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Original Article

Relationship between hepatic function recovery and postoperative cholangitis in neonates undergoing hepaticojejunostomy for biliary atresia

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Abstract: Objective: To explore the association between hepatic function recovery and the incidence of postoperative cholangitis in neonates with biliary atresia (BA) who underwent hepaticojejunostomy. Methods: We conducted a retrospective analysis of medical records from 173 newborns diagnosed with BA and treated with hepaticojejunostomy (Kasai procedure) between February 2020 and October 2022. Participants were categorized into two cohorts: those who developed cholangitis post-surgery (cholangitis group, n=125) and those who did not (non-cholangitis group, n=48). Liver function indices pre- and post-treatment, the extent of postoperative liver function recovery, and jaundice resolution rates were compared. Risk factors for cholangitis development post-surgery were identified using univariate and multifactorial logistic regression analyses. Results: The cholangitis group exhibited higher surgical weight (P=0.030) and elevated preoperative levels of total bilirubin (TB, P<0.001), direct bilirubin (DB, P<0.001), aspartate aminotransferase (AST, P<0.001), and gamma-glutamyl transferase (GGT, P<0.001). This group also showed better postoperative liver function recovery (P=0.002) and jaundice clearance rates (P=0.003). Logistic regression identified postoperative jaundice clearance (P=0.013), TB (P=0.004), DB (P=0.011), AST (P<0.001), and GGT (P<0.001) as independent risk factors for cholangitis. The nomogram model had a C-index of 0.930 with a goodness-of-fit test *p*-value of 0.873, and an AUC of 0.930. Conclusion: Postoperative jaundice clearance, TB, DB, AST, and GGT are independent risk factors for cholangitis. The nomogram model offers high predictive accuracy for cholangitis development, aiding early intervention and prognosis improvement in high-risk neonates.

Keywords: Neonatal biliary atresia, hepatic portal jejunostomy, hepatic function recovery, cholangitis

Introduction

Biliary atresia (BA) is a critical hepatobiliary disorder in neonates, characterized by persistent inflammation and progressive fibrosis of the hepatic bile ducts [1]. The Kasai procedure, or hepatoportoenterostomy, has significantly revolutionized the treatment landscape of BA, elevating the five-year survival rate from 30% to an impressive 75% since its widespread implementation [2, 3]. This surgical strategy plays a pivotal role in halting the further decline of liver function, effectively delaying the urgency for liver transplantation, simplifying the transplantation process, and enhancing both liver and patient survival chances [4].

Cholangitis, a common complication following Kasai surgery, significantly impacts the recovery, with reported prevalence ranging from 40% to 90% [5, 6]. This complication typically presents with the sudden onset of high fever, distinct yellowish stools, and positive blood cultures. The treatment regimen often includes antibiotics, steroids, and the hepatoprotective agent ursodeoxycholic acid. While antibiotics are initially effective, their prolonged use can lead to increased bacterial resistance, alteration of bacterial strains, and dysbiosis [7]. Consequently, there is a need to shift toward more potent broad-spectrum antibiotics, such as third-generation cephalosporins and carbapenems, to counteract drug-resistant strains [8]. For children with advanced disease, combination therapy targeting both bacilli and cocci may become necessary.

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Notably, each episode of cholangitis can intensify liver fibrosis, deteriorate liver function, and precipitate various complications. Previous reports have indicated a significant association between poor hepatic function recovery and a higher incidence of cholangitis [9]. Studies have shown that children with poor postoperative hepatic function recovery are more prone to developing cholangitis, and frequent episodes of cholangitis further deteriorate liver function, creating a vicious cycle [10]. Moreover, the medications employed to manage this complication may further burden the liver, jeopardizing the child's long-term hepatic recovery. Although the Kasai procedure has significantly improved the survival of children with BA, the high incidence of postoperative cholangitis and its detrimental effect on hepatic function recovery remain important clinical challenges. Studies have investigated the risk factors and prognosis of cholangitis with most of them focusing on single clinical or biochemical indicators, lacking comprehensive assessment of the combined effects of these factors. In addition, existing studies usually have limited sample sizes and lack multicenter data support, resulting in limited generalizability and applicability of the results [11]. Furthermore, there is a lack of effective predictive models to guide early intervention and risk assessment in clinical practice [12].

