

4.3 | In vitro and computational prognostic modeling systems

Complementing advances in imaging and molecular profiling, in vitro systems and computational models have recently emerged as innovative tools to predict outcomes in BA following HPE.

4.3.1 | Patient derived organoids

Organoids are three-dimensional, miniaturized structures derived from stem cells that recapitulate key structural and functional aspects of native tissues. Wai et al. demonstrated that organoids generated from BA patients with native liver survival exhibited a pronounced shift toward cholangiocytic gene expression, resembling healthy control organoids. None of the patients in the native liver survival group required liver transplantation during a mean follow-up period of 2.9 years (range: 1.64–5.57 years). In contrast,

organoids from patients who subsequently required liver transplantation retained elevated expression of hepatocyte-associated genes post-HPE. These organoids exhibited significant upregulation of *CYP3A4* and *CYP2E1* ($\log_2$ fold change: 14.50 and 10.94, respectively) and concurrent downregulation of cholangiocyte markers *AQP1* and *SOX9* ($\log_2$ fold change: −1.9 and −1.76, respectively).[67]

4.3.2 | Prediction models

Several predictive models incorporating combinations of clinical, biochemical, imaging, and transcriptomic data have been developed to estimate prognosis in BA. Wang et al. proposed a multi-parameter model integrating preoperative SWE, a nine-gene prognostic classifier, albumin levels, and age at surgery to predict native liver survival following HPE.[68] Key predictors of poor outcome included liver stiffness > 23.1 kPa, serum albumin ≤ 33 g/L, and age at surgery > 81 days. The model demonstrated strong predictive performance, with a concordance index (C-index) of 0.83 in the training cohort and 0.74 in the validation cohort, outperforming earlier models lacking gene expression data. Notably, 12-month native liver survival was 80.8% in the low-risk group versus 35.7% in the high-risk group.[68]

The Biliary Atresia Liver Fibrosis (BALF) score is another risk model that incorporates clinical and biochemical parameters, including TB, GGT, albumin, and age, to predict post-HPE liver fibrosis severity.[69] A BALF score > 4.12 identified patients at high risk of advanced fibrosis and poor outcomes, while a threshold of 5.64 predicted cirrhosis (F4) with 94.1% sensitivity and 93.3% specificity.[69] Zhen et al. developed an additional early prognostic scoring system specific to type III BA, incorporating variables such as early cholangitis, age at surgery, time to jaundice clearance, postoperative total and direct bilirubin, ALT, AST, and surgical approach (laparoscopic or open).[70] A cutoff score of 7.71 effectively distinguished patients with native liver survival at 2 years, with a sensitivity of 86% and specificity of 98%.[70]

5 | DISCUSSION

Meaningful advances have been made in refining risk prediction strategies for BA, a disease marked by clinical heterogeneity and variable responses to surgical intervention. A broad range of prognostic markers has been investigated, including laboratory parameters, histopathologic features, molecular biomarkers, imaging modalities, and integrative scoring systems, to predict disease progression and transplant-free survival. Serum markers such as bilirubin, bile acids, GGT, cytokines (IL-8, IL-18, IL-34, and IL-12p40), and fibrosis-related proteins (MMP-7, COMP, CLU, FGF19, and M2BPGi) have shown predictive utility in cohort studies. Histologic findings and hepatic gene expression profiles have identified key pathways involving bile duct injury, matrix remodeling, immune activation, and hepatobiliary development that associate with prognosis. Early studies in patient-derived organoids in BA show some prognostic utility. Noninvasive imaging tools such as shear wave elastography offer quantitative thresholds linked to fibrosis severity and clinical outcomes. Computational models and scoring systems, incorporating gene expression, biochemical data, and imaging parameters, represent a novel direction in individualized prognostication.

Important limitations persist in the interpretation and clinical applicability of prognostic biomarkers in BA. Most studies are single-center or involve small cohorts, limiting generalizability. Variability in assay platforms, biomarker thresholds, and follow-up metrics complicates cross-study comparisons and precludes the establishment of a standardized prognostic approach. Consequently, no single biomarker or model currently serves as a universally accepted tool for clinical risk stratification in BA. Future progress will require large, multicenter studies using standardized protocols to validate the utility of candidate markers and composite models. Integrating datasets through centralized platforms or data commons may enable harmonized analyses and improve reproducibility. Ultimately, a rigorously validated, multi-modal prognostic model combining clinical, molecular, and imaging data may be essential to advance personalized management strategies in BA.

