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ORIGINAL RESEARCH

Prognostic Outcomes by Ishak Fibrosis Score Grouping in Biliary Atresia After Kasai Surgery

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Objective: This study aimed to assess the native liver survival (NLS) of biliary atresia (BA) patients with varying Ishak scores post Kasai portoenterostomy (KPE).

Methods: A prospective cohort study analyzed 83 BA patients who underwent KPE. Patients were stratified into Mild Fibrosis Group (Ishak 1–2, n=20), Moderate Fibrosis Group (Ishak 3–4, n=39), and Cirrhosis Group (Ishak 5–6, n=24) based on postoperative Ishak scores. At the 6-month postoperative follow-up, clinical characteristics and liver function test outcomes were compared between groups to evaluate postoperative recovery profiles.

Results: Generalized estimating equations (GEE) revealed time-dependent declines in ALT, AST, ALP, and Total Bile Acid (TBA) across groups (P<0.05), with cirrhosis patients exhibiting higher GGT and bilirubin levels vs. mild fibrosis (P<0.05). 6-month Clearance of Jaundice (CoJ) differed significantly: 55.0% (mild) vs. 38.5% (moderate) vs. 8.3% (cirrhosis) (P=0.003). Six-month NLS sharply declined with fibrosis severity: 80.0% (mild) vs. 16.7% (cirrhosis) (P<0.001). Multivariate logistic regression identified lower Ishak scores and younger surgical age as independent predictors of survival (P<0.05).

Conclusion: KPE improved liver function, but the Cirrhosis Group had poorer outcomes. Hepatic fibrosis severity correlated negatively with NLS, highlighting the importance of early surgery.

Keywords: biliary atresia, Kasai portoenterostomy, liver fibrosis, Ishak score, prognostic

Introduction

BA is a life-threatening neonatal cholestatic disorder of unknown etiology, characterized by progressive fibro-obliteration of the intra- and extrahepatic bile ducts. This pathological process leads to cholestasis and irreversible hepatic fibrosis, culminating in cirrhosis if untreated. The global prevalence of BA ranges from 1 in 5000 to 1 in 20,000 live births.[1,2] First-line management involves the Kasai procedure (hepatic portoenterostomy) to restore bile drainage.[3] A recent meta-analysis underscores the critical importance of early intervention in BA, demonstrating that performing the KPE within the first 30 days of life significantly improves long-term native liver survival compared to later surgery, and thus advocates for effective newborn screening to facilitate timely diagnosis.[4] However, the surgery fails to establish adequate bile flow in nearly 50% of patients, resulting in persistent intrahepatic ductal fibrosis and progressive fibrosis.[5] Without timely intervention, BA rapidly progresses to end-stage cirrhosis and liver failure within the first year of life.[6] Even after technically successful portoenterostomy, over 50% of survivors eventually require liver transplantation (LT) to prevent mortality, necessitating lifelong immunosuppression with associated complications.[7] Recent advancements in LT techniques have prompted proposals for primary one-stage LT to replace the conventional two-step approach (Kasai procedure followed by LT. This strategy may mitigate secondary surgical trauma and reduce transplant complexity associated with post-Kasai abdominal adhesions.[8,9]

Accurate identification of prognostic risk factors and development of validated predictive models are critical to inform personalized clinical management in BA. In a multicenter observational study, Tomita et al developed the iBALF

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scoring system incorporating age, total bilirubin, and platelet count. Patients with iBALF scores >5.27 demonstrated markedly reduced 1-year NLS (14%-34.7%) compared to lower-score counterparts. These findings suggest that KPE provides limited benefit for high iBALF-score patients, positioning one-stage LT as a potentially preferable initial intervention in this subgroup.[10] While the iBALF system represents an innovative approach to preoperative risk stratification, its clinical utility remains investigational pending validation through multicenter prospective trials. Current evidence does not justify using iBALF scores as a standalone criterion for one-stage LT selection. Gunadi et al demonstrated that advanced hepatic fibrosis independently predicts adverse clinical outcomes in BA.[11]

The histopathological landscape of BA in liver tissue is defined by a constellation of progressive changes culminating in a severe obstructive cholangiopathy. Core features include a prominent ductular reaction—comprising ductular proliferation, activation of hepatic progenitor cells, and stromal expansion with extracellular matrix deposition and neutrophilic infiltration. This is accompanied by bile plug formation within proliferated and tortuous portal bile ducts or dilated ductules, and a portal-based inflammatory infiltrate. A hallmark of disease progression is the development of portal and bridging fibrosis, which can advance to cirrhosis. In a subset of cases, ductal plate malformation (DPM) is also observed. Collectively, these features reflect a relentless process of inflammatory and obstructive injury, with the extent and pattern of liver fibrosis serving as a critical prognostic indicator, a focus of the present study.[12–14]

Current histopathological staging systems for liver fibrosis encompass the Scheuer system, METAVIR, and Ishak scoring (0–6 stages), each with distinct diagnostic applications.[15,16] The Ishak system (0–6 stages) is the most widely adopted fibrosis classification framework in multicenter studies, enabling standardized assessment of fibrotic progression in pre- and post-intervention cohorts.[17]

Although previous studies have confirmed the correlation between advanced liver fibrosis and poor prognosis in BA,[11,18,19] precise risk stratification based on the Ishak scoring system remains underexplored. Our prospective study design overcomes the inherent limitations of retrospective analyses by employing GEE to quantitatively model temporal recovery patterns. Through this approach, we have successfully established both a precise correlation between Ishak stages and 6-month NLS rates and clinically actionable threshold values for therapeutic decision-making. This prospective study aims to develop an Ishak score-based system to predict 6-month native liver survival, thereby informing the critical choice between primary liver transplantation and the Kasai procedure.

Methods

Study Population

A single-center prospective study was carried out. Patients diagnosed with BA at the Affiliated Hospital of Zunyi Medical University, a tertiary-level hospital in China, between June 1, 2021, and December 31, 2023, were recruited as the study subjects.