The uniqueness of this study lies in its comprehensive examination of the direct relationship between hepatic function recovery and the occurrence of cholangitis following the Kasai procedure. Through detailed clinical observations and statistical analyses, this study revealed a correlation between postoperative hepatic function recovery, jaundice regression, and the development of cholangitis in children, providing new insight for early identification and intervention. We improved the accuracy of cholangitis risk prediction by constructing a nomogram prediction model, which provides an important clinical guidance tool and helps to improve the prognosis of high-risk children.

Methods and data

Clinical information

The medical records of newborns with congenital biliary atresia (BA) treated with hepatic hilar jejunostomy (Kasai) from February 2020 to October 2022 at West China Second Hospital of Sichuan University were retrospectively analyzed. Inclusion criteria: the infants who underwent surgical treatment for BA at West China Second Hospital of Sichuan University, where the diagnosis of BA was confirmed during surgery and the Kasai procedure was performed; the infants with complete medical records, including record of the consultation process and follow-up records. Exclusion criteria: postoperative cholangitis due to other identifiable causes, such as infections from other surgical procedures; non-BA related bile duct obstructions, or systemic infections that could independently cause cholangitis; infants with hepatic genetic metabolic disease, liver failure, hepatic encephalopathy, gastrointestinal bleeding, systemic coagulation disorders, etc.; and infants with allergies, previous allergies to certain drugs, or serious adverse disease events. This study was conducted with the approval of the Medical Ethics Committee of West China Second Hospital of Sichuan University.

Diagnostic criteria for cholangitis

Based on the 2018 BA Treatment Guidelines, the diagnostic criteria for cholangitis [6] include: 1. Fever (>38.5°C) without an apparent cause following the Kasai procedure; 2. A noticeable lightening of stool color or deepening of urine color; 3. Laboratory tests showing elevated indicators of infection; and 4. The presence of jaundice [13]. Definition and time frame of postoperative cholangitis: cholangitis occurring within one year after Kasai's surgery. This timeframe encompasses both the immediate postoperative recovery phase and the period most susceptible to surgery-related complications [14].

Case selection

We reviewed 173 cases from the eligible samples based on the inclusion-exclusion criteria. The patients were then divided into a cholangitis group (n=125) and a non-cholangitis group (n=48) based on the diagnostic criteria of cholangitis. The study was conducted with the approval from the Medical Ethics Committee of West China Second Hospital of Sichuan University.

Clinical data collection

Clinical data were collected through hospital's medical records system. Clinical data included age, gender, weight at the time of surgery, height, duration of anesthesia, type of disease, length of hospital stay, postoperative recovery of liver function, postoperative clearance of jaundice, and intraoperative blood loss. Laboratory parameters included total bilirubin (TB), direct bilirubin (DB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bile acid (TBA), and albumin (Alb). Note: Laboratory bloodwork was obtained 1 d before surgery.

Criteria for postoperative liver function recovery and jaundice clearance

1. Postoperative liver function recovery [15]: Good recovery: A significant improvement in liver function within one year post-surgery, including the reduction of liver enzyme levels to less than 30% of their preoperative levels, or the normalization of total bilirubin levels. Poor recovery: Within 1 year after surgery, liver function indicators (e.g., liver enzyme levels) do not decrease to less than 30% of preoperative levels, or total bilirubin levels do not return to normal.

2. Postoperative clearance of jaundice [16]: Good clearance: Evidenced by a change in the stool color to standard yellow, significant subsidence of skin jaundice, or a decrease in serum direct bilirubin to less than 20 μmol/L within one year after surgery. Poor clearance: No significant change in stool color (stool remains light), skin jaundice shows no substantial improvement, or serum direct bilirubin levels stay above 20 μmol/L within one year post-surgery.

