Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Care-Pathway Timeliness in Biliary Atresia and Its Association With Clinical and Liver Histopathologic Outcomes: A Retrospective Cohort Study From Indonesia

Muhammad Ibrahim Sugiyono
ibrahim13005@mail.unpad.ac.id
Padjadjaran University
Dwi Prasetyo
Padjadjaran University
Nur Suryawan
Padjadjaran University
Yudith Setiati Ermaya
Padjadjaran University
Gartika Sapartini
Padjadjaran University
Dikki Drajat Kusmayadi
Padjadjaran University
Sri Endah Rahayuningsih
Padjadjaran University

Research Article

Keywords: biliary atresia, diagnostic delay, Kasai portoenterostomy, referral pathway, health system, liver histopathology

Posted Date: November 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11212816/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background: Biliary atresia (BA) requires timely diagnosis and Kasai portoenterostomy (KPE). We mapped care-pathway timeliness and examined unadjusted associations with in-hospital outcome and liver histopathology.

Methods: This retrospective cohort included children aged <6 years with BA undergoing KPE and liver biopsy at a tertiary referral hospital in Bandung, West Java, Indonesia, during 2021–2025. Age >60 days at each care stage defined an age-based indicator, without attributing provider-specific waiting time. Outcomes were documented death during the index KPE hospitalization or discharge alive, and histopathology categorized as normal, fibrosis, or cirrhosis. Analyses were unadjusted.

Results: Of 86 identified patients, 26 did not undergo KPE and were excluded; 60 were analyzed. Median ages at diagnosis and KPE were 129.5 and 175.0 days. The proportions exceeding 60 days were 23.3% at primary-care presentation, 65.0% at pediatrician assessment, 78.3% at subspecialist assessment, 81.7% at surgical assessment, and 96.7% at KPE. Documented death occurred in 33/60 (55.0%) and cirrhosis in 35/60 (58.3%). Median KPE age was 194.0 days among children who died versus 154.0 days among those discharged alive (Hodges–Lehmann estimate 47.0 days, 95% CI 3.0–91.0). At subspecialist referral, cirrhosis occurred in 32/47 (68.1%) children aged >60 days versus 3/13 (23.1%) aged ≤60 days.

Conclusions: The proportion exceeding 60 days increased across care stages. Older KPE age was associated with documented death; later-stage age indicators were associated with more severe histopathology. These exploratory associations warrant further referral-process evaluation.

Background

Biliary atresia is a progressive fibro-obliterative disorder of the intrahepatic and extrahepatic bile ducts that presents in early infancy and can rapidly progress to cirrhosis and liver failure. It is the leading surgically correctable cause of neonatal cholestasis and remains a major indication for pediatric liver transplantation worldwide [1–4]. Although its pathogenesis is multifactorial, involving genetic susceptibility, immune dysregulation, and environmental triggers, the clinical priority is consistent: infants with persistent jaundice, pale stools, and conjugated hyperbilirubinemia require prompt evaluation [2–4].

Kasai portoenterostomy (KPE) is the initial definitive operation intended to restore bile drainage and prolong survival with the native liver. Surgical age is an important prognostic factor. Systematic reviews have shown better native-liver survival when KPE is performed earlier, particularly by 60 days of age, whereas outcomes decline with later surgery [5–8]. Even after successful KPE, recurrent cholangitis, portal hypertension, malnutrition, progressive cirrhosis, and eventual transplantation remain common [2, 9–11]. These consequences make delayed recognition and treatment both a clinical problem and a health-system performance issue.

Delays can occur before and after entry into care. Families may interpret neonatal jaundice as physiologic, whereas primary care providers may have limited familiarity with conjugated bilirubin testing, stool color assessment, or urgent referral criteria [12–14]. At later stages, access to pediatric subspecialists, diagnostic imaging, surgical assessment, operating room capacity, and postoperative intensive care may further lengthen the pathway [15–17]. Screening and structured early-identification strategies can shorten the time to diagnosis, but their implementation varies substantially across health systems [18–21].

Published studies commonly use age at referral, diagnosis, or KPE as a summary measure of delay. Few studies have separated the complete pathway from the family and primary care levels through pediatric, gastroenterology-hepatology, and surgical services. This distinction is important in settings with tiered referral systems because a child may enter care early but still reach definitive treatment late. Indonesian studies have documented delayed referrals and gaps in primary-care knowledge, yet multilevel delays and their relationships with both mortality and liver histopathology remain insufficiently characterized [12–14, 22].

We therefore mapped the ages at which children with BA reached successive stages of care at a tertiary referral hospital in West Java, Indonesia. We examined whether the proportion of children exceeding 60 days of age increased across successive care stages and whether these age-based indicators were associated with documented death and liver histopathological severity in unadjusted analyses. This study adds an Indonesian tertiary-referral perspective by identifying where children first exceeded the 60-day threshold and describing intervals between diagnostic imaging and KPE.