Inclusion Criteria: (1) Patients were definitively diagnosed with BA at our center through comprehensive evaluations, including laparoscopic exploration and intraoperative cholangiography. The diagnosis was confirmed by the surgical team performing KPE and further validated by histopathological examination. (2) Patients received standardized perioperative management under the care of our multidisciplinary team and completed regular follow-up assessments. (3) Patients had no concurrent congenital hepatobiliary malformations.

Exclusion Criteria: (1) Patients whose families opted to discontinue medical care due to life-threatening complications or other critical circumstances. (2) Patients with concurrent congenital gastrointestinal malformations necessitating prioritized surgical intervention.

A cohort of 100 patients with BA was initially screened, with 17 excluded per predefined criteria. The final study population comprised 83 children (50 male, 33 female) who underwent KPE and maintained protocol-compliant follow-up (Figure 1). Postoperative liver biopsy specimens, independently evaluated by two senior hepatopathologists using the Ishak scoring system, stratified patients into three histologic severity groups: mild fibrosis (Ishak 1–2, n=20), moderate fibrosis (Ishak 3–4, n=39), and severe fibrosis (Ishak 5–6, n=24), all prospectively monitored per study protocol (Figure 2). Comparative analysis of predefined prognostic biomarkers across subgroups was conducted at the 6-month postoperative interval.

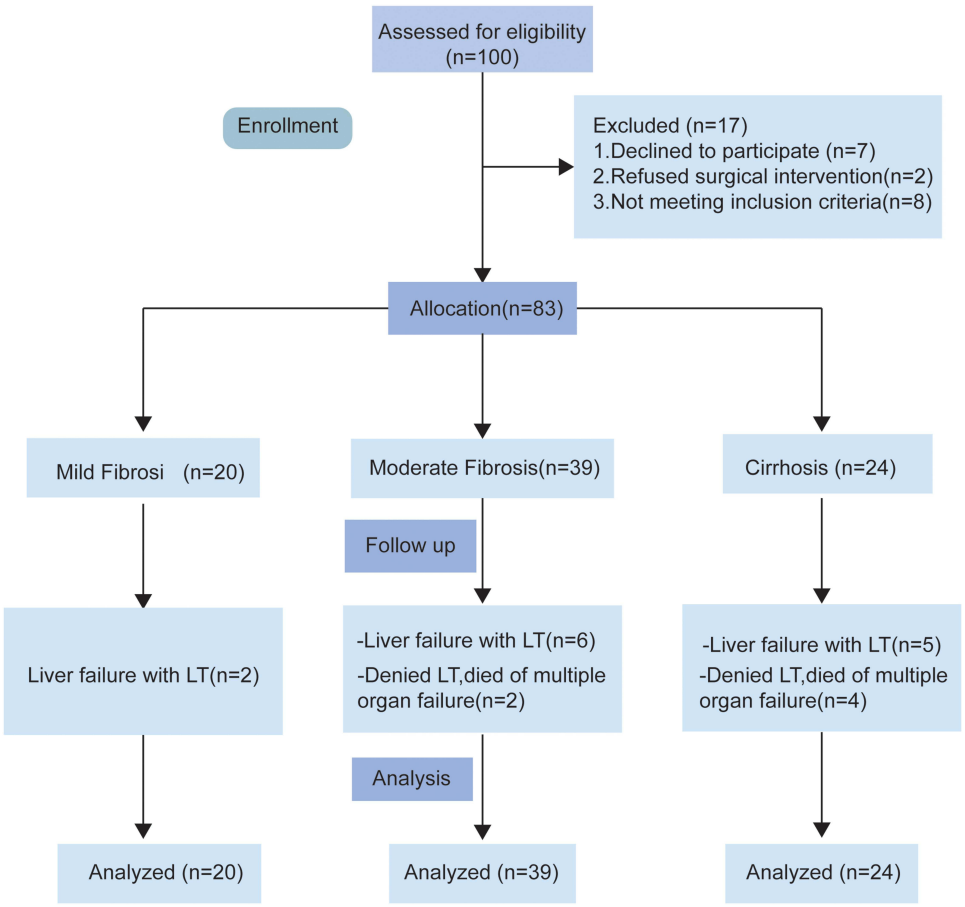

Figure 1 Study Flow Chart.