Observation indicators

Primary observation indicators: The postoperative liver function recovery and jaundice clearance were compared in the children. Logistic regression was used to analyze the risk factors for cholangitis.

Secondary outcome: The differences in children's baseline data and the changes in preoperative laboratory indicators were compared. A nomogram prediction model for developing cholangitis was constructed (**Figure 1**).

Statistical analysis

All data were statistically processed using SPSS 26.0 software. For quantitative data with normal distribution (mean ± SD), the paired samples t-test was used for comparisons before and after treatment within the same group, while the independent sample t-test was used for comparisons between different groups. For quantitative data with non-normal distribution, Mann-Whitney U rank sum test for comparison. For categorical data (n, %), the chi-square test was employed to assess differences between groups. We utilized R language version 4.3.2 for advanced statistical modeling and visualization. The rms package was used to construct the nomogram model, with Decision Curve Analysis (DCA) curves employed to evaluate the clinical utility of the model. The pROC package was used for ROC curve analysis to assess the model's discriminative ability, while the precrec package was used for calibration curve analysis to evaluate the accuracy of the predictive model. The ggplot2 package was used for graphic plotting to visualize data and results. Logistic regression analysis was performed to identify risk factors affecting the development of cholangitis in the children. Differences were considered statistically significant at $P<0.05$.

Results

Comparison of preoperative baseline data of children with cholangitis

A comparison of the baseline data revealed no significant differences in age (P=0.576), gender (P=0.796), height (P=0.719), duration of anesthesia (P=0.255), type of disease (P=0.815), duration of hospitalization (P=0.454), and intraoperative blood loss (P=0.140) between the two groups; however, the weight of the children in the cholangitis group was found to be higher at the time of surgery (P=0.030) than in the non-cholangitis group (**Table 1**).

A comparison of laboratory indicators revealed that the preoperative TB, DB, AST, and GGT values were significantly higher in the cholangitis group than those in the non-cholangitis group; however, there were no significant differences in preoperative ALT (P=0.337), TBA (P=0.347), and ALB (P=0.565) between the two groups (**Table 2**).

