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Impact of Biliary Atresia on Neurodevelopment in Children: A Systematic Review

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Abstract:

Background: Survival in children with biliary atresia (BA) has improved substantially, shifting clinical focus toward long-term morbidity, including neurodevelopmental outcomes. However, existing evidence remains fragmented, and prior reviews have not comprehensively addressed motor, behavioral, and autism-related domains. This study aimed to synthesize current evidence on neurodevelopmental outcomes in children with BA across cognitive, motor, and behavioral domains, and to identify clinical factors associated with adverse developmental trajectories.

Methods: A systematic search of PubMed, Scopus, and Wiley was conducted from database inception to October 17, 2025, following PRISMA 2020 guidelines. Observational studies reporting neurodevelopmental outcomes in children (≤18 years) with BA were included. Risk of bias was assessed using the Newcastle–Ottawa Scale and the Joanna Briggs Institute checklist. Due to substantial heterogeneity, a narrative synthesis was performed.

Result: Seven studies involving infants to adolescents with BA were included. Motor impairment was the most consistent finding, detectable from early infancy and persisting into later childhood. Cognitive outcomes were heterogeneous, ranging from significant impairment to age-appropriate or above-normative performance in selected cohorts. Behavioral and adaptive difficulties, including attention problems and autism spectrum–related traits, were frequently reported. Markers of disease severity such as unsuccessful Kasai portoenterostomy (KPE), delayed jaundice clearance, growth failure, ascites, and portal hypertension were consistently associated with poorer neurodevelopmental outcomes.

Conclusion: Children with BA are at increased risk of multidimensional neurodevelopmental impairment, particularly affecting motor and behavioral domains. Early identification and longitudinal neurodevelopmental surveillance are essential to optimize long-term functional outcomes in this vulnerable population.

Keyword: behaviour, biliary atresia, cognitive, motoric, neurodevelopment

Introduction

Biliary atresia (BA) is a rare but severe neonatal cholangiopathy characterized by progressive fibro-obliteration of the intrahepatic and extrahepatic bile ducts, leading to cholestasis and biliary cirrhosis early in life. Its incidence varies geographically, affecting approximately 1 in 15,000–20,000 live births in Europe, the United Kingdom, and North America, and up to 1 in 5,000–10,000 in East Asia.[1] Kasai portoenterostomy (KPE) remains the first-line surgical intervention, aiming to reestablish bile flow and delay progression to end-stage liver disease.[2] Although early KPE can slow hepatic fibrosis and improve short-term outcomes, more than half of affected children ultimately require liver transplantation, frequently within the first five years of life.[3] Advances in screening, surgical timing, and perioperative management have nonetheless resulted in substantial improvements in survival.

Improved survival has led to a growing cohort of children with BA who reach later childhood and adolescence, either with their native liver or following transplantation.[4] Consequently, clinical priorities have shifted from survival alone to long-term morbidity and health-related quality of life. Neurodevelopmental outcomes have emerged as a particularly important concern, given their relevance to cognitive functioning, educational attainment, and psychosocial adaptation.[5] The etiopathogenesis of BA is multifactorial and incompletely understood, involving genetic susceptibility and prenatal or perinatal insults that provoke immune-mediated bile duct injury.[6] Persistent cholestasis exposes the developing brain to prolonged metabolic stress, systemic inflammation, and bile acid dysregulation, while malabsorption of fat-soluble vitamins may further compromise neuromuscular and neurological development. In addition, complications of chronic liver disease, including growth failure, portal hypertension, recurrent infections, and prolonged hospitalization, may disrupt critical periods of neurodevelopment.[7]

Neurodevelopment is a multidimensional construct encompassing cognitive, motor, language, behavioral, and adaptive domains, all of which are essential determinants of long-term functional outcomes.[8] Despite growing interest in this area, the existing literature is fragmented and methodologically heterogeneous, with inconsistent evaluation of neurodevelopmental domains and wide variation in follow-up duration and outcome measures.[9]

To date, comprehensive syntheses integrating evidence across neurodevelopmental domains in children with BA remain limited. Therefore, this systematic review aims to critically appraise and synthesize the available evidence on neurodevelopmental outcomes in children with BA, identify domains most susceptible to impairment, and explore clinical factors associated with adverse developmental trajectories. Such data are essential to inform standardized neurodevelopmental surveillance and targeted early interventions in this vulnerable population.

Method

Review Design

This systematic review was designed and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD420251173999).