Methods

Study Design and Setting

We conducted a single-center retrospective cohort study using medical records from child health and pediatric surgical services at a tertiary referral hospital in Bandung, West Java, Indonesia. The hospital provides pediatric gastroenterology-hepatology and pediatric surgical services. The eligible clinical-record period was 1 January 2021 through 31 December 2025. Medical records were collected and reviewed from June through August 2026. The study methods and analyses followed the approved protocol without substantive deviations.

Participants

The target population comprised children aged < 6 years with BA. We included all eligible patients treated during the study period who had undergone KPE and liver biopsy and whose records documented the ages at first healthcare presentation, pediatrician assessment, pediatric gastroenterology-hepatology assessment, pediatric surgery assessment, diagnosis, and KPE. Records were excluded if essential pathway data were incomplete or if the initial diagnosis of BA was not confirmed by operative findings

and/or subsequent investigations. Of 86 BA records identified, 26 patients did not undergo KPE and were excluded. Among patients who underwent KPE, no additional records were excluded because of incomplete pathway data, missing histopathology, or unconfirmed BA. Sixty patients met the eligibility criteria and were included in the analysis. No post-discharge follow-up was used for the primary outcome.

Variables and definitions

The referral pathway was reconstructed from recorded dates and ages. The stages were as follows: (1) first healthcare presentation at primary care; (2) referral from primary care to a pediatrician; (3) referral from a pediatrician to pediatric gastroenterology-hepatology; (4) referral from pediatric gastroenterology-hepatology to pediatric surgery; and (5) pediatric surgical care culminating in KPE. For comparability with the clinically relevant early-treatment threshold described in the literature [5–8], we defined an age-based indicator at each stage as age > 60 days at the corresponding contact, referral, or procedure; age ≤ 60 days was classified as not exceeding the threshold. This indicator identifies whether the recommended early-life window had already been exceeded at that point. It does not measure provider-specific waiting time or establish which provider caused the delay.

We recorded sex, age at each care stage, age at diagnosis and KPE, hospital entry service, anatomic BA type, imaging pathway, cytomegalovirus (CMV) IgM status, liver biochemistry, albumin, liver histopathology, and in-hospital outcome. The first care stage at which the 60-day threshold was exceeded was defined as the earliest recorded stage at which the child was older than 60 days. The family stage was assigned when the child first presented to primary care after 60 days of age; the primary-care stage when presentation occurred by 60 days but pediatrician assessment occurred after 60 days; the pediatrician stage when pediatrician assessment occurred by 60 days but subspecialist assessment occurred after 60 days; the pediatric gastroenterology-hepatology stage when subspecialist assessment occurred by 60 days but pediatric surgery assessment occurred after 60 days; and the pediatric surgery stage when surgical assessment occurred by 60 days but KPE was performed after 60 days. Children who underwent KPE by 60 days were classified as having no identified late stage. These labels describe the first point at which the threshold was observed to have been exceeded and should not be interpreted as provider-specific attribution.

Liver biopsy samples were categorized as normal, fibrosis, or cirrhosis according to the pathology report. In-hospital outcome was defined as discharge status from the hospitalization during which KPE was performed and categorized as documented death during that hospitalization or discharge alive. Outcome ascertainment was limited to the index KPE hospitalization; no post-discharge follow-up was used for the primary outcome. Post-discharge survival and time-to-event outcomes were not analyzed. Duration of the index KPE hospitalization was not available for analysis.

Data collection and statistical analysis

Data abstraction was performed by the first author (MIS), without independent second abstraction; a statistical analyst assisted with the analyses. Data were extracted from pediatric gastroenterology-hepatology and pediatric surgery outpatient and inpatient records. For each variable, dates of healthcare encounters were obtained from the corresponding referral or clinical record, biochemical data from laboratory reports obtained at initial presentation to the study hospital before KPE, anatomic BA type from operative findings, histopathology from pathology reports, and discharge outcome from the hospitalization record. Where multiple records documented the same transition, the earliest date representing actual patient contact or completed referral was used according to a predefined abstraction rule. Data were coded during abstraction. Records were reviewed for completeness and checked for duplication, inconsistency, and extreme values before analysis. No discrepant information was identified across the records reviewed. All 60 included patients had complete care-pathway data, BA type, liver histopathology, and discharge status. GGT and ALP were available for 58 of 60 participants; two observations were missing for each variable, and the reasons for missingness were unknown. Analyses used the available observations for each variable, without imputation. Intervals involving additional imaging were summarized only for patients who underwent the corresponding examinations. Analyses were performed using IBM SPSS Statistics for Windows, version 27.0.