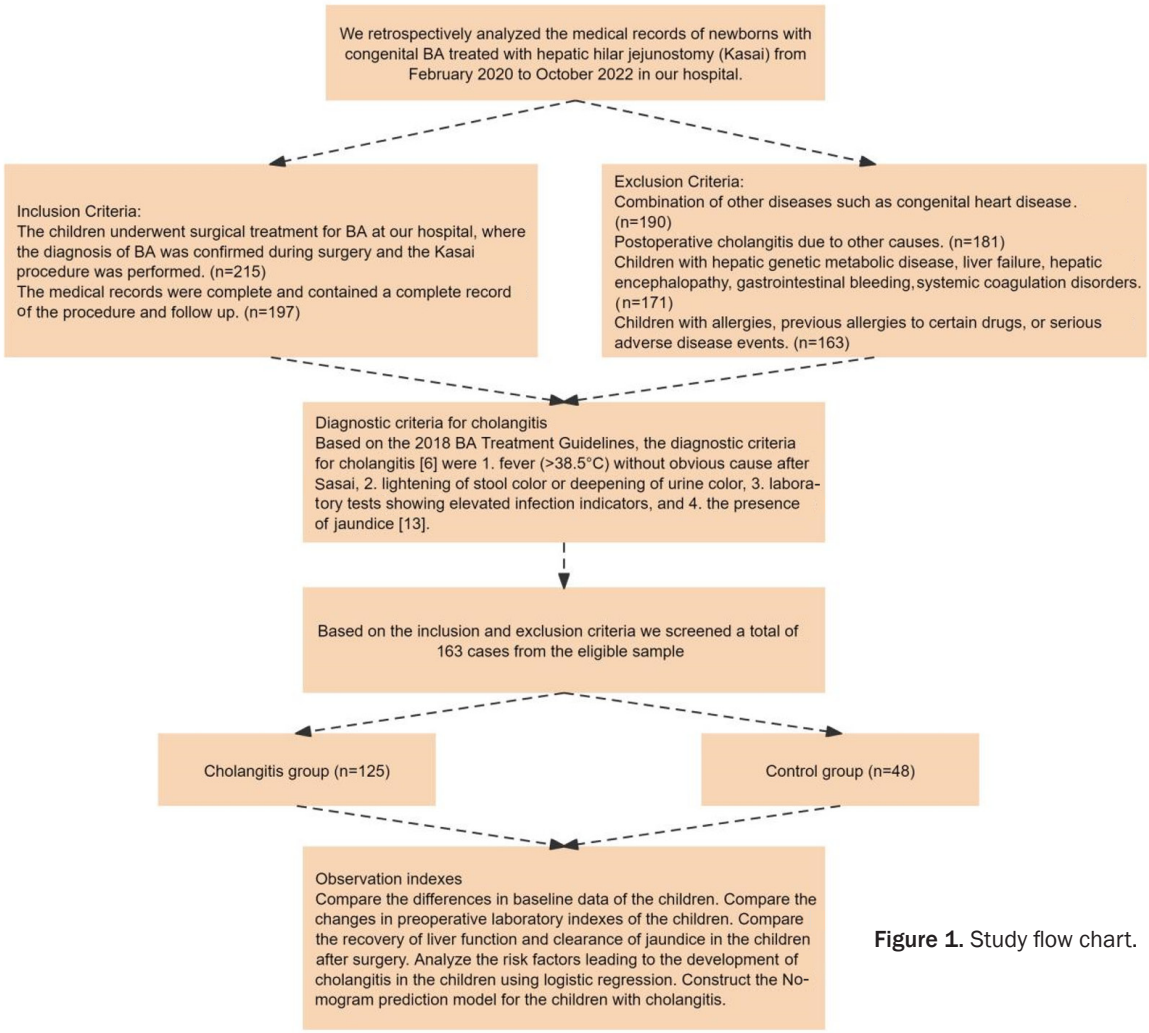

Figure 1. Study flow chart.

Recovery of liver function and clearance of jaundice in children after surgery

Comparison of postoperative hepatic function recovery and jaundice clearance between the two groups revealed that cholangitis group exhibited significantly lower postoperative hepatic function recovery (P=0.002) and jaundice clearance (P=0.003) than the non-cholangitis group (**Table 3**).

Logistic regression analysis of risk factors for the development of cholangitis

Logistic regression analysis was conducted to identify risk factors for cholangitis. Data were dichotomized using cut-off values derived from the ROC curve, allowing for categorization based on the presence of discrepant laboratory indicators (**Table 4**). Subsequent univariate analysis revealed that body weight at the time of surgery (P=0.032), postoperative recovery of liver function (P=0.002), postoperative clearance of jaundice (P=0.004), TB (P=0.004), DB (P=0.011), AST (P<0.001), and GGT (P<0.001) were associated with the development of cholangitis in children (**Table 5**). Further multifactorial logistic regression analysis underscored that postoperative jaundice clearance (P=0.013), TB (P=0.004), DB (P=0.011), AST (P<0.001), and GGT (P<0.001) were independent risk factors for the development of cholangitis in children (**Table 6**).

