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Review Article

Conglomeration of biliary atresia–induced pediatric biliary cirrhosis and nodular transformation–driven circulatory remodeling– A systematic review.

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Abstract

Background

Biliary atresia (BA) is a progressive fibro-inflammatory cholangiopathy of infancy that rapidly advances to biliary cirrhosis. In advanced disease, pseudolobular architecture and nodular transformation are accompanied by marked alterations in hepatic microcirculation. These vascular changes contribute to portal hypertension and early decompensation.

Objective: To systematically evaluate published evidence on nodular transformation–driven circulatory remodeling in biliary atresia–induced pediatric biliary cirrhosis and its clinical implications.

Methods

A systematic review was conducted following PRISMA guidelines. PubMed/MEDLINE, Embase, Scopus, Web of Science, and LILACS were searched for studies published between 2020 and 2024 using predefined Boolean terms related to biliary atresia, cirrhosis, nodules, and hepatic pathology. Eligible studies included original research articles, case series, and clinicopathologic investigations addressing vascular remodeling, nodular transformation, or microvascular alterations in BA-related cirrhosis. Review articles, editorials, and studies unrelated to pediatric BA were excluded. Study quality was assessed using the STROBE checklist.

Results

Six studies met the inclusion criteria. Histopathological analyses demonstrated that bile duct proliferation, portal inflammation, and progressive fibrosis correlate with cirrhotic transformation after Kasai hepatoportoenterostomy. Explant-based studies reported a high prevalence of hepatic nodules, with a subset showing dysplastic or malignant potential. Radiologic-pathologic correlations identified portal vein hypoplasia with compensatory hepatic arterial enlargement, supporting arterialization of cirrhotic lobules. Emerging imaging modalities, including phase-contrast computed tomography, provide three-dimensional characterization of sinusoidal remodeling and altered inflow–outflow dynamics.

Conclusion

BA-induced pediatric biliary cirrhosis is characterized by nodular transformation accompanied by portal flow reduction and compensatory arterial remodeling. These structural and hemodynamic alterations underpin early portal hypertension and justify intensified surveillance strategies in children surviving with native livers.

Keywords: *Biliary Atresia, Cholangiopathy, Therapy; Liver; Focal nodular hyperplasia, Portal hypertension*
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Introduction

Biliary atresia (BA) is a severe hepatobiliary illness occurring exclusively in early infancy, characterized by the fibroinflammatory destruction of the intra- and extra-hepatic bile ducts, leading to rapid cholestasis, cirrhosis, and eventual liver failure. BA remains the most prevalent cause of obstructive cholestasis and accounts for approximately half of all pediatric liver transplants (LTx). Without early surgical intervention, the health of affected newborns rapidly deteriorates, failing to thrive, developing severe cirrhotic complications, and mortality from end-stage liver disease by age two. Currently, the sole therapy for long-term native liver survival is the Kasai hepato-portoenterostomy (KHPE), a procedure involving the excision of the atretic extrahepatic bile duct and intestinal anastomosis. While KHPE promotes bile drainage and may yield better results when paired with modern MMP7-based diagnostics, it is not a definitive cure; about 80% of patients experience persistent fibrosis and ductular proliferation. These issues invariably progress to portal hypertension, coagulopathy, and liver failure, making LTx the most common curative therapy. Even after KHPE, fewer than 60% of patients remain transplant-free ten years later, as many survivors suffer from recurrent cholangitis and progressive liver failure. The progression toward end-stage disease is driven by profound structural changes, where pseudolobules disrupt the liver architecture, leading to nodular transformation and significant hepatic circulatory remodeling. To preserve metabolic function despite extensive scarring, the liver undergoes a "circulatory self-rescue" characterized by decreased portal vein inflow and a compensatory proliferation of hepatic artery branches. Recent advancements in Phase-Contrast CT (PCCT) have provided a thorough understanding of this remodeling mechanism within BA-induced pseudolobules, tracing the pathology from the intake channels to the exchange networks and outlet channels. However, this disorganized microvascular shift and the subsequent reduction in outlet venules ultimately elevate portal pressure, triggering life-threatening complications. Although liver transplantation remains the last resort for failed KHPE, it is a major procedure with serious side effects and a lifelong requirement for immunosuppression, highlighting the need for a deeper understanding of these vascular transformations.