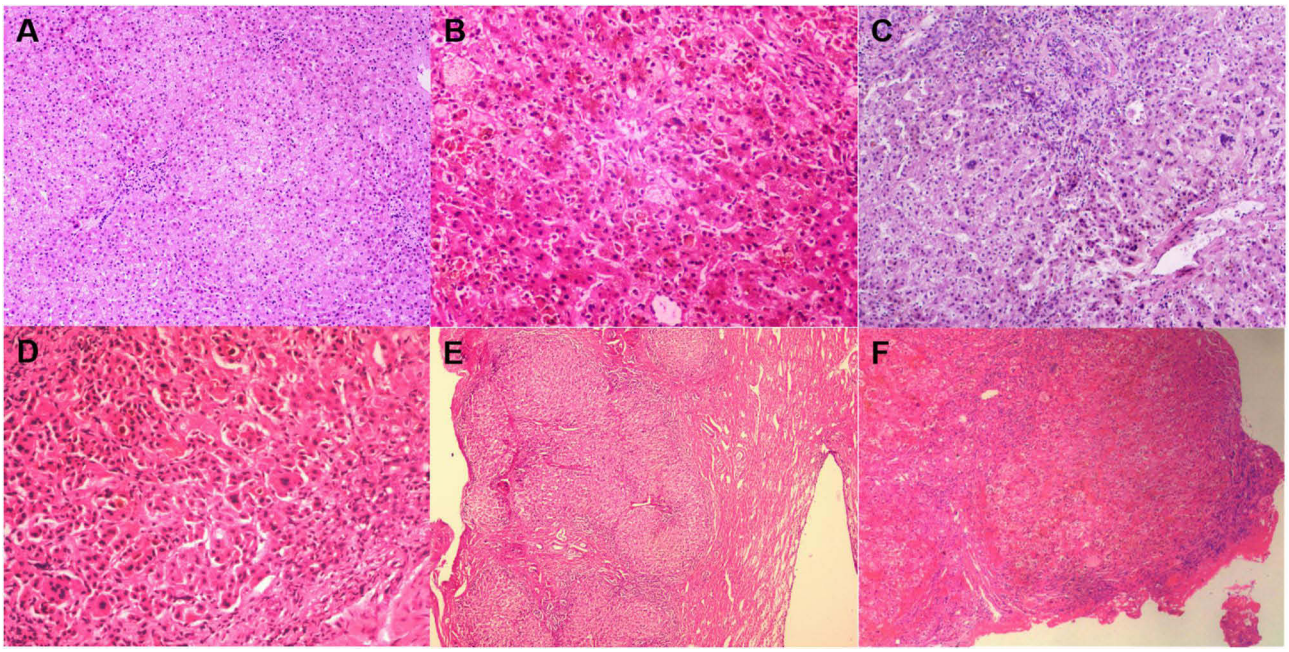

Figure 2 Histopathological Staging of BA Using Ishak Fibrosis Scoring System.Schematic of Ishak scoring criteria: Stage 1: No fibrous septa Stage, 2: Single short fibrous septum, Stage 3: 2–3 bridging septa, Stage 4: ≥4 incomplete septa, Stage 5: ≥4 septa with 1–3 pseudolobules, Stage 6: >3 pseudolobules with architectural distortion.Mild fibrosis (Ishak 1–2): (**A**) (×40), (**B**) (×100), Moderate fibrosis (Ishak 3–4): (**C**) (×100), (**D**) (×100), cirrhosis (Ishak 5–6): (**E**) (×40), (**F**) (×40).

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The observed 30% cirrhosis prevalence at diagnosis in our cohort likely reflects delayed initial presentation patterns. This can be attributed to limited neonatal jaundice recognition capabilities in primary healthcare facilities across Guizhou's remote regions, a province in southwestern China.

Ethical Considerations

Ethical approval for this study (KLLY-2021-122, 24 May 2021) was provided by the Ethical Committee of the Affiliated Hospital of Zunyi Medical University, China. All research was conducted by the Helsinki Declaration. Written informed consent was provided by the parents or legal guardians of all participants.

Therapeutic Approach

Following diagnostic confirmation of BA via laparoscopic exploration with intraoperative cholangiography, we proceeded with KPE. The surgical protocol included: (1) meticulous excision of the fibrous remnant at the hepatic portal plate; (2) creation of a 30–35 cm Roux-en-Y jejunal limb passed retromesenterically through the transverse mesocolon; (3) hepaticojejunostomy performed with interrupted 5–0 polyglactin sutures in a single-layer, extra-mucosal anastomosis technique; (4) Before abdominal closure, a routine liver biopsy was performed (Figure 3). A random liver lobe was selected, and a 0.2-cm-diameter tissue sample was excised by electrocautery for biopsy.[19] Postoperative management comprised: Intravenous cefoperazone-sulbactam (100 mg/kg/day) for 14 days followed by oral amoxicillin-clavulanate (40 mg/kg/day) until 21 days postop; Methylprednisolone pulse therapy initiated on postoperative day 5 (4 mg/kg/day IV), tapered by 1 mg/kg every 72 hours, transitioning to oral prednisolone (2 mg/kg/day) at week 2, with complete cessation by week 16; Adjunctive therapy with ursodeoxycholic acid (20 mg/kg/day) and fat-soluble vitamin supplementation (Vitamins A 5000 IU, D 400 IU, E 15 IU, K 2 mg daily).[20,21]

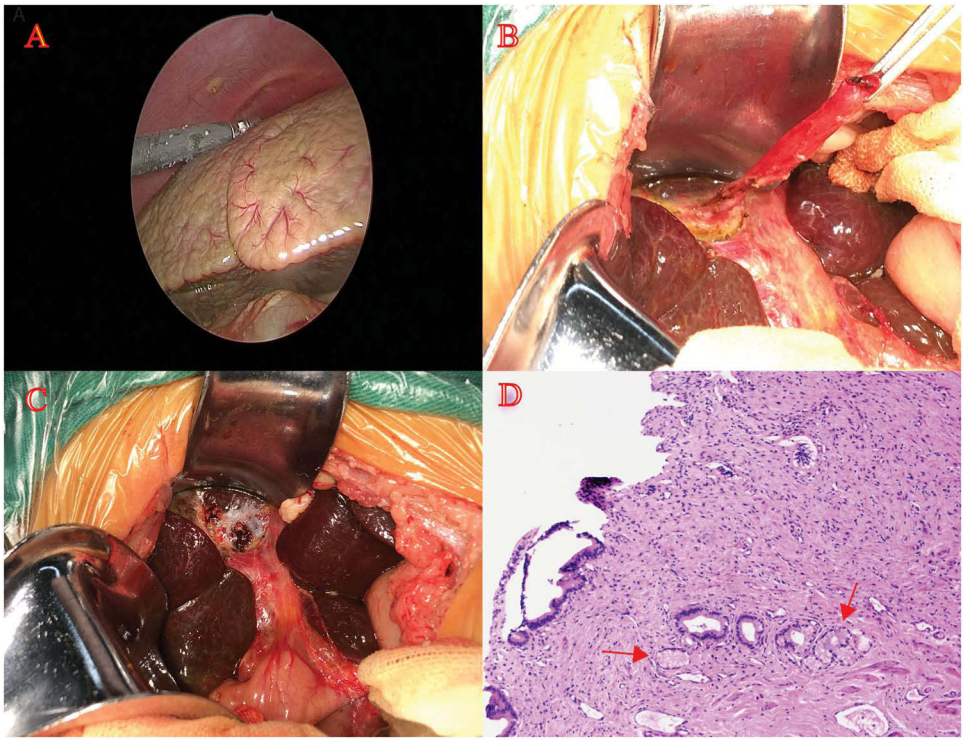

Figure 3 Intraoperative images of the Kasai procedure and ductal plate malformation. (**A**–**C**) Intraoperative findings during the Kasai procedure; (**D**) Pathological section demonstrating ductal plate malformation (red arrows indicate ductal plate malformation) (×40).