Construction of nomogram predictive model for children with cholangitis

Subsequently, a nomogram predictive model based on logistic regression of independent risk factors was constructed. The model demonstrated a strong correlation between GGT

Table 1. Baseline data of children

	Cholangitis group (n=125)	Non-cholangitis group (n=48)	χ^2-value	*P*-value
Age				
>60 d	71 (56.80%)	24 (50.00%)	0.312	0.576
≤60 d	54 (43.20%)	24 (50.00%)		
Gender				
Male	94 (75.20%)	37 (77.08%)	0.067	0.796
Female	31 (24.80%)	11 (22.92%)		
Weight at surgery				
≥4.5 kg	75 (60.00%)	20 (41.67%)	4.708	0.030
<4.5 kg	50 (40.00%)	28 (58.33%)		
Height				
≥50 cm	85 (68.00%)	34 (70.83%)	0.129	0.719
<50 cm	40 (32.00%)	14 (29.17%)		
Duration of anesthesia				
≥240 min	48 (38.1%)	23 (47.92%)	1.298	0.255
<240 min	78 (61.9%)	25 (52.08%)		
Type of disease				
I	17 (13.60%)	6 (12.50%)	0.408	0.815
II	3 (2.40%)	2 (4.17%)		
III	105 (84.00%)	40 (83.33%)		
Length of hospitalization				
≥2 weeks	93 (73.81%)	33 (68.75%)	0.560	0.454
<2 weeks	33 (26.19%)	15 (31.25%)		
Intraoperative blood loss				
≥30 ml	13 (10.40%)	9 (18.75%)	2.179	0.140
<30 ml	112 (89.60%)	39 (81.25%)		

Table 2. Comparison of preoperative laboratory values in children

Value	Cholangitis group (n=125)	Non-cholangitis group (n=48)	t/Z value	*P*-value
TB (μmol/L)	155.92±7.17	148.42±7.55	5.931	<0.001
DB (μmol/L)	100.48±4.58	94.95±4.64	7.035	<0.001
ALT (U/L)	96.56±5.83	97.84±8.48	-0.967	0.337
AST (U/L)	155.16±9.92	145.10±11.14	5.477	<0.001
GGT (U/L)	632.17±53.28	568.98±56.48	6.692	<0.001
TBA (μmol/L)	150.18±4.50	151.35±8.13	-0.948	0.347
Alb (g/L)	39.23±5.61	38.71±5.23	0.577	0.565

Note: TB, Total Bilirubin; DB, Direct Bilirubin; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; TBA, Total Bile Acid; Alb, Albumin.

and cholangitis (**Figure 2A**). Subsequent calibration curve analysis revealed that the nomogram prediction had a high predictive probability for cholangitis, with a C-index of 0.930 (0.886-0.975) and a *p*-value of 0.873 for the goodness-of-fit test (**Figure 2B**). Furthermore, the decision-curve analysis (DCA) curve revealed that the risk score exhibited a high predictive value in identifying children at risk of developing cholangitis (**Figure 2C**). Finally, the receiver operating characteristic (ROC) curve analysis confirmed the robustness of the logistic risk factors, with an area under the curve (AUC) of 0.930, underscoring the model's strong discriminative ability in predicting cholangitis in children (**Figure 2D**).

Table 3. Comparison of postoperative recovery of liver function and clearance of jaundice in children

Cluster	Postoperative liver function recovery		Postoperative clearance of jaundice	
	Good recovery	Poor recovery	Good clearance good	Poor clearance
Cholangitis group (n=125)	61 (62.89%)	64 (84.21%)	68 (64.15%)	57 (85.07%)
Non-cholangitis group (n=48)	36 (37.11%)	12 (15.79%)	38 (35.85%)	10 (14.93%)
χ^2-value	9.665		8.965	
P-value	0.002		0.003	

Table 4. Factor assignment table

Factor	Factor assignment content
Weight at surgery	≥4.5 kg=1, <4.5 kg=0
TB (μmol/L)	≥152.045=1, <152.045=0
DB (μmol/L)	≥98.31=1, <98.31=0
AST (U/L)	≥151.475=1, <151.475=0
GGT (U/L)	≥663.95=1, <663.95=0
Postoperative liver function recovery	Good recovery =1, poor recovery =0
Postoperative clearance of jaundice	Good clearance =1, poor clearance =0
Occurrence of cholangitis	Yes =1, No =0

Note: TB, Total Bilirubin; DB, Direct Bilirubin; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase.