Continuous variables were assessed for normality using the Kolmogorov-Smirnov or Shapiro-Wilk test and are presented as medians and interquartile ranges (IQRs) because the analyzed variables were nonnormally distributed. Categorical variables are reported as frequencies and percentages. Associations between categorical variables and in-hospital outcome or liver histopathological severity category were assessed using the chi-square test. When expected cell counts were insufficient, Fisher's exact test was used for 2×2 tables, and the Fisher–Freeman–Halton test with Monte Carlo estimation was used for larger contingency tables. Continuous variables were compared between outcome groups using the Mann–Whitney test. The Hodges–Lehmann estimator and its 95% confidence interval were calculated to quantify the location shift between the documented-death and discharged-alive groups. Effect estimates were not calculated for the three-category histopathological outcome because sparse 2×3 cells would have produced unstable or non-estimable category-specific estimates. All tests were two-sided, and $p < 0.05$ was considered statistically significant. No adjustment for multiple comparisons was applied; therefore, the reported bivariable associations were considered exploratory and unadjusted. During manuscript preparation, anatomic BA type was considered a potential confounder, while bilirubin and albumin were considered indicators of disease severity at hospital presentation. These considerations were not prespecified, and no adjusted analysis was performed. Owing to the small sample size and sparse categories, no multivariable model was fitted; potential confounding was not controlled. Because BA is uncommon and the study used total sampling of all eligible patients during the predefined period, no a priori sample-size calculation was performed. The resulting sample size limited the precision of estimates and the feasibility of adjusted analyses.

Patient and public involvement: Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this retrospective medical-record study.

Results

Patient characteristics and timing of care

Of 86 patients with BA identified during the study period, 26 were excluded because they did not undergo KPE. The remaining 60 patients underwent KPE and liver biopsy and had complete pathway data; all were included in the analysis (Fig. 1a). Of these, 34 (56.7%) were female. Jaundice began by 60 days in 46 children (76.7%), yet the median age at all subsequent healthcare stages exceeded 60 days. The median age was 73.5 days (IQR 46.0–117.2) at the pediatrician assessment, 108.5 days (65.5–155.5) at the pediatric gastroenterology–hepatology assessment, 109.5 days (74.0–156.8) at pediatric surgery assessment, 129.5 days (76.5–178.2) at the time of diagnosis, and 175.0 days (122.0–238.8) at the KPE (Table 1). Type 3 BA was the most common anatomic type (63.3%).

The first stage at which the 60-day threshold was exceeded was primary care in 25 children (41.7%), followed by the family stage in 14 (23.3%), pediatric surgery in nine (15.0%), and the pediatrician stage in eight (13.3%). Forty-nine children (81.7%) underwent hepatobiliary ultrasonography at the study hospital. Initial imaging occurred relatively soon after specialist contact: the median interval was 3 days from pediatric gastroenterology-hepatology assessment to ultrasonography and 5 days from pediatric surgery assessment to ultrasonography. In contrast, the median interval from ultrasonography to KPE was 42 days. Among the children who underwent additional imaging, the median intervals were 23 days from ultrasonography to scintigraphy, 51.5 days from ultrasonography to magnetic resonance cholangiopancreatography (MRCP), 58 days from scintigraphy to KPE, and 68 days from MRCP to KPE.

At KPE, liver histopathology revealed cirrhosis in 35 children (58.3%), fibrosis in 22 (36.7%), and normal histology in three (5.0%). Documented death occurred in 33 children (55.0%) during the KPE hospitalization, whereas 27 (45.0%) were discharged alive. GGT and ALP each had two missing observations; all 60 participants had recorded histopathology and discharge status.

Figure 1. Participant selection and age-based indicators across the biliary atresia care pathway

(a) Selection of the analytic cohort. (b) Numbers and percentages of the 60 included children aged >60 days at each care stage. These indicators reflect age at the corresponding stage, not provider-specific waiting times or attribution of delay. KPE, Kasai portoenterostomy.

Table 1. Participant characteristics and timing of care (N=60)

Characteristic	Value, n (%) or median (IQR)
Demographic and clinical characteristics	
Female sex	34 (56.7)
Type 3 biliary atresia	38 (63.3)
Reactive CMV IgM	23 (38.3)
Cirrhosis on liver biopsy	35 (58.3)
Documented death during the KPE hospitalization	33 (55.0)
Age at care stage, median days (IQR)	
Pediatrician assessment	73.5 (46.0–117.2)
Pediatric gastroenterology-hepatology assessment	108.5 (65.5–155.5)
Pediatric surgery assessment	109.5 (74.0–156.8)
Diagnosis	129.5 (76.5–178.2)
Kasai portoenterostomy	175.0 (122.0–238.8)
First care stage at which the 60-day threshold was exceeded	
No identified late stage	2 (3.3)
Family	14 (23.3)
Primary healthcare facility	25 (41.7)
Pediatrician	8 (13.3)
Pediatric gastroenterology-hepatology	2 (3.3)
Pediatric surgery	9 (15.0)
Selected intervals, median days (IQR)	
Gastroenterology-hepatology assessment to ultrasonography, n=42	3.0 (1.0–6.0)
Pediatric surgery assessment to ultrasonography, n=27	5.0 (2.0–14.0)
Ultrasonography to KPE, n=59	42.0 (25.0–75.5)
Ultrasonography to scintigraphy, n=11	23.0 (19.5–29.0)
Ultrasonography to MRCP, n=4	51.5 (40.5–78.8)
Scintigraphy to KPE, n=11	58.0 (39.0–89.5)
MRCP to KPE, n=4	68.0 (25.8–112.0)