Eligibility Criteria

Studies were eligible for inclusion if they fulfilled the following predefined criteria: (1) involved pediatric participants (≤18 years of age) with a confirmed diagnosis of BA, including children surviving with their native liver, both with and without prior KPE, or with KPE performed within the first two years of life; (2) reported quantitative or qualitative assessments of neurodevelopmental outcomes, including cognitive, motor, language, behavioral, or psychosocial domains, measured using validated developmental or neuropsychological assessment tools; (3) adopted observational (prospective or retrospective cohort, case–control, or cross-sectional) or interventional study designs; and (4) were published as full-length articles in peer-reviewed journals. Studies were excluded if they consisted of case reports, small case series (<5 participants), narrative or systematic reviews, editorials, letters to the editor, conference abstracts, animal or in vitro studies. Furthermore, studies enrolling heterogeneous pediatric liver disease populations without stratified or extractable data specific to BA, or those lacking explicit reporting of neurodevelopmental outcomes, were excluded.

Timing of Neurodevelopmental Assessment

Neurodevelopmental assessments were conducted across a broad age range, reflecting the developmental domains evaluated in the included studies. Motor development was assessed primarily during infancy and early childhood, with evaluations performed from as early as 3 months of age and extending up to 22 years in studies reporting long-term motor outcomes. In contrast, assessments of neurocognitive and behavioral domains were conducted at later developmental stages, with evaluations performed in children aged 3 to 17 years, corresponding to periods when cognitive abilities and behavioral characteristics can be reliably measured using age-appropriate, standardized assessment tools. This age-specific approach aligns with established developmental trajectories and ensures appropriate interpretation of domain-specific outcomes.

Information Sources and Search strategy

A comprehensive and systematic literature search was conducted across the PubMed, Scopus, and Wiley databases to identify relevant studies. All articles published from database inception up to October 17, 2025, were considered. The search strategy combined controlled vocabulary and free-text terms related to biliary atresia ("biliary

atresia" OR "extrahepatic biliary atresia"), neurodevelopmental outcomes ("neurodevelopmental outcome" OR "neurocognitive" OR "psychomotor development" OR "brain development" OR "neurobehavioral" OR "developmental delay"), and pediatric populations ("infant" OR "newborn" OR "child" OR "pediatric"). The search was restricted to full-text articles published in the English language.

Study Selection and Data Extraction

All records identified through the database searches were imported into a reference management software, and duplicate entries were removed prior to screening. Two reviewers independently screened the titles and abstracts for eligibility based on the predefined inclusion and exclusion criteria. Full-text articles were subsequently retrieved and independently assessed for final inclusion. Any discrepancies between reviewers at each stage of the selection process were resolved through discussion, and when consensus could not be reached, a third reviewer was consulted. Data extraction was independently performed by two reviewers using a standardized and pilot-tested data extraction form. Extracted data included study characteristics (first author, year of publication, country, and study design), participant characteristics (sample size, age at assessment, birth weight, and gestational age), neurodevelopmental assessment tools, and key neurodevelopmental outcomes. Any disagreements in data extraction were resolved by consensus to ensure accuracy and completeness of the collected data.

Quality Assessment

The risk of bias of the included studies was independently evaluated by two reviewers using validated assessment tools according to study design. Cohort and case–control studies were assessed using the Newcastle–Ottawa Scale (NOS), whereas cross-sectional studies were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. The assessment encompassed key methodological domains, including participant selection, exposure and outcome measurement, confounding control, and completeness of data. Any disagreements between reviewers were resolved through discussion or, when necessary, consultation with a third reviewer. The overall risk of bias was summarized narratively and taken into account in the interpretation of the review findings.

Data Analysis

Due to substantial clinical and methodological heterogeneity among the included studies, a quantitative meta-analysis was not performed. Instead, a structured narrative synthesis was conducted. Neurodevelopmental outcomes were categorized into cognitive, motor, and behavioral domains, findings were descriptively synthesized with attention to the direction and consistency of effects. Where relevant, key clinical factors, including age at diagnosis, timing of intervention, and treatment modality, were considered to support an integrated interpretation of the evidence.

Result

Study Selection and Identification

The systematic literature search identified a total of 316 records from PubMed (n = 42), Scopus (n = 75), and Wiley (n = 199). After removal of 24 duplicate records, 292 articles remained for title and abstract screening, of which 279 were excluded for irrelevance. Ten full-text reports were sought for retrieval, and nine were successfully assessed for eligibility. Following full-text evaluation, two studies were excluded due to irrelevant clinical data. Ultimately, seven studies met the predefined inclusion criteria and were included in the final systematic review. The study selection process is summarized in the PRISMA flow diagram **(Figure 1)**.