Table 5. One-way logistic regression analysis

Factor	β	SE	χ^2	*P*-value	OR value	95% CI	
						Lower Limit	Limit
Weight at surgery	0.742	0.345	4.624	0.032	2.100	1.068	4.13
Postoperative liver function recovery	-1.147	0.378	9.186	0.002	0.318	0.151	0.667
Postoperative clearance of jaundice	-1.159	0.398	8.465	0.004	0.314	0.144	0.685
TB (μmol/L)	-2.280	0.400	32.499	<0.001	0.102	0.047	0.224
DB (μmol/L)	-2.278	0.388	34.535	<0.001	0.102	0.048	0.219
AST (U/L)	-2.176	0.385	31.988	<0.001	0.113	0.053	0.241
GGT (U/L)	-2.556	0.451	32.182	<0.001	0.078	0.032	0.188

Note: TB, Total Bilirubin; DB, Direct Bilirubin; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase.

Table 6. Multifactor logistic regression analysis

Factor	β	SE	χ^2	*P*-value	OR value	95% CI	
						Lower Limit	Limit
Weight at surgery	0.614	0.551	1.244	0.265	1.848	0.628	5.438
Postoperative liver function recovery	-1.092	0.588	3.455	0.063	0.336	0.106	1.061
Postoperative clearance of jaundice	-1.598	0.644	6.148	0.013	0.202	0.057	0.715
TB (μmol/L)	-1.616	0.560	8.327	0.004	0.199	0.066	0.596
DB (μmol/L)	-1.419	0.556	6.510	0.011	0.242	0.081	0.720
AST (U/L)	-2.501	0.609	16.861	<0.001	0.082	0.025	0.271
GGT (U/L)	-2.725	0.711	14.694	<0.001	0.066	0.016	0.264

Note: TB, Total Bilirubin; DB, Direct Bilirubin; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase.

Finally, two sample sets were randomly selected for validation purposes. One set consisted of children with cholangitis, while the other consisted of children without cholangitis. The Rand function was used to shuffle the data of the cholangitis and control groups and pick the first