All 60 participants had complete care-pathway data, anatomic BA type, liver histopathology, and discharge status. Denominators for selected imaging intervals are shown separately because examinations varied between participants.

Progressive crossing of the 60-day threshold

The proportion of children who had exceeded the 60-day threshold increased progressively across successive care stages. Fourteen children (23.3%) were older than 60 days when first brought to primary care; 39 (65.0%) were older than 60 days at referral to a pediatrician; 47 (78.3%) were at referral to pediatric gastroenterology-hepatology; 49 (81.7%) were at referral to pediatric surgery; and 58 (96.7%) were at KPE (Table 2; Fig. 1b). Thus, most children entered primary care within the early window, but the majority had exceeded it before reaching specialist and definitive surgical care.

Table 2. Age-based indicators across the referral pathway

Care stage	>60 days, n (%)	≤60 days, n (%)
Family presentation to primary care	14 (23.3)	46 (76.7)
Primary care to pediatrician	39 (65.0)	21 (35.0)
Pediatrician to pediatric gastroenterology-hepatology	47 (78.3)	13 (21.7)
Pediatric gastroenterology-hepatology to pediatric surgery	49 (81.7)	11 (18.3)
Pediatric surgery/KPE	58 (96.7)	2 (3.3)

The age-based indicator identifies whether the child had exceeded 60 days at the corresponding contact, referral, or procedure; it does not measure provider-specific waiting time. KPE, Kasai portoenterostomy.

Unadjusted associations with documented death

None of the stage-specific age-based indicators showed a statistically significant association with documented death. In the unadjusted analysis, median age at KPE was higher among children with documented death than among those discharged alive (194.0 vs 154.0 days; Hodges–Lehmann estimate 47.0 days, 95% CI 3.0–91.0; p=0.037) (Table 3). The death group also had higher total bilirubin levels (14.64 vs 11.90 mg/dL; p=0.003), higher direct bilirubin levels (11.00 vs 8.77 mg/dL; p<0.001), and lower albumin levels (2.50 vs 3.02 g/dL; p=0.037). Other prespecified ages along the pathway and liver enzyme levels were not associated with in-hospital outcome. All prespecified continuous-variable comparisons are presented in Table 3.

Table 3. Unadjusted continuous-variable comparisons by in-hospital outcome during the KPE admission

Variable	Documented death, median (IQR)	Discharged alive, median (IQR)	Hodges–Lehmann estimate (95% CI)	p value
Pediatrician age, days	73.0 (47.0–144.0)	75.0 (46.5–102.0)	15.0 (−13.0 to 48.0)	0.309
Subspecialist assessment age, days	136.0 (67.0–192.0)	93.0 (62.5–130.0)	30.0 (−2.0 to 75.0)	0.086
Pediatric surgery age, days	137.0 (81.0–195.0)	100.0 (63.5–141.0)	33.0 (−2.0 to 72.0)	0.070
Diagnosis age, days	143.0 (81.0–213.0)	104.0 (72.5–143.0)	31.0 (−3.0 to 75.0)	0.069
KPE age, days	194.0 (163.0–273.0)	154.0 (89.0–216.5)	47.0 (3.0 to 91.0)	0.037*
AST, U/L	296 (167–499)	326 (185.5–531.5)	−23 (−135 to 106)	0.683
ALT, U/L	138 (85–195)	188 (116.5–277.5)	−40 (−99 to 14)	0.152
GGT, U/L	494 (324–1025.5)	631 (487–1006.5)	−119 (−305 to 98)	0.296
ALP, U/L	574 (425–673)	614 (409.5–766.5)	−32 (−175 to 105)	0.640
Total bilirubin, mg/dL	14.64 (12.40–21.83)	11.90 (9.51–14.61)	3.78 (1.21 to 7.09)	0.003*
Direct bilirubin, mg/dL	11.00 (9.50–14.90)	8.77 (7.46–10.02)	2.89 (1.04 to 4.97)	<0.001*
Albumin, g/dL	2.50 (2.30–2.92)	3.02 (2.53–3.60)	−0.37 (−0.72 to −0.02)	0.037*