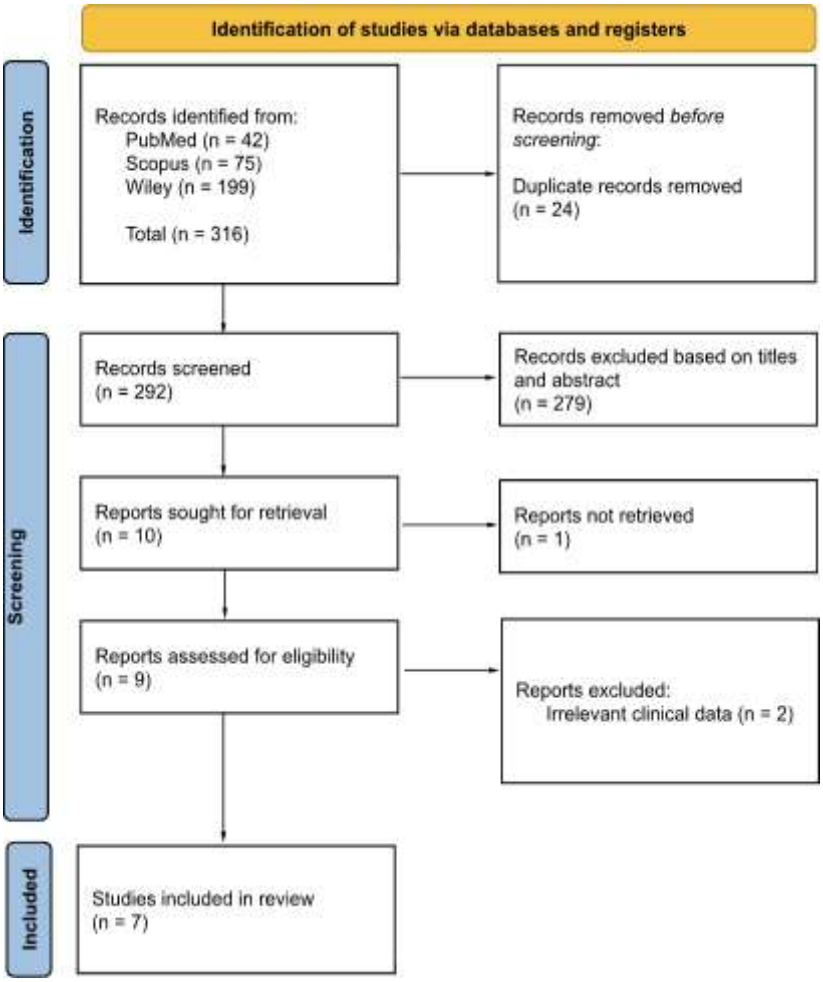

Figure 1. Diagram PRISMA Flow of Searching Strategies

Quality Assessment

Table 1 and Table 2 presents the risk of bias assessment using NOS for cohort studies and the JBI tool for cross-sectional studies. None of the cohort studies incorporated a control or comparison group, resulting in a maximum score of three

points in the NOS selection domain; one study was not awarded a score in this domain due to inadequate follow-up. Additionally, two cross-sectional studies did not sufficiently identify or control for potential confounding factors. Overall, five studies were judged to have a low risk of bias, while two cross-sectional studies were considered to have a moderate risk of bias.

Table 1. Risk of bias of the cohort study included

Study	Selection				Comparability	Outcome			Risk of Bias
	1	2	3	4	5	6	7	8	
Ng et al., 2018[10]	*	-	*	*	**	*	*	-	Low risk
Squires et al., 2020[11]	*	-	*	*	**	*	*	*	Low risk
Rodijk eta l., 2021[12]	*	-	*	*	*	*	-	*	Low risk
Dibbits et al., 2023[13]	*	-	*	*	*	*	*	*	Low risk

1. Representativeness of the exposed cohort
2. Selection of the non-exposed cohort
3. Ascertainment of exposure
4. Demonstration that outcome of interest was not present at start of study
5. Comparability of cohorts on the basis of the design or analysis controlled for confounders
6. Assessment of outcome
7. Was follow-up long enough for outcomes to occur?
8. Adequacy of follow-up of cohorts

Table 2. Risk of bias of the cross-sectional study included

Study	JBI Critical Appraisal Checklist								Risk of Bias
	1	2	3	4	5	6	7	8	
Rodijk et al., 2020[14]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate risk
Ruuska et al., 2021[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Earl et al., 2025[16]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate risk

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Summaries of Included Studies

Seven studies published between 2018 and 2025 were included in this systematic review, comprising four prospective cohort studies and three cross-sectional studies conducted across Europe and the United States.[10-16] Sample sizes ranged from 35 to