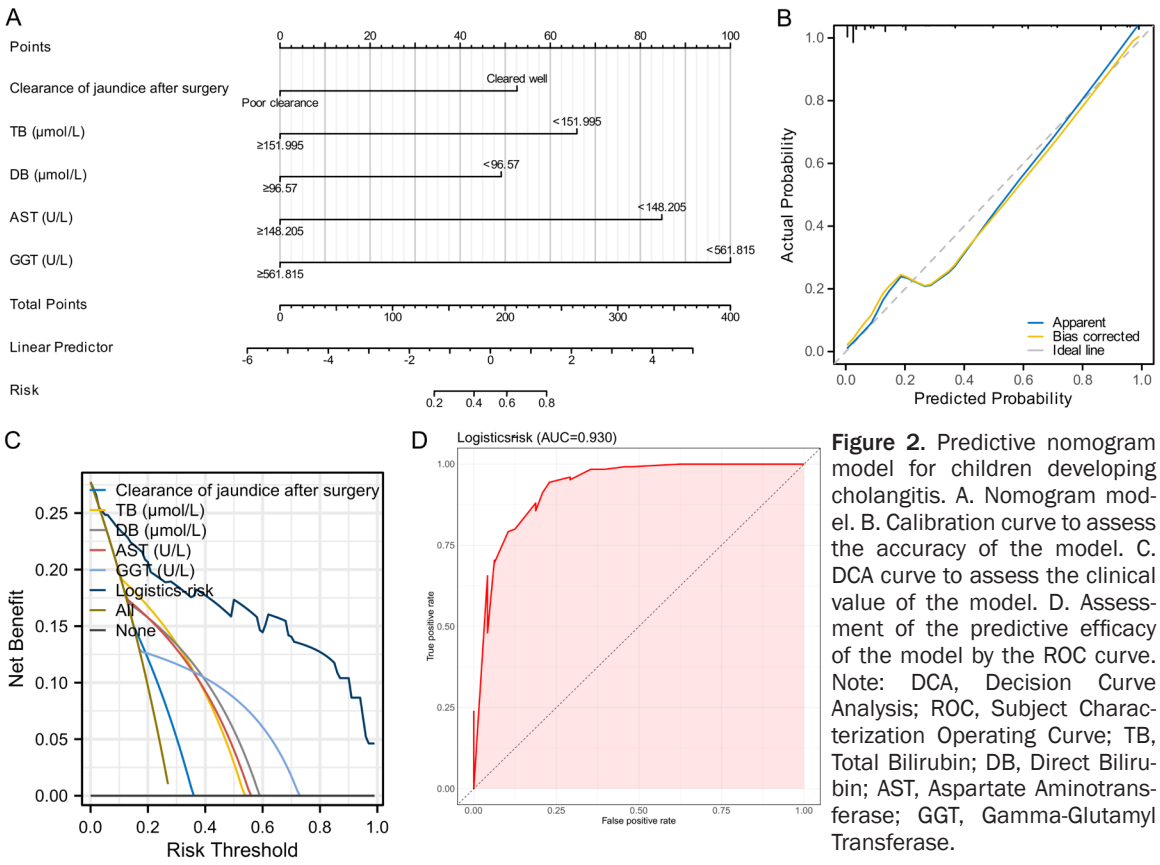

Figure 2. Predictive nomogram model for children developing cholangitis. A. Nomogram model. B. Calibration curve to assess the accuracy of the model. C. DCA curve to assess the clinical value of the model. D. Assessment of the predictive efficacy of the model by the ROC curve. Note: DCA, Decision Curve Analysis; ROC, Subject Characterization Operating Curve; TB, Total Bilirubin; DB, Direct Bilirubin; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase.

Table 7. Random sampling predictions

Factor	Cholangitis cases	No-cholangitis cases
Postoperative clearance of jaundice	Clearance difference (0)	Good clearance (52.5)
TB (μmol/L)	148.38 (66)	135.6 (66)
DB (μmol/L)	100.26 (0)	90.19 (58)
AST (U/L)	169.07 (0)	126.36 (85)
GGT (U/L)	790.63 (0)	498.38 (100)
Totals	66	361.5
Rate of occurrence	17.5%	91.5%

Note: TB, Total Bilirubin; DB, Direct Bilirubin; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase.

case of each set to calculate the incidence rate. According to the findings, the probability of developing cholangitis in the case at low risk was 17.5%, while that in the case at high risk was 91.5% (**Table 7**).

Discussion

The Kasai procedure is a pivotal intervention for biliary atresia (BA), significantly extending liver survival and dramatically enhancing the prognosis for affected children [17]. Nonetheless, the nature of postoperative recovery critically influences the long-term health and quality of life of these children. Insufficient recovery diminishes survival rates and imposes a considerable burden on the patients, their families, and society [18]. Among the spectrum of complications following Kasai surgery, cholangitis emerges as the most prevalent, profoundly affecting the prognosis and quality of life of the children. The incidence of cholangitis is notably high, with 60-90% of children experiencing at least one episode before reaching two years of age [19]. This condition significantly compromises postoperative outcomes and quality of

life, underlining the necessity for a deeper understanding of its pathogenesis and contributing factors, which are uncertain.

In the present study, we observed that a significantly higher percentage of children in the cholangitis group had a body weight of ≥4.5 kg at the time of surgery compared to those in the control group. We also found that TB, DB, AST, and GGT were higher in the cholangitis group than in the non-cholangitis group. We hypothesize that higher body weight may indicate more severe nutritional status or disease progression preoperatively, indicating that the liver may have been in a state of inflammation or infection. This leads to more significant challenges during the child's postoperative recovery and increases the risk of cholangitis. Additionally, greater body weight may present technical difficulties during surgery, such as increased complexity of the hepatic hilar anatomy, which may prolong the surgery and raise the risk of infection, thus increasing the incidence of cholangitis [20-22].