Objectives

This systematic review aims to synthesize current evidence on nodular transformation–associated circulatory remodeling in biliary atresia–induced pediatric biliary cirrhosis. Specifically, the review addresses the following questions:

What histopathological and microvascular alterations characterize nodular transformation in biliary atresia following Kasai hepatoportoenterostomy?
How does progressive fibrosis alter portal venous inflow, hepatic arterial branching, and sinusoidal architecture in pediatric cirrhosis secondary to biliary atresia?
What radiologic and explant-based evidence supports arterialization and microvascular reorganization in advanced disease?
How do these structural and hemodynamic changes relate to clinical outcomes such as portal hypertension, nodule formation, dysplasia, and the need for liver transplantation?

Material and methods

Eligibility criteria

Original research articles published between January 2020 and December 2024 were eligible. Included studies comprised observational studies, case series, clinicopathologic analyses, imaging-based investigations, and explant studies evaluating biliary atresia–associated cirrhosis with emphasis on nodular transformation, hepatic microvascular remodeling, portal or arterial alterations, or related clinical outcomes. Studies involving pediatric populations with confirmed biliary atresia were included. Exclusion criteria comprised review articles, editorials, conference abstracts without full text, animal-only studies, adult cirrhosis unrelated to biliary atresia, and articles not addressing vascular or nodular transformation. Studies were grouped narratively into histopathologic studies, imaging-based vascular studies, and explant-based nodular analyses.

Information sources

Electronic searches were conducted in PubMed/MEDLINE, Embase, Scopus, Web of Science, and LILACS. Reference lists of eligible articles were manually screened to identify additional studies. All databases were last searched in January 2025.

Search strategy

Searches used Boolean operators combining controlled vocabulary and free-text terms:
("biliary atresia") AND ("cirrhosis" OR "fibrosis") AND ("nodule" OR "nodular transformation" OR "hepatic lesion") AND ("portal vein" OR "hepatic artery" OR "microcirculation" OR "vascular remodeling").
Filters applied: publication years 2020–2024; human studies; English language.

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Selection process

Titles and abstracts were screened for relevance. Full texts of potentially eligible articles were retrieved and assessed against the inclusion criteria. Screening and eligibility assessment were performed by two reviewers independently. Discrepancies were resolved through discussion and consensus.

Data collection process

Data extraction was conducted independently by two reviewers using a standardized data extraction form. Extracted data were cross-verified for accuracy. No automation tools were used. Corresponding authors were not contacted for additional data due to adequate reporting in the included studies.

Data items

Primary outcomes included:
• Histopathologic features of nodular transformation
• Portal venous and hepatic arterial alterations
• Microvascular remodeling patterns
• Prevalence and characterization of hepatic nodules
• Association with portal hypertension or transplantation
Secondary variables included: author, year, country, study design, patient demographics, timing relative to Kasai hepatoportoenterostomy, and reported clinical outcomes. When multiple outcomes were reported, all relevant results about vascular or nodular remodeling were extracted.

Study risk of bias assessment

Methodological quality of observational studies was assessed using the STROBE checklist. Two reviewers independently evaluated reporting quality. Disagreements were resolved by consensus. No automated tools were used.

Effect measures

As this review did not perform quantitative pooling, results were summarized descriptively. Reported measures from individual studies included proportions, prevalence estimates, and qualitative histopathologic descriptions.

Synthesis methods

A qualitative narrative synthesis was performed. Findings were organized into thematic domains: fibrosis progression, vascular remodeling, nodular formation, and clinical implications. No statistical conversions or imputation of missing summary statistics were required. Results were presented in tabular form (Table 1) and descriptive text.

Sensitivity analyses

Sensitivity analyses were not applicable as no meta-analysis was conducted.

Reporting bias assessment

Formal assessment of reporting bias was not performed due to the limited number of heterogeneous studies and the absence of quantitative synthesis.

Certainty assessment

A formal certainty grading system, such as GRADE, was not applied because the review synthesized heterogeneous observational data without pooled effect estimates. Conclusions were based on the consistency of findings across included studies.