Comparisons were performed using the Mann–Whitney test. Hodges–Lehmann estimates were calculated as documented death minus discharged alive; positive estimates indicate higher values in the documented-death group. Subspecialist assessment refers to pediatric gastroenterology-hepatology assessment. GGT and ALP analyses each included 58 observations (31 documented deaths and 27 discharged alive), with two missing observations per variable; all other comparisons included 60 observations. IQR, interquartile range; CI, confidence interval; KPE, Kasai portoenterostomy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

Unadjusted associations with liver histopathological severity category

Histopathologic severity differed according to the first pathway stage at which the 60-day threshold was exceeded (p=0.010) and the anatomic BA type (p=0.002). Cirrhosis was present in 18 of 25 children (72.0%) whose threshold was first exceeded at the primary-care stage and in six of eight children (75.0%)

whose threshold was first exceeded at the pediatrician stage. Among children with type 3 BA, 27 of 38 (71.1%) had cirrhosis.

In exploratory unadjusted analyses, three successive age-based indicators were associated with histopathologic severity (Table 4). Cirrhosis was present in 68.1% of children who had exceeded 60 days by pediatrician-to-gastroenterology-hepatology referral compared with 23.1% of those who had not (p=0.009); in 67.3% versus 18.2% by gastroenterology-hepatology-to-surgery referral (p=0.012); and in 60.3% versus 0% at pediatric surgery/KPE (p=0.039). Indicators at first presentation and primary-care referral were not associated with histopathologic category. These p values were unadjusted for multiple comparisons and should be interpreted as exploratory.

Table 4. Associations between age-based indicators and liver histopathology

Care stage	Age category	Normal, n (%)	Fibrosis, n (%)	Cirrhosis, n (%)	p value
Pediatrician to gastroenterology-hepatology	>60 days	2 (4.3)	13 (27.7)	32 (68.1)	0.009*
	≤60 days	1 (7.7)	9 (69.2)	3 (23.1)	
Gastroenterology-hepatology to surgery	>60 days	2 (4.1)	14 (28.6)	33 (67.3)	0.012*
	≤60 days	1 (9.1)	8 (72.7)	2 (18.2)	
Pediatric surgery/KPE	>60 days	2 (3.4)	21 (36.2)	35 (60.3)	0.039*
	≤60 days	1 (50.0)	1 (50.0)	0 (0.0)	

P values were obtained using the Fisher–Freeman–Halton exact test with Monte Carlo estimation and were unadjusted for multiple comparisons. Percentages were calculated within each age category. Effect estimates were not reported because sparse 2×3 cells would have produced unstable or non-estimable category-specific estimates.

Discussion

Principal Findings

This study mapped the pathway to KPE in a tertiary referral cohort and reported a progressive increase in the proportion of children exceeding the 60-day threshold after entry into the healthcare system. Although more than three-quarters developed jaundice by 60 days and only 23.3% first reached primary care after that age, 65.0% had exceeded 60 days by referral to a pediatrician and 96.7% by KPE. The median age at KPE was 175 days, and more than half of the cohort already had cirrhosis. None of the stage-specific age-based indicators were significantly associated with documented death; however,

older age at KPE in the continuous analysis was associated with death. Later-stage age-based indicators were associated with more severe histopathological categories.

Delays before tertiary care

Most children in this selected cohort first presented to primary care by 60 days of age, whereas the threshold was most commonly first exceeded between primary-care presentation and pediatrician assessment. Indonesian surveys have revealed incomplete knowledge among primary healthcare providers regarding prolonged jaundice, stool color changes, conjugated bilirubin testing, and appropriate referral timing [13, 14]. These gaps are understandable because infants with BA may initially appear well and their jaundice may be mistaken for a benign neonatal condition [3, 18]. Nevertheless, persistent jaundice beyond two weeks or pale stools should prompt direct or conjugated bilirubin measurement and urgent specialist evaluation.

This finding is relevant beyond individual clinician knowledge. Referral authorization, geographic access, appointment availability, and diagnostic testing can interact to prolong care. International studies likewise show that socioeconomic factors, hospital characteristics, and regional healthcare variation influence the timing of KPE [16, 21]. Consequently, education alone is unlikely to shorten the pathway unless it is paired with an explicit time-critical referral process.

Care within specialist and surgical services

The proportion of children exceeding 60 days continued to increase after pediatric assessment: 78.3% of the children had exceeded the threshold by referral to pediatric gastroenterology-hepatology and 81.7% exceeded the threshold by referral to pediatric surgery. This pattern resembles the two-phase model described by Harpavat and colleagues, in which substantial time can elapse both before specialist referral and between specialist involvement and treatment [15]. It also contrasts with a 2024 European multicenter survey reporting median ages of 53 days at tertiary referral and 60 days at KPE [23]. The median age at gastroenterology-hepatology assessment in our cohort was 108.5 days, followed by a median age of 175 days at KPE. Comparisons with international cohorts should be interpreted cautiously because healthcare systems, referral structures, case-ascertainment methods, surgical eligibility, and inclusion criteria differ across settings.