Follow-Up Evaluation

All patients underwent standardized postoperative surveillance through scheduled outpatient evaluations at 1-,3-, and 6-month intervals following KPE. Monitoring parameters included anthropometric measures (weight, age), surgical covariates (sex and operative age), serial hepatic biochemistry such as ALT, AST, GGT, total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin(IBIL), and TBA, and the primary clinical endpoint of 6-month NLS. CoJ was rigorously defined as achieving serum TBIL ≤20 μmol/L (1.17 mg/dL) within the study period.[22]

Attrition

Attrition Definition: Despite documented reasonable follow-up attempts (including repeated telephone contacts and home visits), no valid outcome data were retrieved from the participants.: (1) Loss to follow-up (unable to contact despite ≥3 documented attempts via phone/email), (2) Geographic relocation beyond catchment area.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 29.0. Normally distributed continuous variables were expressed as mean ± standard deviation, and intergroup comparisons were conducted using one-way ANOVA. Non-normally distributed data were presented as median (Q1-Q3), with intergroup comparisons performed by Kruskal–Wallis test. Categorical variables were reported as frequencies (percentages), with group comparisons conducted through χ^2 or Fisher's exact tests as appropriate. All statistical tests were two-tailed, with $P<0.05$ considered significant.

Repeated measures data were analyzed using GEE. The primary analysis utilized the Full Analysis Set (FAS) following the intention-to-treat (ITT) principle, with missing data assumed to be missing at random (MAR). To evaluate the robustness of findings, a sensitivity analysis was conducted by applying the same GEE method after multiple imputation (MI) of missing values. The imputation model included all variables in the final logistic regression model, plus auxiliary variables predictive of missingness and outcomes (eg., group allocation, baseline disease severity, and outcomes at available visits). We performed 20 imputations. Logistic regression analysis was employed to identify factors associated with 6-month native liver survival (NLS) and to construct a predictive model. Potential predictors were initially screened through univariate logistic regression (α=0.1), with three clinically established prognostic variables (ALT, TBA, and sex) forced into the model (Supplementary Table 5). The final multivariable model included 9 variables. Collinearity diagnostics indicated no substantial multicollinearity (variance inflation factor range: 1.3–4.2; tolerance values>0.3). Forward stepwise selection was used for variable selection, and parameter estimate stability was assessed via sensitivity analysis using the full-model approach.

Results

Baseline Characteristics

The sample demographics and stratified characteristics are overviewed in Table 1. The study cohort comprised 83 eligible patients stratified by Ishak fibrosis staging into Mild fibrosis (1–2, n=20), moderate fibrosis (3–4, n=39), and cirrhosis (5–6, n=24) groups, with baseline demographics demonstrating comparable distributions across groups: median ages 76 (IQR 54.8–92), 70 (53–87), and 90 days (59–118.5) respectively (Kruskal–Wallis P=0.313); female predominance decreasing from 50.0% to 29.2% (χ^2=2.01, P=0.363); mean weights 5.3±1.6, 4.9±1.0, and 5.4±1.1kg (ANOVA P=0.363). Biochemical profiling revealed significant intergroup variance in bilirubin metabolism: TBIL escalated from 159 ± 35 μmol/L (mild) to 195 ± 53 μmol/L (cirrhosis) (P=0.043), paralleled by DBIL increases (88.4 vs. 102.6 μmol/L, P=0.024), while IBIL showed marginal significance (68.8–84.6 μmol/L, P=0.055). Hepatic enzymes, including ALT (78–91 U/L), AST (102–117 U/L), GGT (210–255 U/L), and ALP (350–420 IU/L), exhibited nonsignificant trends (all P>0.05), with TBA remaining comparable (35.2–38.7 μmol/L, P=0.544).

Comparison of Liver Function Indices Across Ishak Groups

GEE was used to compare changes in liver function indicators among the three groups. Gamma or Gaussian distributions were selected as the probability distribution types (gamma for GGT, Gaussian for others), with exchangeable working

Table 1 Comparison of Baseline Characteristics Across Ishak Groups

Baseline Data	Mild Fibrosis (n=20)	Moderate Fibrosis (n=39)	Cirrhosis (n=24)	*P*
Socio-demographic				
Age (days)	76(54.8–92)	70(53–87)	90(59–118.5)	0.313[a]
Female sex (%)	10(50.0)	16(41.0)	7(29.2)	0.363[b]
Weight (kg)	5.3±1.6	4.9±1.0	5.4±1.1	0.363[c]
Hepatic Panel				
ALT	121(101.5–183.5)	158.5(83.8–205.5)	161(90.3–205.8)	0.677[a]
AST	208.5(174.3–294.2)	263(156.5–351.3)	250(182.3–383.0)	0.674[a]
GGT	347(189–720.8)	374(164–891)	409(221–1064)	0.409[a]
ALP	691.7±164.4	667.4±215.4	783.2±317.5	0.187[c]
TBIL	159(141–186)	168(141–221)	195(159–230)	**0.043**[a]
DBIL	88.4(78.9–103.7)	90.8(76.4–116.9)	102.6(93–124.1)	**0.024**[a]
IBIL	68.8(64.0–84.7)	79.6(65.2–106.8)	84.6(74.0–104.4)	0.055[a]
TBA	155.8±56.6	152.2±56.9	170.6±58.6	0.544[c]

Notes: [a] Kruskal–Wallis test, [b] χ^2 test, [c] one-way ANOVA, bold values represent P < 0.05.
Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; ALP, Alkaline Phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; TBA, total bile acids; T0: Baseline; T1-T3: Postoperative follow-up at 1, 3, and 6 months.

correlation matrices. The choice of distributions and link functions was strictly based on minimizing QIC values (a standard metric for GEE model fit). Both unadjusted and adjusted models (controlling for gender and age at surgery) were employed to analyze the main effects of group and time.