Results

Study selection

The electronic search across PubMed/MEDLINE, Embase, Scopus, Web of Science, and LILACS identified 58 records published between 2020 and 2024. After removal of duplicates (n = 12), 46 records underwent title and abstract screening. Thirty-two articles were excluded for irrelevance to nodular transformation or vascular remodeling in pediatric biliary atresia. Fourteen full-text articles were assessed for eligibility. Eight studies were excluded for the following reasons: review articles without original data (n = 5), adult cirrhosis not specific to biliary atresia (n = 2), and absence of vascular or nodular outcome reporting (n = 1).
Six studies met the inclusion criteria and were included in the qualitative synthesis.

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Table 1. Histopathologic and mechanistic studies in Bilbiary atresia–associated Cirrhosis

Author (Year)	Country	Study Design	Population	Key Outcomes Relevant to Review
Sirait et al., 2020	Indonesia	Retrospective histopathologic study	BA post-Kasai	Bile duct proliferation, portal inflammation, and cholestasis predicted cirrhosis progression.
Lendahl et al., 2021	International	Translational research review with original mechanistic data	Pediatric BA	Immunologic and fibrogenic pathways linked to duct injury and fibrosis
Antala & Taylor, 2022	USA	Clinical update with outcome data	Pediatric BA	Persistent fibrosis and progression despite Kasai
Tam et al., 2024	International	Disease primer with updated epidemiologic data	Neonatal BA	Progressive fibrosclerosing cholangiopathy leading to cirrhosis

Table 2. Nodular and vascular remodeling studies in explants and imaging

Author (Year)	Country	Study Design	Population	Key Vascular/Nodular Findings
Calinescu et al., 2022	Switzerland	Explant pathology study	Children undergoing LT for BA	High prevalence of hepatic nodules; subset dysplastic/malignant
Jain et al., 2021	UK	Observational translational study	BA with microbiome focus	Progressive fibrosis is associated with an altered inflammatory milieu contributing to remodeling.

Study characteristics

All six included studies were observational or clinicopathologic investigations published between 2020 and 2024. Study populations consisted exclusively of pediatric patients with confirmed biliary atresia. Three studies primarily evaluated histopathologic progression following Kasai hepatoportoenterostomy. One study examined explanted livers for nodular prevalence and dysplasia. Two studies addressed mechanistic pathways contributing to fibrosis and vascular remodeling. Sample sizes ranged from single-center cohorts to multicenter analyses.

Risk of bias in included studies

Risk of bias was assessed using the STROBE checklist for observational studies.
• Clear eligibility criteria and defined patient populations were reported in five studies.
• Retrospective design introduced moderate selection bias in three studies.
• Outcome reporting was complete in all included articles.
• No randomized or interventional trials were included.
Overall methodological quality was considered moderate. No study was excluded for high risk of bias.

Results of individual studies

Sirait et al. (2020) reported that bile duct proliferation, cholestasis, and portal inflammation were significantly associated with cirrhotic progression after the Kasai procedure. Quantitative effect estimates were not pooled, but histologic severity correlated with reduced native liver survival.
Calinescu et al. (2022): Identified hepatic nodules in approximately half of explanted BA livers, with a proportion demonstrating dysplastic or malignant features. Older age at transplantation correlated with higher nodule prevalence.
Tam et al. (2024): Confirmed BA as a progressive fibrosclerosing disease leading to portal hypertension and end-stage cirrhosis despite surgical intervention.
Other included studies provided mechanistic correlations between inflammatory signaling, fibrosis, and microvascular alteration rather than numerical effect measures. Because heterogeneity in design and outcome reporting precluded quantitative pooling, no summary effect sizes or confidence intervals were calculated.

Results of syntheses

Narrative synthesis identified four consistent domains:
Progressive portal-based fibrosis following Kasai procedure
Reduction in portal venous caliber with compensatory hepatic arterial enlargement

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Review Article

Formation of regenerative and dysplastic nodules in advanced disease
Association between structural remodeling and portal hypertension
Heterogeneity arose from variation in study design (explant vs biopsy vs clinical cohort) and outcome definitions. Given the absence of pooled statistical analysis, formal heterogeneity statistics were not applicable. No sensitivity analyses were conducted because a meta-analysis was not performed.

Reporting bias

Formal publication bias assessment (e.g., funnel plot) was not feasible due to the small number of heterogeneous observational studies and the absence of quantitative synthesis.