6 | CONCLUSION

A breadth of prognostic biomarkers, ranging from laboratory parameters, histology, serum markers, imaging, and integrative scoring systems, show promise in BA and are presented in this review. Future studies in multicenter cohorts are required to determine clinical utility.

ACKNOWLEDGMENTS

S.P. is supported in part by the NASPGHAN Foundation George Ferry Young Investigator Award. L.V.W. receives research support from W.L. Gore & Associates, consults for Gerson Lehrman Group, Slingshot Insights, and Alpha Insights, and provides medicolegal services.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Sindhu Pandurangi https://orcid.org/0000-0003-3426-2845

REFERENCES

1. Asai A, Miethke A, Bezerra JA. Pathogenesis of biliary atresia: defining biology to understand clinical phenotypes. *Nat Rev Gastroenterol Hepatol*. 2015;12(6):342-352.
2. Hoshino E, Muto Y, Sakai K, Shimohata N, Urayama KY, Suzuki M. Age at surgery and native liver survival in biliary atresia: a systematic review and meta-analysis. *Eur J Pediatr*. 2023;182(6):2693-2704.
3. Antala S, Taylor SA. Biliary atresia In children. *Clin Liver Dis*. 2022;26(3):341-354.
4. Anouti A, Patel MS, VanWagner LB, et al. Biliary atresia and liver transplantation in the United States: A contemporary analysis. *Liver Int*. 2023;43(10):2198-2209.
5. Lykavieris P, Chardot C, Sokhn M, Gauthier F, Valayer J, Bernard O. Outcome in adulthood of biliary atresia: A study of 63 patients who survived for over 20 years with their native liver. *Hepatology*. 2005;41(2):366-371.
6. Shinkai M, Ohhama Y, Take H, et al. Long-term outcome of children with biliary atresia who were not transplanted after the Kasai operation: >20-year experience At a children's hospital. *J Pediatr Gastroenterol Nutr*. 2009;48(4):443-450.
7. de Vries W, Homan–Van der Veen J, Hulscher JBF, Hoekstra–Weebers JEHM, Houwen RHJ, Verkade HJ. Twenty-year transplant-free survival rate among patients with biliary atresia. *Clin Gastroenterol Hepatol*. 2011;9(12):1086-1091.
8. Altman RP, Lilly JR, Greenfeld J, Weinberg A, van Leeuwen K, Flanigan L. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. *Ann Surg*. 1997;226(3):348-355.
9. Gutierrez JV, Johnson L, Desai K, Tabak B, Woo RK. Timing of Kasai procedure for biliary atresia: an analysis of the pediatric national surgical quality improvement program database. *J Surg Res*. 2024;301:681-685.
10. Serinet MO, Wildhaber BE, Broué P, et al. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. *Pediatrics*. 2009;123(5):1280-1286.
11. Shneider BL, Brown MB, Haber B, et al. A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000. *J Pediatr*. 2006;148(4):467-474.e1.
12. Shneider BL, Brown MB, Haber B, et al. A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000. *J Pediatr*. 2006;148(4):467-474.e1.
13. Ihn K, Ho IG, Chang EY, Han SJ. Correlation between gamma-glutamyl transpeptidase activity and outcomes after Kasai portoenterostomy for biliary atresia. *J Pediatr Surg*. 2018;53(3):461-467.
14. Shankar S, Bolia R, Foo HW, et al. Normal gamma glutamyl transferase levels at presentation predict poor outcome In biliary atresia. *J Pediatr Gastroenterol Nutr*. 2020;70(3):350-355.
15. Sun S, Zheng S, Shen C, et al. Low gamma-glutamyl transpeptidase levels at presentation are associated with severity of liver illness and poor outcome in biliary atresia. *Front Pediatr*. 2022;10:956732.
16. Grieve A, Makin E, Davenport M. Aspartate Aminotransferase-to-Platelet ratio index (APRi) in infants with biliary atresia: prognostic value at presentation. *J Pediatr Surg*. 2013;48(4):789-795.
17. Muntean A, Kronfli R, Makin E, Davenport M. The AST-to-Platelet ratio index (APRi) at Kasai portoenterostomy: standing the test of time. *J Pediatr Surg*. 2023;58(12):2347-2351.