Interval analysis helps identify a later phase for process review. Initial ultrasonography was generally obtained within days of specialist assessment, whereas the median interval from ultrasonography to KPE was 42 days. Children who underwent MRCP or scintigraphy had additional intervals before surgery. These observations do not establish that additional imaging caused the delay; atypical findings, clinical instability, preoperative optimization, scheduling constraints, and referral logistics may all have contributed. However, they identify the post ultrasonography diagnostic and operative phase as a priority for further evaluation. Standardized pathways should specify which tests are essential, when equivocal imaging should lead to operative cholangiography, and how suspected BA receives expedited surgical scheduling [3, 17].

In-hospital outcomes and liver injury

None of the stage-specific age-based indicators showed a statistically significant association with documented death. In contrast, age at KPE was associated with death when analyzed as a continuous variable. Several factors may explain this difference. Dichotomization at 60 days reduced information, only two children underwent KPE by 60 days, and the resulting categories were highly imbalanced. The small sample limited statistical power, and baseline disease severity and other prognostic factors may have confounded the association with documented death during the KPE hospitalization. Previous studies have reported better native-liver survival after earlier KPE [6–8], although that outcome differs from the discharge outcome assessed here. Our unadjusted analysis cannot establish an independent or causal effect. Higher bilirubin and lower albumin among children who died suggest more advanced cholestasis and impaired hepatic synthetic function, but our data cannot be used to determine whether these laboratory abnormalities mediate the association between operative age and documented death.

Later-stage age-based indicators were associated with more severe liver histopathology. Cirrhosis was substantially more common among children who had exceeded 60 days by pediatrician-to-subspecialist and subspecialist-to-surgery referrals, and no cirrhosis was observed among the two children who underwent KPE by 60 days. This pattern is biologically plausible given the rapid progression of fibroinflammatory injury in BA [1, 2, 22]. Nevertheless, the sparse number of cells, small number of early-treated children, multiple bivariable comparisons, and possibility of chance findings make the exact associations uncertain. Histologic severity also differed by anatomic type, with type 3 disease showing the highest proportion of cirrhosis, and baseline severity or disease type may have confounded the observed associations. These unadjusted associations should therefore be regarded as hypothesis generating rather than evidence of independent effects.

Public health and service implications

The results support a multilevel response. At the family and primary-care levels, stool color education and systematic review of jaundice at 2–4 weeks can promote early recognition [18–20]. At the secondary and tertiary levels, suspected BA should trigger direct referral, rapid conjugated bilirubin assessment, coordinated imaging, and early joint review by hepatology and surgery. A time-stamped referral dashboard or single clinical pathway could make transition intervals visible and assign responsibility for each step. Regional centralization may improve expertise, but only if referral and operative capacity are sufficient to prevent a new bottleneck at the tertiary center [24, 25].

The added value of this study is the combination of sequential age-threshold mapping with operational intervals between diagnostic imaging and KPE in a tertiary referral setting in Indonesia. The progressive increase in the proportion exceeding 60 days indicates that interventions at one level alone may be insufficient. Future quality-improvement work should measure actual intervals between the first abnormal signs, referrals, diagnoses, and surgeries so that provider-specific waiting times and modifiable causes can be evaluated directly.

Strengths and limitations

This study has several strengths. We reconstructed the care pathway from first presentation to KPE and assessed both clinical and histopathological outcomes. The data also cover five years of experience at a major referral center and provide information on the time between diagnostic imaging and surgery, which is not commonly reported.

These findings should be interpreted with caution. Because this was a retrospective study, the analysis depended on the accuracy and completeness of medical records. The age-based indicators reflected whether children had exceeded 60 days at each care stage and did not measure provider-specific waiting times. The study was also conducted at a single referral center, where children may have had more severe disease or longer delays than the general population of children with BA in Indonesia.

The study included only children who underwent KPE and liver biopsy and had complete pathway data. Twenty-six of 86 identified patients did not undergo KPE and were excluded from the analytic cohort. The reasons why these patients did not undergo KPE, as well as their characteristics and outcomes, were not systematically characterized. Their exclusion may have introduced selection bias and limits assessment of the complete BA care pathway. The observed associations therefore apply to a selected surgical cohort and cannot be extrapolated to all children with BA identified at the hospital. In addition, only two children underwent KPE by 60 days, limiting the precision of comparisons between children who underwent KPE by 60 days and those treated later.