148 participants, encompassing infants, children, and adolescents with BA. Neurodevelopmental outcomes were assessed across multiple age groups, from early infancy to young adulthood, using validated and age-appropriate instruments, including the Bayley Scales of Infant and Toddler Development (BSID), Wechsler Intelligence Scales (WISC), General Movement Assessment (GMA), and standardized motor and adaptive behavior assessments. The primary objectives of the included studies were to characterize neurodevelopmental status in children with BA and to examine associations with clinical and disease-related factors, such as early neurological markers and long-term native liver survival. Collectively, the studies provided a comprehensive evaluation of cognitive, motor, language, and behavioral outcomes across different developmental stages. The key characteristics of the included studies are summarized in **Table 3.**

Table 3. Summaries of characteristics included studies

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
1	Earl et al., 2025[16]	Cross sectional (UK)	107 (<5 years old)	3.13 (1.04 - 4 .28)	39.00 (32.86 - 42.00)	MSEL, VABS, ADOS-2	• Parental concerns regarding neurodevelopment were reported in 37% of children, and 47% required at least one supportive service. • Children with BA under 5 years of age demonstrated significantly lower adaptive and cognitive scores than reference cohorts (P<.001). • ASD was identified in approximately 30% of children older than two years. • Earlier surgery and faster postoperative jaundice clearance were associated with better overall neurodevelopmental outcomes but not with autistic traits.

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
2	Dibbits et al., 2023[13]	Prospective Cohort (Netherlands)	41 (<3 years old)	3384 ± 470 gr	39 (IQR 36-42)	GMA, BSID-III	• Neurodevelopmental assessment in 38 toddlers with BA (mean age 29 ± 5 months; 70% post liver transplantation) showed below-average motor and cognitive performance in 39% and 17% of patients, respectively. • Abnormal GMA after KPE accurately predicted later motor and cognitive impairment, demonstrating high sensitivity (91% and 80%) and negative predictive value (94% for both). • These results suggest that motor impairment affects nearly one-third of toddlers with BA and that post KPE, GMA is a robust early predictor of neurodevelopmental risk
3	Rodijk et al., 2021[12]	Prospective Cohort (Netherlands)	35	3370 (IQR 2015 - 4285)	41 (IQR 36-42)	GMA	• Among 35 infants with BA assessed at diagnosis, atypical general movements were observed in 46%, a significantly higher prevalence than in healthy reference infants ($P < 0.001$). • No significant associations were found between atypical movements and clinical, biochemical, or anthropometric variables. • These results suggest early neurological vulnerability in infants with BA, supporting the need for close neurodevelopmental follow-up

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
4	Rodijk et al., 2020[14]	Cross sectional (Netherlands)	46 (6 –12 years old)	NR	39 (IQR 30-42)	WISC-III	• In a cohort of 46 school-aged children with BA (median age 11 years; 78% post–LT), 26% required special education, a rate significantly higher than the norm population (P < .01). • Motor performance and cognitive function were markedly impaired compared with population norms, with half of the children demonstrating low motor scores and a lower mean total IQ (91 vs 100; P < .01). • Neurodevelopmental outcomes did not differ between children with native livers and those who had undergone LT, indicating persistent impairments irrespective of transplant status.
5	Ruuska et al., 2021[15]	Cross sectional (Finland)	39 (1 – 20 years old)	3.270 ± 0.510	39 ± 1.7	BSID-III, WPPSI-III, WISC-IV, WAIS-IV	• Among 39 children with BA, mean total IQ was significantly below normative values (91 ± 15 vs 100 ± 15; P < 0.01), with earlier clearance of jaundice (< 0.05). • Motor development was impaired or at risk in 43% of assessed participants, and caregivers reported frequent functional difficulties in daily activities. • Neurodevelopmental outcomes did not differ significantly between children with native livers and those who had undergone LT

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
6	Squires et al., 2020[11]	Prospective Cohort (US)	93 (3 –12 years old)	NR	NR	WPPSI-III, WISC-IV	• In 93 children with BA and native liver, cognitive test scores on WPPSI III and WISC-IV were significantly higher than population norms across full-scale IQ and multiple domain indices. • Parental educational level was a strong positive predictor of full-scale IQ, whereas male sex and elevated bilirubin and GGT levels were associated with lower preschool IQ, and portal hypertension predicted reduced school-age IQ. • Overall, neurodevelopmental delay was not more prevalent in this cohort, although markers of advanced liver disease identified a vulnerable subgroup at risk for poorer cognitive outcomes.
7	Ng et al., 2018[10]	Prospective Cohort (US)	148 (1 –2 years old)	NR	NR	BSID-II, BSID-III	• In 148 children with BA assessed using BSID-III, neurodevelopmental scores at 12 and 24 months were significantly below normative values. • Ascites, growth faltering, and unsuccessful hepatoportoenterostomy independently predicted motor and cognitive language impairment, with failed surgery increasing risk more than fourfold at 2 years. • These results highlight early neurodevelopmental vulnerability in BA, particularly in those with advanced liver disease or poor growth.