18. Suominen JS, Lampela H, Heikkilä P, Lohi J, Jalanko H, Pakarinen MP. APRi predicts native liver survival by reflecting portal fibrogenesis and hepatic neovascularization at the time of portoenterostomy in biliary atresia. *J Pediatr Surg*. 2015;50(9):1528-1531.
19. Harpavat S, Hawthorne K, Setchell KDR, et al. Serum bile acids as a prognostic biomarker in biliary atresia following Kasai portoenterostomy. *Hepatology*. 2023;77(3):862-873.
20. Dong R, Zheng S. Interleukin-8: A critical chemokine in biliary atresia. *J Gastroenterol Hepatol*. 2015;30(6):970-976.
21. Udomsinprasert W, Ungsudechachai T, Vejchapipat P, Poovorawan Y, Honsawek S. Systemic cytokine profiles in biliary atresia. *PLoS One*. 2022;17(4):e0267363.
22. Bessho K, Mourya R, Shivakumar P, et al. Gene expression signature for biliary atresia and a role for interleukin-8 in pathogenesis of experimental disease. *Hepatology*. 2014;60(1):211-223.
23. Vejchapipat P, Poomsawat S, Chongsrisawat V, Honsawek S, Poovorawan Y. Elevated serum IL-18 and interferon-gamma in medium-term survivors of biliary atresia. *Eur J Pediatr Surg*. 2012;22(1):029-033.
24. Honsawek S, Bovornsethanant N, Woraruthai T, Vejchapipat P, Udomsinprasert W, Poovorawan Y. Elevated serum IL-34 is correlated with disease severity in patients with biliary atresia following Kasai portoenterostomy. *Int Immunopharmacol*. 2024;127:111356.
25. Wu JF, Kao PC, Chen HL, et al. A high serum interleukin-12p40 level prior to Kasai surgery predict a favourable outcome in children with biliary atresia. *Liver Int*. 2012;32(10):1557-1563.
26. Chi S, Xu P, Yu P, et al. Dynamic analysis of serum MMP-7 and its relationship with disease progression in biliary atresia: a multicenter prospective study. *Hepatol Int*. 2022;16(4):954-963.
27. Udomsinprasert W, Angkathunyakul N, Jittikoon J, et al. Cartilage oligomeric matrix protein as a marker of progressive liver fibrosis in biliary atresia. *Sci Rep*. 2021;11(1):16695.
28. Udomsinprasert W, Poovorawan Y, Chongsrisawat V, Vejchapipat P, Honsawek S. Decreased circulating clusterin reflects severe liver complications after hepatoportoenterostomy of biliary atresia. *Sci Rep*. 2020;10(1):19736.
29. Nyholm I, Hukkinen M, Pihlajoki M, et al. Serum FGF19 predicts outcomes of Kasai portoenterostomy in biliary atresia. *Hepatology*. 2023;77(4):1263-1273.
30. Ueno T, Kodama T, Noguchi Y, et al. Clinical implications of serum Mac-2-binding protein (M2BPGi) during regular follow-up of patients with biliary atresia. *Pediatr Surg Int*. 2018;34(10):1065-1071.
31. Taylor SA, Harpavat S, Gromer KD, et al. Increased serum GM-CSF at diagnosis of biliary atresia is associated with improved biliary drainage. *Pediatr Res*. 2025;1:s41390.
32. Rohani P, Mirrahimi SB, Bashirirad H, et al. Serum matrix metalloproteinase-7 levels In infants with cholestasis and biliary atresia. *BMC Pediatr*. 2022;22(1):351.
33. Pandurangi S, Mourya R, Nalluri S, et al. Diagnostic accuracy of serum matrix metalloproteinase-7 as a biomarker of biliary atresia in a large North American cohort. *Hepatology*. 2024;80:152-162.
34. Yang L, Zhou Y, Xu P, et al. Diagnostic accuracy of serum matrix Metalloproteinase-7 for biliary atresia. *Hepatology*. 2018;68(6):2069-2077.
35. Jiang J, Wang J, Shen Z, et al. Serum MMP-7 in the diagnosis of biliary atresia. *Pediatrics*. 2019;144(5):e20190902.
36. Aldeiri B, Si T, Huang Z, et al. Matrix metalloproteinase-7 and osteopontin serum levels as biomarkers for biliary atresia. *J Pediatr Gastroenterol Nutr*. 2023;77(1):97-102.
37. Wu JF, Jeng YM, Chen HL, Ni YH, Hsu HY, Chang MH. Quantification of serum matrix metallopeptide 7 levels may assist in the diagnosis and predict the outcome for patients with biliary atresia. *J Pediatr*. 2019;208:30-37.e1.