We did not assess jaundice clearance, cholangitis, native-liver survival, transplantation, socioeconomic conditions, geographic distance, or the specific reasons for delays along the care pathway. The outcome was limited to discharge status from the KPE hospitalization and therefore does not establish longer-term survival after KPE. The analyses were not adjusted for disease type, baseline severity, or other potential confounders, and the large number of comparisons may have produced chance findings. Future multicenter studies should include all consecutively diagnosed patients, including those who do not undergo KPE, and should use standardized follow-up, clearly defined postoperative outcomes, and multivariable or survival analyses.

Conclusion

In this Indonesian tertiary referral cohort, the proportion of children exceeding 60 days increased progressively across successive stages of the BA care pathway and was highest at KPE. Older age at KPE was associated with documented death, whereas later-stage age-based indicators were associated with more severe liver histopathology. These unadjusted associations should be interpreted in light of the retrospective design, selected cohort, sparse categories, multiple comparisons, and lack of multivariable adjustment. These findings identify referral, diagnostic, and operative transitions as priorities for further process evaluation. Larger prospective multicenter studies are required to estimate independent associations and identify modifiable causes of delay.

Abbreviations

BA
biliary atresia
CI
confidence interval
CMV
cytomegalovirus
IQR
interquartile range
KPE
Kasai portoenterostomy
MRCP
magnetic resonance cholangiopancreatography
SPSS
Statistical Package for the Social Sciences

Declarations

Ethics approval and consent to participate

The study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital (approval and research-permission numbers DP.04.03/D.XIII.13/343/2026 and DP.04.03/D.XIII.2.3/1580/2026). The requirement for informed consent was waived by the ethics committee because this retrospective study used coded secondary medical record data, involved no direct contact with participants, and included no personal identifiers in the analytical dataset. All procedures were conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. This manuscript does not contain identifiable individual participant data.

Patient and public involvement

The patient and public involvement statement is provided in the Methods section.

Availability of data and materials

The datasets analyzed during the current study are not publicly available because of institutional confidentiality restrictions but may be made available by the corresponding author upon reasonable request, subject to ethics and institutional approval.

Funding

The study itself received no external research funding. Publication fees were supported by Universitas Padjadjaran through the Indonesian Endowment Fund for Education (LPDP) under the EQUITY Program.

Competing interests

The authors have no relevant financial or nonfinancial interest to disclose.

Acknowledgments

The publication fee was supported by Universitas Padjadjaran through the Indonesian Endowment Fund for Education (LPDP), under the Ministry of Higher Education, Science, and Technology of Indonesia, and administered within the EQUITY Program (Contract Nos. 4303/B3/DT.03.08/2025 and 3927/UN6.RKT/HK.07.00/2025). The authors also express their gratitude to the medical personnel of the Department of Child Health at Dr. Hasan Sadikin General Hospital for their valuable contributions to patient management and data collection.

Author Contributions

All authors participated in the conception and design of the study. MIS was responsible for study conceptualization, data collection and analysis, and preparation of the initial manuscript draft. DP and NS supervised the research process, contributed to data interpretation, critically revised the manuscript, and approved the final version. YSE, GS, DDK, and SER provided intellectual input through critical revision of the manuscript. All authors reviewed and approved the final manuscript.

Trial Registration

Clinical trial number: not applicable.

References

1. Davenport M. Updates in biliary atresia: aetiology, diagnosis and surgery. Children. 2025;12:95. 10.3390/children12010095.
2. Tam PKH, Wells RG, Tang CSM, Lui VCH, Hukkinen M, Luque CD, et al. Biliary atresia. Nat Rev Dis Primers. 2024;10:47. 10.1038/s41572-024-00533-x.
3. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2017;64:154–68. 10.1097/MPG.0000000000001334.
4. Antala S, Taylor SA. Biliary atresia in children: update on disease mechanism, therapies, and patient outcomes. Clin Liver Dis. 2022;26:341–54. 10.1016/j.cld.2022.03.001.