Increased preoperative levels of TB, DB, AST, and GGT suggest impaired hepatic metabolism, hepatocellular damage, and the presence of inflammation in the biliary system in children, which may lead to increased susceptibility to cholangitis during recovery from surgery [23]. Previously, Liu et al. [14] found that children who developed cholangitis after Kasai surgery had higher body weight than those who did not develop cholangitis, and also presented with higher GGT levels, which aligns with the results of our study. However, Liu et al. did not observe differences in TB, DB, or AST levels between the groups, which may be due to differences in sample selection, disease severity, or time point of evaluation.

Postoperative liver function recovery and clearance of jaundice are essential indicators for assessing the success of Kasai surgery [24]. These indicators not only reflect the functional status of the liver and biliary system after surgery but also significantly affect the occurrence and prognosis of cholangitis [25]. In our study, we also analyzed the postoperative hepatic function recovery and jaundice clearance in children. Our study found that children in the cholangitis group exhibited significantly inferior postoperative liver function recovery and jaundice clearance compared to the non-cholangitis group. This suggests that the improvement of liver function and the clearance of jaundice after Kasai's surgery are closely related to the development of cholangitis. Therefore, strict postoperative monitoring and management are critical, especially for children with improved liver function and unresolved jaundice.

At the end of the study, we used logistic regression to analyze the independent risk factors for the development of cholangitis in children with BA after Kasai surgery. Our study showed that postoperative clearance of jaundice, TB, DB, AST, and GGT were independent risk factors for the development of cholangitis in children. Poor clearance of jaundice indicates potential bile duct obstruction or insufficient liver function, which can increase the risk of cholangitis [26]. Elevated levels of TB and DB suggest bile stasis and hepatocellular injury, indicative of impaired liver detoxification and metabolism, thereby heightening the risk of infection and cholangitis [27]. High level of AST is a marker of hepatocellular damage, which can compromise liver function and increase vulnerability to infection. Similarly, elevated GGT levels are indicative of bile duct injury or inflammation, which is closely associated with the occurrence of cholangitis [28]. Given these risk factors, it is crucial for healthcare providers to remain vigilant and adopt proactive strategies to prevent the onset of cholangitis. Strategies include improving bile flow, controlling infections, optimizing nutritional support, and enhancing liver protection [29, 30].

Based on these findings, a nomogram model was constructed, which demonstrated an exceptionally high predictive value for the development of cholangitis in children following Kasai surgery. The AUC value of the model was 0.930, indicating high accuracy and reliability in distinguishing children at risk for cholangitis from those who are not likely to develop it. Furthermore, the utility and accuracy of the model was validated by calculating the nomogram model scores for two cases of children. For one case, the calculation indicated a 17.5% probability of not developing cholangitis, consistent with the actual occurrence of cholangitis. In contrast, another case of a child who did not develop cholangitis showed a high probability of not developing cholangitis at 91.5%, verifying the model's predictive accuracy. These findings highlight the model's robust theoreti-

cal and practical predictive value, making it a significant tool for clinical decision-making, enhancing the outcomes for children with biliary atresia (BA) by guiding early intervention strategies.

However, there are still some limitations to this study, including its retrospective design, limited sample size, and the single-center nature of research. These factors may affect the generalizability of the findings. Future studies should overcome these limitations by implementing a prospective design, expanding the sample size, and conducting multicenter collaborations.

In conclusion, logistic regression analysis identified postoperative jaundice clearance, TB, DB, AST, and GGT as independent risk factors for the development of cholangitis in infants with biliary atresia after Kasai surgery. The constructed nomogram model effectively predicts the likelihood of cholangitis, offering a valuable tool for early intervention and substantially improving the prognosis for children at high risk of this postoperative complication.

Disclosure of conflict of interest

None.

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