For GGT, the unadjusted GEE model revealed a significant main effect of time on GGT levels across all groups ($P < 0.05$), and the Mild Fibrosis Group exhibited significantly lower GGT levels than the Cirrhosis Group. Results from the adjusted model were consistent (Table 2, Supplementary Table 1 and Figure 4A).

Similarly, TBIL, DBIL, and IBIL showed significant time effects ($P < 0.001$) and group differences between Mild Fibrosis and Cirrhosis groups ($P < 0.05$), with lower bilirubin levels in the former. Adjusted analyses yielded concordant findings (Table 2, Supplementary Table 1, Figure 4B–4D).

ALT, AST, ALP, and TBA analyses indicated significant time effects ($P < 0.05$) but no group differences. Collectively, all groups showed reduced liver function indices within six months post-K, though the Cirrhosis Group had persistently higher GGT and bilirubin levels, indicating poorer improvement (Supplementary Table 2).

Sensitivity analyses using GEE revealed distinct biomarker dynamics: cholestatic markers (GGT, bilirubin) exhibited fibrosis-dependent associations, with GGT demonstrating robust correlations in cirrhosis subgroups (6.7% β attenuation post-

Table 2 Results of the GEE Analysis for Comparison of Liver Function

Item	Unadjusted Model				Adjusted Model[a]			
	β	95% CI		*P*	β	95% CI		*P*
		Lower	Upper			Lower	Upper	
GGT Group								
Mild fibrosis	Reference				Reference			
Moderate fibrosis	0.198	−0.113	0.510	0.212	0.192	−0.119	0.502	0.227
Cirrhosis	0.419	0.063	0.775	**0.021**	0.394	0.041	0.747	**0.029**

(*Continued*)

Table 2 (Continued).

Item	Unadjusted Model				Adjusted Model[a]			
	β	95% CI		*P*	β	95% CI		*P*
		Lower	Upper			Lower	Upper	
Time								
T0	Reference				Reference			
T1	0.658	0.485	0.831	**<0.001**	0.660	0.485	0.834	**<0.001**
T2	0.409	0.220	0.598	**<0.001**	0.421	0.231	0.610	**<0.001**
T3	−0.284	−0.544	−0.023	**0.033**	−0.277	−0.540	−0.014	**0.039**
TBIL Group								
Mild fibrosis	Reference				Reference			
Moderate fibrosis	26.635	−11.754	65.023	0.174	25.313	−13.945	64.570	0.206
Cirrhosis	62.032	20.482	103.582	**0.003**	48.455	9.118	87.792	**0.016**
Time								
T0	Reference				Reference			
T1	−65.533	−85.288	−45.777	**<0.001**	−64.143	−83.514	−44.773	**<0.001**
T2	−62.818	−91.722	−33.914	**<0.001**	−61.041	−89.618	−32.464	**<0.001**
T3	−93.237	−128.917	−57.558	**<0.001**	−90.612	−125.871	−55.353	**<0.001**
Dbil Group								
Mild fibrosis	Reference				Reference			
Moderate fibrosis	12.573	−6.063	31.208	0.186	12.088	−6.859	31.035	0.211
Cirrhosis	33.234	12.727	53.740	**0.001**	26.925	7.382	46.469	**0.007**
Time								
T0	Reference				Reference			
T1	−30.324	−40.618	−20.029	**<0.001**	−29.627	−39.807	−19.447	**<0.001**
T2	−31.947	−47.111	−16.783	**<0.001**	−31.086	−46.135	−16.037	**<0.001**
T3	−51.113	−68.203	−34.024	**<0.001**	−49.875	−66.826	−32.923	**<0.001**
IBIL Group								
Mild fibrosis	Reference				Reference			
Moderate fibrosis	13.795	−6.700	34.290	0.187	13.109	−7.882	33.920	0.222
Cirrhosis	27.989	6.385	49.594	**0.011**	21.016	0.552	41.480	**0.044**
Time								
T0	Reference				Reference			
T1	−35.409	−45.871	−24.948	**<0.001**	−34.706	−44.907	−24.504	**<0.001**
T2	−30.980	−45.758	−16.203	**<0.001**	−30.011	−44.590	−15.432	**<0.001**
T3	−43.326	−63.706	−22.946	**<0.001**	−41.999	−62.085	−21.913	**<0.001**

Notes: [a] indicates adjusted for gender and age at surgery, bold values represent $P < 0.05$.

Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; T0: Baseline; T1-T3: Postoperative follow-up at 1, 3, and 6 months.