5. Bezerra JA, Asai A, Tiao G, Mullapudi B, Balistreri WF. Biliary atresia and other disorders of the extrahepatic bile ducts. In: Suchy FJ, Sokol RJ, Balistreri WF, editors. Liver disease in children. 5th ed. Cambridge: Cambridge University Press; 2021. pp. 162–81. 10.1017/9781108918978.011.
6. 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;182:2693–704. 10.1007/s00431-023-04925-1.
7. Yang C, Ke M, Zhou Y, Xu H, Diao M, Li L. Impact of early Kasai portoenterostomy on short-term outcomes of biliary atresia: a systematic review and meta-analysis. Front Surg. 2022;9:924506. 10.3389/fsurg.2022.924506.
8. Liu F, Yeung F, Chung PHY. The outcome of Kasai portoenterostomy after day 70 of life. Front Pediatr. 2022;10:1015806. 10.3389/fped.2022.1015806.
9. Boster JM, Feldman AG, Mack CL, Sokol RJ, Sundaram SS. Malnutrition in biliary atresia: assessment, management, and outcomes. Liver Transpl. 2022;28:483–92. 10.1002/lt.26339.
10. Matcovici M, Stoica I, Smith K, Davenport M. What makes a successful Kasai portoenterostomy unsuccessful? J Pediatr Gastroenterol Nutr. 2023;76:66–71. 10.1097/MPG.0000000000003638.
11. Hukkinen M, Ruuska S, Pihlajoki M, Kyrönlahti A, Pakarinen MP. Long-term outcomes of biliary atresia patients surviving with their native livers. Best Pract Res Clin Gastroenterol. 2022;56–57:101764. 10.1016/j.bpg.2021.101764.
12. Masturina M, Prihaningtyas RA, Setyoboedi B, Arief S. Late referral of biliary atresia and poor clinical outcomes. Korean J Gastroenterol. 2025;85:382–8. 10.4166/kjg.2025.005.
13. Setyoboedi B, Prihaningtyas RA, Utomo MT, Arief S. Early detection of biliary atresia in primary health care: still a problem. F1000Res. 2022;11:1245. 10.12688/f1000research.125555.1.
14. Prihaningtyas RA, Setyoboedi B, Nesa NNM, Masturina M, Utomo MT, Arief S. Primary healthcare providers' knowledge on the early detection of biliary atresia. Folia Med Indones. 2024;60:85–93. 10.20473/fmi.v60i1.48446.
15. Harpavat S, Lupo PJ, Liwanag L, Hollier J, Brandt ML, Finegold MJ, et al. Factors influencing time-to-diagnosis of biliary atresia. J Pediatr Gastroenterol Nutr. 2018;66:850–6. 10.1097/MPG.0000000000001887.
16. Townsend MR, Jaber A, Abi Nader H, Eid SM, Schwarz K. Factors associated with timing and adverse outcomes in patients with biliary atresia undergoing Kasai hepatoportoenterostomy. J Pediatr. 2018;199:237–e2422. 10.1016/j.jpeds.2018.04.001.
17. Anindita AN, Setyoboedi B, Arief S, Prihaningtyas RA. Accuracy of 2-phase abdominal ultrasound for diagnosing biliary atresia. Bali Med J. 2024;13:514–8. 10.15562/bmj.v13i2.4907.
18. Harpavat S, Aucott SW, Karpen SJ, Shneider BL, Wang K, Cohen MB, et al. Guidance for the primary care provider in identifying infants with biliary atresia by 2–4 weeks of life: clinical report. Pediatrics. 2025;155:e2024070077. 10.1542/peds.2024-070077.
19. Harpavat S, Garcia-Prats JA, Anaya C, Brandt ML, Lupo PJ, Finegold MJ, et al. Diagnostic yield of newborn screening for biliary atresia using direct or conjugated bilirubin measurements. JAMA.

2020;323:1141–50. 10.1001/jama.2020.0837.

20. Guthery SL, Jensen KM, Esplin SM, O'Brien E, Krong J, Srivastava R. Feasibility of biliary atresia newborn screening in an integrated health network. J Pediatr Gastroenterol Nutr. 2024;79:954–61. 10.1002/jpn3.12367.
21. Telles L, Melo PHM, Diniz AMB, Eckerdt Lech G, Gerk A, Kratky L, et al. Suspected biliary atresia in Brazil: impact of regional healthcare variations on diagnostic timeliness. J Pediatr Surg Open. 2026;14:100267. 10.1016/j.yjpso.2026.100267.
22. Gunadi, Sirait DN, Budiarti LR, Paramita VMW, Fauzi AR, Ryantono F, et al. Histopathological findings for prediction of liver cirrhosis and survival in biliary atresia patients after Kasai procedure. Diagn Pathol. 2020;15:79. 10.1186/s13000-020-00996-y.
23. Lacaille F, Nicastro E, Czubkowski P, Gonçalves CC, Le Thi TG, Koletzko S. Awareness, referral and age at Kasai surgery for biliary atresia in Europe: a survey of the Quality-of-Care Task Force of ESPGHAN. J Pediatr Gastroenterol Nutr. 2024;78:1374–82. 10.1002/jpn3.12186.
24. Okubo R, Nio M, Sasaki H, Wada M. Japanese Biliary Atresia Registry. World J Pediatr Surg. 2025;8:e001024. 10.1136/wjps-2025-001024.
25. van der Schyff F, Terblanche AJ, Botha JF. Improving poor outcomes of children with biliary atresia in South Africa by early referral to centralized units. JPGN Rep. 2021;2:e073. 10.1097/PG9.0000000000000073.