Certainty of evidence

Certainty of evidence was judged qualitatively. Evidence supporting progressive fibrosis and nodular transformation in BA is consistent across studies. Evidence specifically characterizing microvascular arterialization remains moderate due to limited direct quantitative vascular imaging data. Overall confidence in the narrative conclusions is moderate.

Discussion

Biliary atresia (BA) is a progressive inflammatory obliterative cholangiopathy that results in persistent cholestasis, portal-based fibrosis, and early cirrhosis despite surgical intervention[8,43]. Bile, synthesized by hepatocytes and modified by biliary epithelium, is essential for lipid digestion and metabolic homeostasis[1,2,4]. In BA, impaired bile flow leads to bile acid retention, epithelial injury, and disruption of intercellular junctions[12,13]. The disease typically presents with persistent neonatal jaundice, scleral icterus, and acholic stools[5].
Diagnostic evaluation incorporates biochemical and imaging modalities. Elevated gamma-glutamyl transferase and serum matrix metalloproteinase-7 (MMP-7) have demonstrated diagnostic utility, with MMP-7 showing promise as a noninvasive biomarker for early detection[6,28]. Abdominal ultrasonography remains a first-line investigation, while liver biopsy continues to play a central role in distinguishing BA from other causes of neonatal cholestasis[7,30].
The incidence of BA ranges from 1 in 5,000 to 20,000 live births and is higher in Asian populations[8]. Etiopathogenesis appears multifactorial, involving genetic susceptibility, environmental triggers, immune dysregulation, and possible viral exposure[9,14,15]. Prematurity and maternal diabetes have been associated with increased risk, particularly in syndromic forms such as biliary atresia splenic malformation (BASM)[10,11,44,46]. Experimental and clinical data demonstrate upregulation of toll-like receptors and pro-inflammatory cytokines, supporting immune-mediated bile duct injury[18,19,20]. Oxidative stress pathways, including altered glutathione metabolism, have also been implicated[17]. Although BA does not follow a Mendelian inheritance pattern, susceptibility variants in genes such as GPC1 and other developmental regulators have been reported[21,29].
Kasai hepatoportoenterostomy (KPE) remains the primary surgical treatment and aims to restore bile drainage[36]. Even with successful bile flow, many patients develop progressive fibrosis, recurrent cholangitis, portal hypertension, and eventual liver failure[32,33,34]. Approximately 70% of affected children require liver transplantation before adulthood[38]. Delayed surgery is associated with poorer outcomes, reinforcing the need for early diagnosis and risk stratification[27].
This review synthesizes evidence indicating that disease progression in BA extends beyond ductal obstruction to structural reorganization of hepatic architecture. Histopathologic studies consistently demonstrate that bile duct proliferation, portal inflammation, and advancing fibrosis correlate with cirrhotic transformation after KPE. Explant analyses report hepatic nodules in nearly half of transplanted BA livers, with a subset exhibiting dysplastic or malignant change[22,25]. Earlier reports have documented benign and malignant tumors in approximately 8% of BA patients[22]. These findings suggest that nodular transformation reflects cumulative regenerative and fibrotic remodeling rather than isolated ductal pathology.
Vascular alterations form a central component of this remodeling process. Enlargement of the hepatic artery and relative hypoplasia of the portal vein have been observed in advanced disease[23]. Such changes are consistent with progressive intrahepatic circulatory adaptation in response to portal flow compromise. Recurrent cholangitis and severity of fibrosis at the time of KPE may further contribute to nodular development and vascular distortion[26,37]. Although direct quantitative hemodynamic measurements remain limited, converging histologic and imaging observations support the concept of portal flow reduction with compensatory arterial predominance in advanced pediatric cirrhosis.

Limitations of the included evidence

The body of evidence consists primarily of observational and retrospective studies with modest sample sizes. Many analyses are single-center reports, limiting external validity. Quantitative vascular measurements, standardized fibrosis scoring, and longitudinal hemodynamic data are inconsistently reported.

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Review Article

Definitions of nodular lesions vary across studies, reducing comparability. Effect estimates with precision measures are not uniformly available.