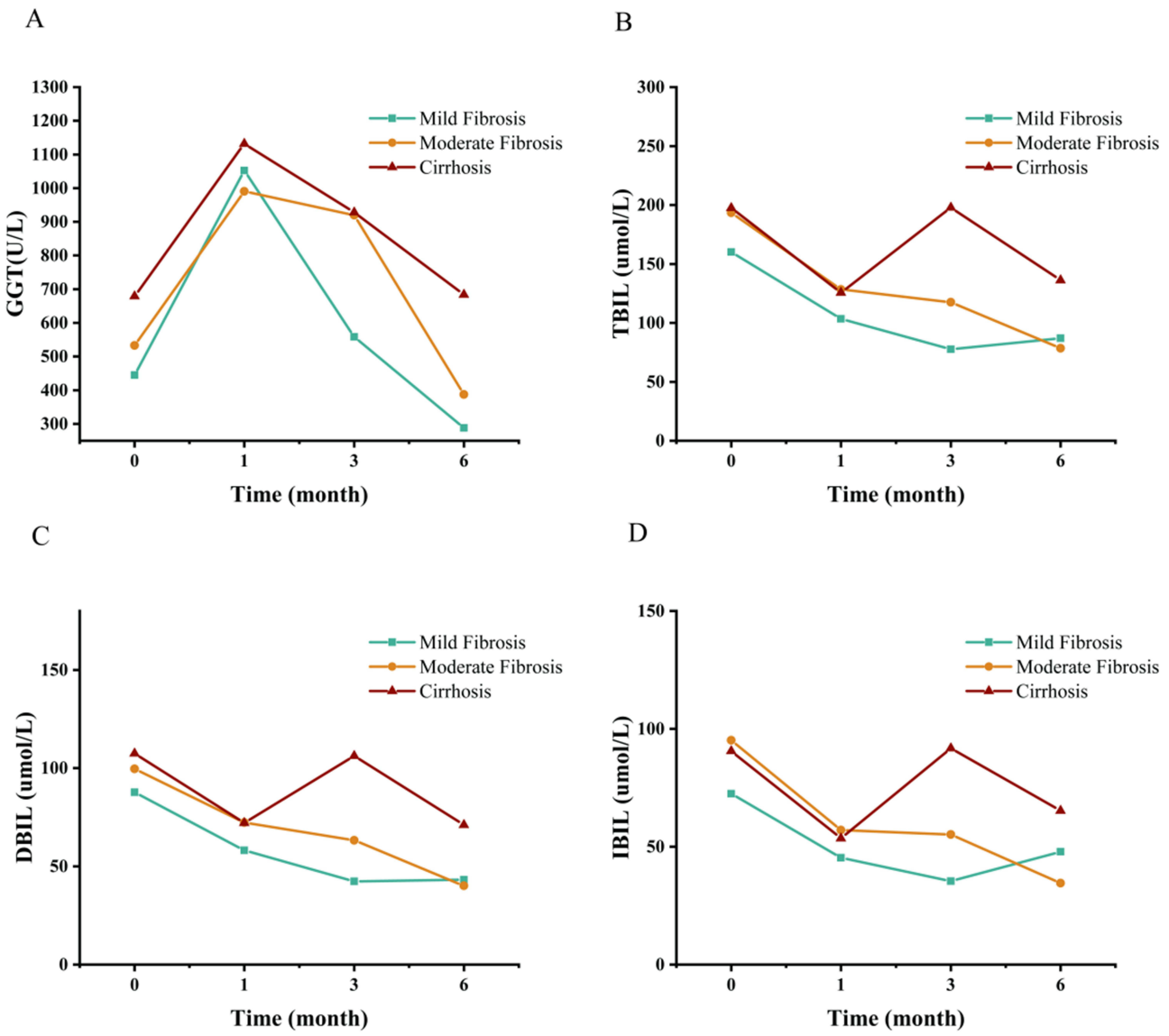

Figure 4 Longitudinal Changes in GGT, TBIL, DBIL, and IBIL Levels— GEE Analysis Across Patient Groups.(**A**) GGT levels. (**B**) TBIL levels. (**C**) DBIL levels. (**D**) IBIL levels.

adjustment) and moderate fibrosis showing a dose-response trend (P=0.051), while TBIL/DBIL associations attenuated significantly (18.5–24.4%) after covariate adjustment. In contrast, hepatocellular enzymes (ALT, ALP) showed strong time-dependent declines (Wald χ^2 >29.87, P<0.001) independent of baseline fibrosis stratification, with no intergroup differences persisting post-adjustment (all P > 0.3). Temporal trajectories remained stable across models, indicating uniform postoperative recovery patterns regardless of Ishak classification (detailed statistics in Supplementary Tables 3 and 4).

Comparison of 6-Month CoJ Among the Three Groups

As presented in Table 3, a significant difference in 6-month CoJ rates was observed across the three groups (χ^2 = 11.363, P = 0.003), with rates of 55.0% in the Mild Fibrosis group, 38.5% in the Moderate Fibrosis group, and 8.3% in the Cirrhosis group. Post hoc pairwise comparisons indicated that while the difference between the Mild and Moderate Fibrosis groups was not statistically significant (55.0% vs. 38.5%; χ^2 = 1.467, P = 0.226), the Moderate Fibrosis group exhibited a significantly higher CoJ rate than the Cirrhosis group (38.5% vs. 8.3%; χ^2 = 6.845, P = 0.009), and the Mild Fibrosis group demonstrated markedly higher CoJ rates compared to the Cirrhosis group (55.0% vs. 8.3%; χ^2 = 11.413, P < 0.001).

Table 3 Comparison of 6-Month CoJ Among the Three Groups

Group	CoJ	n	χ^2	*P*
Mild	55.0%	20	11.363	**0.003**
Moderate	38.5%	39		
Cirrhosis	8.3%	24		
Post hoc analysis				
Mild vs. Moderate	55.0%vs. 38.5%	20 vs. 39	1.467	0.226
Moderate vs. Cirrhosis	38.5% vs. 8.3%	39 vs. 24	6.845	**0.009**
Mild vs. Cirrhosis	55.0% vs. 8.3%	20 vs. 24	11.413	**<0.001**

Note: bold values represent $P < 0.05$.

Comparison of 6-Month NLS Rates

A significant difference in 6-month NLS rates was observed among the three groups ($\chi^2 = 19.714$, $P < 0.001$). The Mild Fibrosis Group had the highest survival rate (80.0%), significantly exceeding the Cirrhosis Group (16.7%; $\chi^2 = 17.649$, $P < 0.001$). The Moderate Fibrosis Group demonstrated an intermediate survival rate (61.5%), which was not statistically different from the Mild Fibrosis Group ($\chi^2 = 2.064$, $P = 0.151$) but markedly higher than the Cirrhosis Group ($\chi^2 = 12.115$, $P < 0.001$). Post hoc pairwise comparisons further confirmed these trends: survival rates differed significantly between the Mild and Cirrhosis Groups (80.0% vs. 16.7%; $P < 0.001$) and between the Moderate and Cirrhosis Groups (61.5% vs. 16.7%; $P < 0.001$), whereas the Low- vs. Moderate Group comparison did not reach significance (80.0% vs. 61.5%; $P = 0.151$). These findings indicate a significant negative correlation between prognostic risk scores and NLS, with the Cirrhosis Group associated with the poorest outcomes (Table 4).