MSEL = Mullens Scale of Early Learning; VABS = Vineland Adaptive Behavioral Scale; ADOS-2 = Autism Diagnostic Observation Schedule; BA = Biliary Atresia; ASD = Autism Spectrum Disorder; BSID-III = Bayley Scales of Infant Development, 3th edition; GMA = Prechtl's General Movement Assessment; KPE

= Kasai portoenterostomy; WISC-III = Wechsler Intelligence Scale for Children, third edition; WPPSI-III = The Wechsler Preschool and Primary Scale of Intelligence, 3rd edition; LT = liver transplantation; IQ = Intelligence Quotient; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition; WAIS-IV = Wechsler Adult Intelligence Scale, 4th edition; GGT = Gamma-glutamyl transferase

Descriptive Analysis of Neurocognitive Domain

Across the included studies, neurocognitive outcomes in children with BA demonstrated heterogeneous patterns across developmental stages and assessment tools. In early childhood, infants with BA demonstrated significantly lower overall neurodevelopmental performance compared with reference populations, as reflected by reduced Early Learning Composite scores on the Mullen Scales of Early Learning, with the most pronounced deficits observed in expressive language and visual reception, and additional impairments in receptive language relative to low-likelihood reference cohorts.[15] Findings reported at toddler age were derived from separate cohorts and study populations, rather than longitudinal follow-up of the same children, and were assessed using different cognitive indices and methodological approaches, including comparisons against population normative cognitive scores with a mean or median value of 100. In these toddler cohorts, median cognitive index scores were not significantly different from normative population values.[13] However, a substantial proportion of children continued to demonstrate clinically meaningful impairment, with up to 17% scoring more than one standard deviation below the population mean. Taken together, these findings do not indicate resolution of early neurodevelopmental deficits but instead reflect methodological heterogeneity and differences in reference standards across studies.[13, 15]

In school-aged children and adolescents, several cross-sectional studies reported significantly lower mean total intelligence quotient (IQ) scores in BA patients compared with normative populations, particularly affecting performance-based indices and specific cognitive domains.[12] Consistent deficits were observed in attention, visuomotor integration, perceptual reasoning, planning, and inhibitory control, while verbal memory and strategy formation were relatively preserved.[10, 12] These findings were supported by age- and sex-adjusted analyses using standardized Wechsler scales, which demonstrated stable cognitive performance across age groups but persistent underperformance relative to population norms.[10]

Longitudinal cohort studies provide the most robust evidence for evaluating neurodevelopmental trajectories over time, as they allow assessment of cognitive outcomes within the same individuals and minimize bias related to cross-sectional comparisons. In this context, the reviewed longitudinal data indicate that children surviving with their native liver can achieve cognitive performance comparable to, or exceeding, standardized test norms across multiple domains, including full-scale IQ,

verbal abilities, perceptual reasoning, and processing speed.[14, 15] Notably, higher parental educational attainment consistently emerged as a significant positive predictor of cognitive outcomes, suggesting an important role of environmental and socioeconomic factors in shaping long-term neurodevelopment. Parental education may reflect differences in cognitive stimulation, health literacy, and access to supportive resources, which could partially mitigate the adverse neurodevelopmental impact of early-life liver disease. Conversely, male sex and markers of more advanced liver disease were associated with lower cognitive performance, underscoring the interplay between biological vulnerability and modifiable environmental influences. These findings highlight the importance of considering parental education when interpreting neurodevelopmental outcomes and designing follow-up and early intervention strategies in this population.[11, 13]

Finally, assessments conducted at 12 and 24 months using Bayley Scales indicated broadly reduced cognitive performance relative to test norms at one year of age, with effect sizes attenuating by two years, particularly among children assessed with the Bayley-III. Overall, the evidence suggests that while a subset of children with BA achieve age-appropriate cognitive outcomes, particularly in cohorts with favorable clinical profiles, BA is frequently associated with domain-specific cognitive vulnerabilities that may persist into later childhood.[11, 13, 15]

Descriptive Analysis of Motoric Domain

Motor development outcomes in children with BA were consistently reported as vulnerable across infancy, toddlerhood, and later childhood, although the magnitude and pattern of impairment varied by age and assessment method. In toddler cohorts, overall motor performance was significantly below population norms, with median total motor index scores indicating clinically meaningful delay. More than one-third of toddlers demonstrated motor impairment exceeding one standard deviation below the population mean, with gross motor skills disproportionately affected compared with fine motor skills.[15]