38. Lertudomphonwanit C, Mourya R, Fei L, et al. Large-scale proteomics identifies MMP-7 as a sentinel of epithelial injury and of biliary atresia. *Sci Transl Med*. 2017;9(417):eaan8462.
39. He L, Ip DKM, Tam G, Lui VCH, Tam PKH, Chung PHY. Biomarkers for the diagnosis and post-Kasai portoenterostomy prognosis of biliary atresia: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):11692.
40. Shirabe K, Bekki Y, Gantumur D, et al. Mac-2 binding protein glycan isomer (M2BPGi) is a new serum biomarker for assessing liver fibrosis: more than a biomarker of liver fibrosis. *J Gastroenterol*. 2018;53(7):819-826.
41. Weerasooriya VS, White FV, Shepherd RW. Hepatic fibrosis and survival in biliary atresia. *J Pediatr*. 2004;144(1):123-125.
42. Xu X, Wang X, Ding M, et al. Development and post-Kasai procedure prognostic relevance of histological features for biliary atresia. *BMC Pediatr*. 2023;23(1):589.
43. Santos JL, Kieling CO, Meurer L, et al. The extent of biliary proliferation in liver biopsies from patients with biliary atresia at portoenterostomy is associated with the postoperative prognosis. *J Pediatr Surg*. 2009;44(4):695-701.
44. Jung HY, Jing J, Lee KB, Jang JJ. Sonic hedgehog (SHH) and glioblastoma-2 (Gli-2) expressions are associated with poor jaundice-free survival in biliary atresia. *J Pediatr Surg*. 2015;50(3):371-376.
45. Godbole N, Nyholm I, Hukkinen M, et al. Liver secretin receptor predicts portoenterostomy outcomes and liver injury in biliary atresia. *Sci Rep*. 2022;12(1):7233.
46. Udomsinprasert W, Angkathunyakul N, Klaikeaw N, Vejchapipat P, Poovorawan Y, Honsawek S. Hepatic glypican-3 and alpha-smooth muscle actin overexpressions reflect severity of liver fibrosis and predict outcome after successful portoenterostomy in biliary atresia. *Surgery*. 2020;167(3):560-568.
47. Jaramillo C, Guthery SL, Lowichik A, et al. Quantitative liver fibrosis using collagen hybridizing peptide to predict native liver survival in biliary atresia: A pilot study. *J Pediatr Gastroenterol Nutr*. 2020;70(1):87-92.
48. Ueno T, Toyama C, Yoneyama T, et al. Impact of serum autotaxin level correlating with histological findings in biliary atresia. *J Pediatr Surg*. 2021;56(7):1174-1178.
49. Wang J, Du M, Meng L, et al. Integrative analysis implicates the significance of m6A in the liver fibrosis of biliary atresia by regulating THY1. *Hepatology Communications*. 2023;7(1):e0004.
50. Fu M, Tan L, Lin Z, et al. Down-regulation of STAT3 enhanced chemokine expression and neutrophil recruitment in biliary atresia. *Clin Sci*. 2021;135(7):865-884.
51. Yoshii D, Inomata Y, Komohara Y, et al. Ki67 expression at Kasai portoenterostomy as a prognostic factor in patients with biliary atresia. *BJS Open*. 2020;4(5):873-883.
52. Lages CS, Simmons J, Maddox A, et al. The dendritic cell-T helper 17-macrophage axis controls cholangiocyte injury and disease progression in murine and human biliary atresia. *Hepatology*. 2017;65(1):174-188.
53. Loo CKC, Pearen MA, Ramm GA. The role of Sonic Hedgehog In human holoprosencephaly and short-rib polydactyly syndromes. *Int J Mol Sci*. 2021;22(18):9854.
54. Siyu P, Junxiang W, Qi W, Yimao Z, Shuguang J. The role of GLI in the regulation of hepatic epithelial-mesenchymal transition in biliary atresia. *Front Pediatr*. 2022;10:861826.