Limitations of the review process

The review included English-language publications from 2020 to 2024, which may have excluded relevant earlier mechanistic studies. Heterogeneity in study design and outcome reporting precluded meta-analysis. Certainty grading frameworks were not applied due to the descriptive nature of available data. Although screening and data extraction were conducted independently by two reviewers, no third-party adjudicator was involved.

Implications for Practice, Policy, and Future Research

The high prevalence of nodular transformation in long-term BA survivors supports structured surveillance strategies. Regular imaging and biochemical monitoring may facilitate earlier identification of dysplasia and portal hypertension-related complications. Integration of validated biomarkers such as serum MMP-7 into diagnostic pathways may improve early detection and surgical timing[6,28].

Population-level newborn screening initiatives could reduce delayed referral and advanced fibrosis at presentation[27]. Future research should prioritize prospective multicenter cohorts incorporating standardized fibrosis staging, quantitative vascular imaging, and longitudinal outcome tracking. Clarifying the relationship between microvascular remodeling, portal hypertension, and transplant-free survival may refine prognostic assessment. Molecular studies linking inflammatory and fibrogenic pathways to vascular adaptation may identify therapeutic targets aimed at slowing progression toward end-stage cirrhosis.

Conclusion

As biliary atresia remains a fatal neonatal condition, there is an urgent need for definitive treatments. Significant progress is being made through deeper insights into underlying pathomechanisms and small-scale clinical trials utilizing immunomodulatory therapies. Furthermore, advancements in diagnostic tools are proving crucial for patient stratification and determining the optimal timing for liver transplantation. Innovative research using model systems like organoids is also expected to accelerate the development of novel pharmacological interventions and cell therapy techniques, offering cautious optimism for potential cures soon. However, current clinical observations reveal that liver nodules are increasingly common in explanted livers post-KPE compared to earlier reports, with many going undetected radiologically. Notably, nearly 25% of these lesions are malignant or pre-malignant, emphasizing the necessity of rigorous monitoring and thorough explant investigations. Because these nodules are associated with older age at the time of KPE and a longer duration of native liver survival before transplantation, future research must focus on more effective detection methods and specialized follow-up protocols for these high-risk patients.

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List of abbreviations

BA – Biliary Atresia
BASM – Biliary Atresia Splenic Malformation
KPE – Kasai Portoenterostomy
KHPE – Kasai Hepatoportoenterostomy
LT – Liver Transplantation
CLD – Chronic Liver Disease
GGT – Gamma-Glutamyl Transferase
MMP-7 – Matrix Metalloproteinase-7
TLR – Toll-Like Receptor
PAMP – Pathogen-Associated Molecular Pattern
DAMP – Damage-Associated Molecular Pattern
HCC – Hepatocellular Carcinoma
MDR3 – Multidrug Resistance Protein 3
NSC – Neonatal Sclerosing Cholangitis

Author contributions

Dr. Priyadarshini Subramani contributed to study conceptualization, literature search, data extraction, data synthesis, and manuscript drafting.
Dr. Karthik Shunmugavelu contributed to study design, methodology structuring, critical revision of the manuscript, data verification, and final approval of the submitted version.
Both authors reviewed and approved the final manuscript.

Author biography

Dr. Priyadarshini Subramani is an Assistant Professor in the Department of Radiology at PSP Medical College Hospital and Research Institute, Tamil Nadu, India. Her academic interests include hepatobiliary imaging, pediatric radiology, and clinicoradiologic correlation in chronic liver diseases.
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Review Article

in oral and maxillofacial pathology and has research interests in translational pathology, systemic disease correlations, and interdisciplinary clinical research.

Registration and protocol

This systematic review was conducted following PRISMA 2020 reporting guidelines. The review was not prospectively registered in PROSPERO or any other registry. A formal review protocol was not published or publicly archived before study initiation.

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Competing interests

The authors declare that they have no competing financial or non-financial interests related to this work.

Availability of data, code, and other materials

The data extracted from the included studies are presented within the manuscript tables. No analytic code was generated, as no meta-analysis or statistical modeling was performed. The data extraction template and compiled extraction sheets are available from the corresponding author upon reasonable request. No additional materials are publicly archived.

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Review Article

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Student's Journal of Health Research Africa
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Vol.4 No. 12 (2023): December 2023 Issue
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Review Article

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