Early motor repertoire abnormalities were frequently identified at the time of BA diagnosis using General Movement Assessment. Among 35 infants younger than 3 months, 46% demonstrated atypical general movements, including abnormal writhing or fidgety patterns. This prevalence substantially exceeds that reported in normative populations. These findings suggest early disruption of motor system development, observable within the first months of life and prior to surgical intervention.[14]

In preschool-aged children, motor outcomes assessed using standardized motor batteries were significantly poorer than normative references across all domains, including fine motor skills, ball skills, and balance, with half of the children classified within the low-performance range. Similarly, among children and adolescents assessed

with the Movement Assessment Battery for Children, distributions of total motor scores differed significantly from test norms, with increased proportions of individuals classified as at risk for or meeting criteria for motor difficulties. Deficits were most prominent in manual dexterity and aiming and catching skills, while balance performance appeared relatively preserved. Motor performance did not differ significantly across age subgroups, suggesting persistence of motor difficulties over time.[13, 14]

Longitudinal cohort data further indicated that motor impairment in early childhood was associated with disease severity and clinical course. Older age at KPE, the presence of medical complications, impaired somatic growth, ascites, and unsuccessful surgical outcomes were identified as key risk factors for physical and motor delay, with unsuccessful portoenterostomy remaining a strong independent predictor of motor impairment at two years of age. The available evidence indicates that children with BA are at increased risk of early and persistent motor development difficulties, particularly affecting gross motor and coordination-related domains, with outcomes closely linked to early disease severity and postoperative clinical status.[11]

Descriptive Analysis of Behavioral Domain

Children with BA demonstrate increased vulnerability in behavioral and adaptive functioning across development. In infancy, Vineland Adaptive Behavior Scales assessments showed significantly lower adaptive composite scores compared with reference cohorts, particularly in communication, socialization, and motor domains, with additional deficits in daily living skills. Autism-related behaviors were frequently observed early, with nearly half of assessed infants exceeding Autism Diagnostic Observation Schedule–2 thresholds and approximately one-third meeting criteria for a clinical or research diagnosis of autism spectrum disorder, showing a male predominance. During toddlerhood and later childhood, behavioral difficulties were identified in a subset of children, primarily affecting overall behavior, attention, and hyperactivity, as assessed using the Vineland Adaptive Behavior Scales (VABS). Additional parent-reported outcomes derived from standardized questionnaires, including the Five-to-Fifteen-Revised (5–15R) and the Child Behavior Checklist (CBCL 1.5–5), suggested increased difficulties in executive functioning, memory, learning, and language domains, whereas impairments in social and emotional functioning were reported less consistently. Formal psychiatric diagnoses were infrequently documented. However, a small number of children were reported to have a clinical diagnosis of attention-deficit/hyperactivity disorder.[16] Overall, behavioral and adaptive difficulties in children with BA appear early and may persist into later childhood, with variability across domains and individuals.[14, 16]

Discussion

This systematic review provides an updated and domain-specific synthesis of neurodevelopmental outcomes in children with BA, a rare neonatal cholangiopathy in which improving survival has shifted clinical focus toward long-term morbidity. Importantly, previous systematic or narrative reviews in BA were limited by inclusion of older cohorts, lack of recently published studies, and a predominant focus on global cognitive outcomes, without specific evaluation of motor, behavioral, and autism-related domains. By incorporating recent studies published up to 2025 and explicitly examining cognitive, motor, and behavioral outcomes, including autism spectrum-related features, this review addresses a critical gap in the literature. Overall, the findings demonstrate that children with BA are at increased risk of neurodevelopmental impairment across multiple domains, with motor dysfunction emerging as the most consistent and early abnormality, and behavioral and adaptive difficulties frequently evident from infancy.

The results are consistent with earlier reports in BA and other pediatric chronic liver diseases, which describe heterogeneous cognitive outcomes and persistent motor and executive function deficits. However, unlike prior reviews, this synthesis highlights that neurodevelopmental vulnerability in BA is not limited to cognition alone.[17, 18] Early motor abnormalities detected using GMA were prevalent even at diagnosis, and behavioral phenotypes, including attention difficulties and increased autism spectrum traits were identified in early childhood.[19] While early KPE and effective bile drainage were associated with more favorable cognitive outcomes, impairments were observed in both native-liver and post-transplant cohorts, suggesting that transplantation does not fully reverse early neurodevelopmental insults.[20] These findings extend previous knowledge by clarifying domain-specific risks and their persistence across developmental stages.