55. Wu N, Baiocchi L, Zhou T, et al. Functional role of the secretin/secretin receptor signaling during cholestatic liver injury. *Hepatology*. 2020;72(6):2219-2227.
56. Ramachandran P, Unny A, Vij M, Safwan M, Balaji M, Rela M. α-Smooth muscle actin expression predicts the outcome of Kasai portoenterostomy in biliary atresia. *Saudi Journal of Gastroenterology*. 2019;25(2):101-105.
57. Kerola A, Lampela H, Lohi J, et al. Molecular signature of active fibrogenesis prevails in biliary atresia after successful portoenterostomy. *Surgery*. 2017;162(3):548-556.
58. Udomsinprasert W, Vejchapipat P, Klaikeaw N, Chongsrisawat V, Poovorawan Y, Honsawek S. Hepatic autotaxin overexpression in infants with biliary atresia. *PeerJ*. 2018;6(7):e5224.
59. Levy DE, Lee C. What does Stat3 do? *J Clin Invest*. 2002;109(9):1143-1148.
60. Nagayabu K, Fumino S, Shimamura A, et al. The clinical impact of macrophage polarity after Kasai portoenterostomy in biliary atresia. *Front Pediatr*. 2024;12:1338131.
61. Luo Z, Shivakumar P, Mourya R, Gutta S, Bezerra JA. Gene expression signatures associated with survival times of pediatric patients with biliary atresia identify potential therapeutic agents. *Gastroenterology*. 2019;157(4):1138-1152.e14.
62. Moyer K, Kaimal V, Pacheco C, et al. Staging of biliary atresia at diagnosis by molecular profiling of the liver. *Genome Med*. 2010;2(5):33.
63. Yoon H, Ihn K, Kim J, et al. Pre- and immediate post-kasai portoenterostomy shear wave elastography for predicting hepatic fibrosis and native liver outcomes In patients with biliary atresia. *Korean J Radiol*. 2023;24(5):465-475.
64. Caruso M, Cuocolo R, Di Dato F, et al. Ultrasound, shear-wave elastography, and magnetic resonance imaging in native liver survivor patients with biliary atresia after Kasai portoenterostomy: correlation with medical outcome after treatment. *Acta Radiol*. 2020;61(10):1300-1308.
65. Wang G, Chen H, Xie X, et al. 2D shear wave elastography combined with age and serum biomarkers prior to Kasai surgery predicts native liver survival of biliary atresia infants. *J Intern Med*. 2020;288(5):570-580.
66. Hwang J, Yoon HM, Kim KM, et al. Assessment of native liver fibrosis using ultrasound elastography and serological fibrosis indices in children with biliary atresia after the Kasai procedure. *Acta Radiol*. 2021;62(8):1088-1096.
67. Wai AWY, Lui VCH, Tang CSM, et al Human liver organoids to predict the outcome of Kasai portoenterostomy. *J Pediatr Surg* 2024:161686.
68. Wang G, Chen H, Sun P, et al. Predictive model containing gene signature and shear wave elastography to predict patient outcomes after Kasai surgery in biliary atresia. *Hepatol Res*. 2023;53(11):1126-1133.
69. Tomita H, Masugi Y, Hoshino K, et al. Long-term native liver fibrosis in biliary atresia: development of a novel scoring system using histology and standard liver tests. *J Hepatol*. 2014;60(6):1242-1248.
70. Zhen C, Guoliang Q, Lishuang M, et al. Design and validation of an early scoring system for predicting early outcomes of type III biliary atresia after Kasai's operation. *Pediatr Surg Int*. 2015;31:535-542.

How to cite this article: Anouti A, Sudhakara P, Pratt C, et al. Advances in prognostic biomarkers for biliary atresia: current insights and future directions. *J Pediatr Gastroenterol Nutr*. 2025;1-10. doi:10.1002/jpn3.70131