Multivariable Regression Analysis of 6-Month Postoperative Survival Outcomes

Univariable logistic regression identified Ishak fibrosis stage as the strongest predictor ($P<0.001$), with surgical age, TBIL, and AST also significant ($P<0.05$) (detailed results in Supplementary Table 5).The multivariable regression model demonstrated that Ishak score (OR=0.463, $P=0.002$) was independently associated with poorer prognosis, whereas younger age at surgery (OR=0.965, $P=0.020$) showed a protective effect. Other clinical parameters, including gender (OR=1.608, $P=0.481$), ALT (OR=1.003, $P=0.513$), AST (OR=0.994, $P=0.133$), GGT (OR=0.999, $P=0.269$), ALP (OR=0.999, $P=0.511$), TBIL (OR=0.816, $P=0.704$), and TBA (OR=1.008, $P=0.288$), did not demonstrate statistically significant associations with survival outcomes in the adjusted analysis (all $P>0.05$, Table 5).

Forward stepwise regression validated Ishak fibrosis score (OR=0.450, $P<0.001$) and surgical age ($P=0.003$) as robust outcome predictors, retaining >90% of univariable effect magnitudes. The Ishak score dominated prognostic stratification, reinforcing histopathological staging and surgical timing as primary determinants (detailed results in Supplementary Table 6). Per one-stage increase in the Ishak score, the odds of 6-month NLS decreased by 46.3% (OR = 0.463, 95% CI 0.287–0.746).

Table 4 Comparison of 6-Month NLS Between the Three Groups

Group	NLS	n	χ^2	*P*
Mild	80.0%	20	19.714	**<0.001**
Moderate	61.5%	39		
Cirrhosis	16.7%	24		
Post hoc analysis				
Mild vs. Moderate	80.0% vs. 61.5%	20 vs. 9	2.064	0.151
Moderate vs. Cirrhosis	61.5% vs. 16.7%	39 vs. 24	12.115	**<0.001**
Mild vs. Cirrhosis	80.0% vs. 16.7%	20 vs. 24	17.649	**<0.001**

Note: bold values represent $P < 0.05$.

Table 5 Multivariable Analysis of Factors Associated with 6-Month Survival After Surgery

Factors	OR	95% CI		*P*
		Lower	Upper	
Ishak Score	0.463	0.287	0.746	**0.002**
Sex	1.608	0.429	6.032	0.481
Surgical age (days)	0.965	0.936	0.994	**0.020**
ALT	1.003	0.993	1.014	0.513
AST	0.994	0.986	1.002	0.133
GGT	0.999	0.998	1.001	0.269
ALP	0.999	0.996	1.002	0.511
TBIL	0.816	0.286	2.329	0.704
TBA	1.008	0.993	1.023	0.288

Note: Bold values represent $P < 0.05$.
Abbreviations: TBIL, total bilirubin; TBA, total bile acids.

Discussion

BA is the leading cause of pediatric end-stage liver disease and the primary indication for LT in children, although the optimal therapeutic strategy remains controversial.[23] In most centers, the standard approach involves sequential therapy with the KPE, followed by LT if jaundice persists or irreversible cirrhosis develops.[24] In contrast, some centers advocate for primary LT as the initial intervention.[25] A cohort study by Yoeli et al demonstrated that children undergoing LT after failed KPE achieved survival rates comparable to those receiving primary one-stage LT, despite the technical challenges of secondary surgery. Notably, delayed LT beyond age 1 year was associated with improved outcomes, likely due to reduced hepatic fibrosis severity and slower disease progression in older recipients. These findings underscore KPE as a critical bridging intervention to optimize LT timing, particularly for patients requiring delayed surgical eligibility.[26]

Developing a validated prognostic model for BA to guide individualized treatment planning before or early after the KPE could significantly alleviate the socioeconomic burden on families and healthcare systems, offering substantial clinical value.[27] Analyzing prognostic indicators across Ishak fibrosis subgroups in BA patients, this study developed a predictive model for early postoperative outcomes.

Our study employed the Ishak scoring system due to its greater discriminatory power in staging advanced fibrosis (stages 5–6) compared to METAVIR and Batts-Ludwig systems, as existing literature has supported its enhanced suitability for clinical stratification research.[15–17]The Kaplan-Meier survival curves (Figure 5) clearly demonstrated this gradation in outcomes: the 6-month native liver survival rate was nearly 100% for the Mild group, >60% for the Moderate group, and only ~20% for the Cirrhosis group. As Ishak fibrosis scores increased, the Cirrhosis group demonstrated significantly lower 6-month native liver survival rates compared to the Mild and Moderate groups. Concurrently, these patients exhibited reduced 3-month CoJ, indicating impaired surgical outcomes and delayed hepatic functional recovery. Higher Ishak scores correlated with shortened native liver survival duration, persistent cholestasis, and overall poorer prognosis.

The timing of surgical intervention, particularly in relation to patient age at the KPE, has been established as a critical prognostic determinant. The clinical impact of age is, however, deeply intertwined with the histopathological progression of BA, as demonstrated by studies explicitly linking operative age, pathological features of liver tissue, and clinical outcomes.[28] The Japanese BA Registry has consistently demonstrated that infants undergoing KPE beyond 70–90 days of age exhibit a significantly higher prevalence of advanced fibrosis (Metavir stage ≥3) and consequently lower 10-year NLS rates compared to those operated on earlier.[29] Similarly, Superina et al identified that the anatomic pattern of fibrosis at the porta hepatis, which worsens with patient age, is a powerful predictor of transplant-free survival.[30] Although our study found no statistically significant differences in operative ages across the three subgroups, multivariable logistic regression analysis identified older age at surgery as an independent risk factor for 6-month NLS. This suggests that even within the same histopathological stage, a delayed KPE may exacerbate subtle but impactful pathological damage—such