The associations between neurodevelopmental outcomes and markers of advanced liver disease support biologically plausible mechanisms.[21] Prolonged cholestasis, systemic inflammation, malnutrition, and fat-soluble vitamin deficiencies may disrupt neurogenesis, myelination, and synaptic maturation during critical periods of brain development.[7, 21] Early surgical intervention and optimized postoperative care may reduce, but not abolish, these effects by limiting metabolic and inflammatory exposure. Notably, none of the included studies reported neurodevelopmental harm attributable to surgical or medical treatment, reinforcing the interpretation that disease severity and chronicity, rather than intervention-related toxicity, drive adverse outcomes.[22]

Beyond cognitive and motor impairment, this review identifies behavioral and adaptive dysfunction as clinically relevant but previously underrecognized aspects of BA. Elevated rates of attention problems, executive dysfunction, and autism spectrum

disorder–related behaviors suggest early alterations in social–communication and self-regulatory development.[5] Parental educational attainment consistently emerged as a positive predictor of cognitive outcomes, highlighting the moderating role of environmental and socioeconomic factors.[21, 22] Clinically, these findings support the need for standardized, longitudinal neurodevelopmental surveillance in children with BA, with particular attention to early motor assessment and behavioral screening to enable timely referral for targeted intervention.[20]

This review is strengthened by adherence to PRISMA guidelines, prospective protocol registration, comprehensive literature searching, and the inclusion of recent studies employing validated behavioral, cognitive, and motor assessment tools. Importantly, a key strength lies in the integrated evaluation of behavioral outcomes, including autism-related features, across different developmental stages. Several limitations should be acknowledged. First, the literature search was restricted to English-language publications, which may have led to the exclusion of relevant studies published in other languages and introduced potential language bias. Although the databases searched are widely used and encompass a broad range of international journals, this restriction may limit the completeness and generalizability of the findings. Additional limitations include heterogeneity in study designs and outcome measures, modest sample sizes, limited use of control groups, and a predominance of data from high-income settings.

Furthermore, all included studies were observational in nature, rendering the findings susceptible to confounding and selection bias and limiting causal inference regarding the relationship between BA and neurodevelopmental outcomes. Future randomized or interventional studies, where feasible, may provide stronger evidence to clarify the effects of clinical and supportive interventions on long-term neurodevelopment. Despite these constraints, the overall consistency of findings across multiple developmental domains supports the conclusion that BA is associated with significant and multidimensional neurodevelopmental risk, underscoring the need for early and longitudinal developmental monitoring as part of standard clinical care.

Conclusion

This systematic review demonstrates that BA is associated with significant and multifaceted neurodevelopmental vulnerability, with motor and behavioral impairments emerging early and frequently persisting into later childhood, while cognitive outcomes remain heterogeneous. Disease severity and postoperative clinical courses consistently influence developmental trajectories, underscoring the importance of early surgical success and optimized medical management. Future research should prioritize large, multicenter longitudinal studies with standardized, domain-specific neurodevelopmental assessments, particularly focusing on behavioral and autism-related outcomes. Additionally, interventional studies evaluating the

effectiveness of early developmental and psychosocial support programs are needed to determine strategies that may improve long-term neurodevelopmental outcomes in children with BA.

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Conflict of Interest

The authors declare no conflict of interest.

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References

1. Davenport M. Updates in biliary atresia: Aetiology, diagnosis and surgery. Children (Basel). 2025;12(1). https://doi.org/10.3390/children12010095
2. Tran TT, Phan TK, Le LAT, Ho PD, Au NH, Pham NT. Biliary cysts in children with biliary atresia after kasai procedure. Clin Ter. 2025;176(1):91-6. https://doi.org/10.7417/ct.2025.5170
3. Nyholm I, Hukkinen M, Lohi J, Sjöblom N, Mutka A, Mutanen A, et al. Accumulation of altered serum bile acids predicts liver injury after portoenterostomy in biliary atresia. J Hepatol. 2025;83(2):440-52. https://doi.org/10.1016/j.jhep.2025.01.025
4. Meng Y, Yang Q, Liu S, Ke X, Zhan J. Genetic background and biliary atresia. World J Pediatr Surg. 2025;8(3):e001023. https://doi.org/10.1136/wjps-2025-001023
5. Hukkinen M, Pihlajoki M, Pakarinen MP. Predicting native liver injury and survival in biliary atresia. Semin Pediatr Surg. 2020;29(4):150943. https://doi.org/10.1016/j.sempedsurg.2020.150943
6. Vij M, Rela M. Biliary atresia: Pathology, etiology and pathogenesis. Future Sci OA. 2020;6(5):Fso466. https://doi.org/10.2144/fsoa-2019-0153
7. Freund C, Gotthardt DN. Vitamin a deficiency in chronic cholestatic liver disease: Is vitamin a therapy beneficial? Liver Int. 2017;37(12):1752-8. https://doi.org/10.1111/liv.13433
8. Tam PKH, Wells RG, Tang CSM, Lui VCH, Hukkinen M, Luque CD, et al. Biliary atresia. Nat Rev Dis Primers. 2024;10(1):47. https://doi.org/10.1038/s41572-024-00533-x
9. Antala S, Taylor SA. Biliary atresia in children: Update on disease mechanism, therapies, and patient outcomes. Clin Liver Dis. 2022;26(3):341-54. https://doi.org/10.1016/j.cld.2022.03.001
10. Ng VL, Sorensen LG, Alonso EM, Fredericks EM, Ye W, Moore J, et al. Neurodevelopmental outcome of young children with biliary atresia and native liver: Results from the children study. J Pediatr. 2018;196:139-47.e3. https://doi.org/10.1016/j.jpeds.2017.12.048
11. Squires JE, Ng VL, Hawthorne K, Henn LL, Sorensen LG, Fredericks EM, et al. Neurodevelopmental outcomes in preschool and school aged children with biliary atresia and their native liver. J Pediatr Gastroenterol Nutr. 2020;70(1):79-86. https://doi.org/10.1097/mpg.0000000000002489
12. Rodijk LH, Bos AF, Verkade HJ, de Kleine RH, Hulscher JBF, Bruggink JLM. Early motor repertoire in infants with biliary atresia: A nationwide prospective cohort study. J Pediatr Gastroenterol Nutr. 2021;72(4):592-6. https://doi.org/10.1097/mpg.0000000000003021
13. Dibbits MHJ, Rodijk LH, den Heijer AE, Bos AF, Verkade HJ, de Kleine RH, et al. Neurodevelopment in patients with biliary atresia up to toddler age: Outcomes and predictability. Early Hum Dev. 2023;180:105754. https://doi.org/10.1016/j.earlhumdev.2023.105754

14. Rodijk LH, den Heijer AE, Hulscher JBF, Alizadeh BZ, de Kleine RHJ, Verkade HJ, Bruggink JLM. Long-term neurodevelopmental outcomes in children with biliary atresia. J Pediatr. 2020;217:118-24.e3. https://doi.org/10.1016/j.jpeds.2019.10.054
15. Ruuska S, Lähteenmäki M, Häyrinen T, Kanerva K, Jahnukainen T, Haataja L, et al. Neurocognitive and motor functions in biliary atresia patients: A cross-sectional, prospective national cohort study. J Pediatr Gastroenterol Nutr. 2021;73(4):491-8. https://doi.org/10.1097/mpg.0000000000003206
16. Earl M, Samyn M, Blackmore C, Brace M, Day J, Javed A, et al. General and autism-related neurodevelopmental difficulties in biliary atresia. J Pediatr. 2025;285:114673. https://doi.org/10.1016/j.jpeds.2025.114673
17. Degtyareva A, Isaeva M, Tumanova E, Filippova E, Sugak A, Razumovsky A, et al. Combined predictors of long-term outcomes of kasai surgery in infants with biliary atresia. Pediatr Gastroenterol Hepatol Nutr. 2024;27(4):224-35. https://doi.org/10.5223/pghn.2024.27.4.224
18. Sun Y, Jia L, Yu H, Zhu M, Sheng M, Yu W. The effect of pediatric living donor liver transplantation on neurocognitive outcomes in children. Ann Transplant. 2019;24:446-53. https://doi.org/10.12659/aot.914164
19. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Longitudinal study of cognitive and academic outcomes after pediatric liver transplantation. J Pediatr. 2014;165(1):65-72.e2. https://doi.org/10.1016/j.jpeds.2014.03.032
20. Talcott JB, Beath SV, Patel T, Griffiths G, Kelly DA. Long-term effects of cholestatic liver disease in childhood on neuropsychological outcomes and neurochemistry. J Pediatr Gastroenterol Nutr. 2019;69(2):145-51. https://doi.org/10.1097/mpg.0000000000002380
21. John CC, Black MM, Nelson CA, 3rd. Neurodevelopment: The impact of nutrition and inflammation during early to middle childhood in low-resource settings. Pediatrics. 2017;139(Suppl 1):S59-s71. https://doi.org/10.1542/peds.2016-2828H
22. Wong ZH, Davenport M. What happens after kasai for biliary atresia? A european multicenter survey. Eur J Pediatr Surg. 2019;29(1):1-6. https://doi.org/10.1055/s-0038-1668146