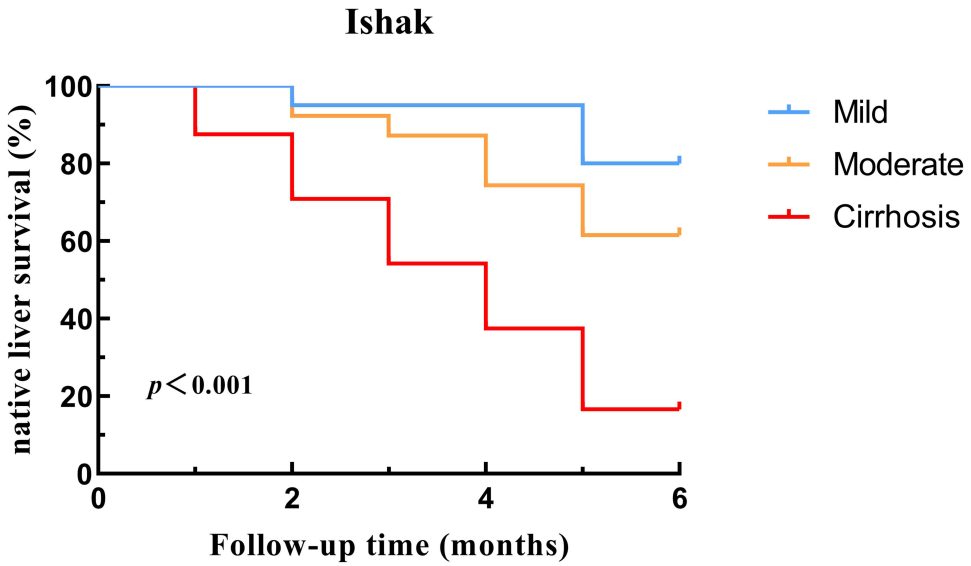

Figure 5 Native liver survival after Kasai surgery, stratified by Ishak fibrosis groups. Kaplan-Meier survival curves compare patients with Mild, Moderate, and Cirrhosis-level Ishak fibrosis scores. The difference in survival between the groups was statistically significant (Log rank test, *P*< 0.001).

as denser bile plug accumulation in ductules or enhanced stromal inflammation—which is not fully captured by gross fibrosis staging alone and ultimately compromises surgical efficacy. Our results echo the findings of Superina et al,[30] which we indirectly observed through the lower rates of CoJ in subgroups with higher Ishak scores This finding aligns with existing evidence demonstrating that early intervention improves biliary drainage efficiency, thereby mitigating cholestatic hepatocyte injury and decelerating fibrogenesis.[31,32] Thus, our results not only substantiate the clinical imperative for timely surgery but also refine this paradigm by quantifying how operative age interacts with histopathological staging (via the Ishak score) to shape prognosis in BA. This provides quantitative evidence to guide optimal intervention timing.

Biochemical analysis revealed progressive elevation of TBIL, DBIL, and IBIL with advancing fibrosis stages. Although TBA showed no statistically significant intergroup differences, a trend toward higher values was observed in the Cirrhosis cohort. These findings align with previous reports,[33] suggesting that advanced fibrosis disrupts biliary excretion pathways, leading to systemic bilirubin accumulation and worsening hepatic synthetic dysfunction.[34]

While GGT levels are typically elevated in BA, normal values may occasionally occur as documented in prior reports.[35] Our data specifically revealed that postoperative GGT levels in the mild fibrosis group were significantly lower than those in the cirrhosis group. Although preoperative levels of ALT, AST, and ALP showed no statistically significant differences among the Ishak subgroups. Following KPE, all subgroups exhibited progressive improvement in liver function parameters during follow-up monitoring. However, when analyzed through the lens of Ishak histopathological staging, patients in cirrhosis subgroups demonstrated slower recovery rates for bilirubin normalization compared to mild subgroups, despite achieving absolute biochemical improvements. This suggests that while the KPE provides functional benefit across disease stages.

This study observed a relatively high 6-month follow-up mortality rate (6/83, 7.2%), which can be primarily attributed to systemic challenges within the local healthcare system. As a region in western China with relatively limited medical resources, Guizhou Province faces issues of uneven distribution and poor accessibility of healthcare. This has directly led to delays in diagnosis and treatment for patients. By the time many patients were referred to our hospital, they had already progressed to severe fibrosis. When the disease reaches a stage requiring expensive treatments such as organ transplantation, the substantial socioeconomic burden makes it unaffordable for many families, ultimately resulting in treatment discontinuation or abandonment, thereby contributing to the observed high mortality rate.

The main limitation of this study is that the follow-up period was only 6 months, which is insufficient to cover 1-year or longer observation period. Nevertheless, sensitivity analysis of the data validated the robustness of the findings. In the

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future, we plan to improve caregiver engagement through digital education and personalized guidance, facilitating 1-year or longer follow-up. Subsequent studies will further consolidate the research evidence by expanding the sample coverage and engaging in multicenter collaboration.

This study not only confirms the established association between cirrhosis and poor prognosis,[11] but also advances precision medicine in BA management through multidimensional analyses. These findings transform the Ishak score from a purely pathological tool into a clinically actionable risk-stratification system, suggesting primary LT over potentially futile Kasai procedures for high-risk infants (Ishak ≥5). Future research should focus on developing a novel multimodal machine learning-based evaluation system (integrating SWE biomechanical parameters with Ishak histological scoring) or constructing a deep learning-powered noninvasive virtual biopsy system,[36,37] to establish a real-time, noninvasive "digital staging" platform.[38,39] This would particularly for providing quantitative guidance on optimal transplant timing decisions in children with advanced fibrosis.[40,41]

Conclusion

This study establishes a precise, Ishak score-based risk stratification system for BA, defining the relationship between liver fibrosis stage and 6-month native liver survival and providing quantifiable thresholds to guide the choice between primary liver transplantation and the conventional Kasai-to-transplant pathway.

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Disclosure

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