Original Article

A nomogram model based on routine serum markers for predicting the occurrence of primary cholangitis after Kasai operation for biliary atresia

Chunxiao Yang[1,2], Tengfei Li[1], Pu Yu[3], Jianghua Zhan[1,4]

[1]Graduate College, Tianjin Medical University, Tianjin, China; [2]Department of General Surgery, Zibo Municipal Hospital, Zibo, China; [3]Department of Neonatal Surgery, Xi'an Children's Hospital, Xi'an, China; [4]Department of General Surgery, Tianjin Children's Hospital, Tianjin, China

Contributions: (I) Conception and design: C Yang; (II) Administrative support: J Zhan; (III) Provision of study materials or patients: J Zhan; (IV) Collection and assembly of data: T Li, P Yu; (V) Data analysis and interpretation: C Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jianghua Zhan, MD. Department of General Surgery, Tianjin Children's Hospital, Longyan Road 238, Beichen District, Tianjin 300134, China; Graduate College, Tianjin Medical University, Tianjin, China. Email: zhanjianghuatj@163.com.

Background: The Kasai procedure is still considered the optimal therapeutic approach for biliary atresia (BA). Nevertheless, the onset of postoperative cholangitis can impede the resolution of jaundice and significantly affect the overall prognosis of the disease. This study aims to develop a nomogram model that precisely forecasted the incidence of cholangitis after the Kasai procedure.

Methods: This study retrospectively collected clinical, preoperative, and postoperative serological data from patients with BA who underwent the Kasai procedure at Tianjin Children's Hospital between January 2017 and November 2023. Utilizing multivariable analysis and logistic regression, a clinical nomogram model was developed to predict the occurrence of primary cholangitis postoperatively. To validate the model's accuracy, data from patients with BA at Xi'an Children's Hospital from January 2018 to November 2019 were employed.

Results: We identified two independent predictors, neutrophil ratio post-operative to pre-operative ratio (NEU% PPR) and alkaline phosphatase post-operative to pre-operative ratio (ALP PPR), that were significantly associated with the occurrence of primary cholangitis following the Kasai procedure. These predictors were subsequently utilized to construct a nomogram model. The model exhibited an area under the curve (AUC) value of 0.829, surpassing the predictive capabilities of individual predictors. Additionally, through Kaplan-Meier (KM) analysis, we observed a significant correlation between ALP PPR and the occurrence of postoperative primary cholangitis, further supporting the reliability of our nomogram model.

Conclusions: This study has successfully established a clinical prediction model that can effectively predict the occurrence of primary cholangitis following the Kasai procedure for BA.

Keywords: Biliary atresia (BA); cholangitis; nomogram; predicting model; alkaline phosphatase

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Introduction

Biliary atresia (BA) constitutes a critical surgical disorder that impacts the hepatobiliary system in children. This condition is chiefly marked by the fibrotic blockage of intrahepatic and extrahepatic bile ducts, culminating in a progressive cascade of inflammation, liver fibrosis, and, eventually, hepatic failure. The implementation of surgical procedures is essential for the effective management of

BA, as the lack of prompt intervention may lead to dire consequences for the affected pediatric population (1-3).

The Kasai procedure continues to be the most favored and efficient treatment method for BA. In cases where the chance to perform Kasai surgery is overlooked, liver transplantation can be regarded as a viable alternative treatment strategy (4,5). It is important to highlight that cholangitis represents the most common complication associated with Kasai surgery, significantly impacting both the quality of life and the survival rates of the children who are affected (6). Statistical data indicates that the occurrence of cholangitis within a year following surgical procedures varies between 54.6% and 91.9% (7,8). Significantly, it is broadly recognized that cholangitis following Kasai surgery can impair the rate of jaundice resolution after the procedure, acting as a vital factor influencing the prognosis of the children affected (6,9). Nonetheless, a substantial gap persists in the availability of a reliable clinical model that can accurately forecast the development of cholangitis subsequent to Kasai surgery.

In this research, our aim is to develop a clinically relevant model capable of forecasting the onset of cholangitis subsequent to Kasai surgery. To improve its applicability, we seek to construct this predictive model using widely available serological indicators. We present this article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-2025-170/rc).

Highlight box

Key findings

- This study has successfully established a clinical prediction model that can effectively predict the occurrence of primary cholangitis following the Kasai procedure for biliary atresia (BA).

What is known and what is new?

- A substantial gap persists in the availability of a reliable clinical model that can accurately forecast the development of cholangitis subsequent to Kasai surgery.
- We established a successful nomogram model on routine serum markers for the first time to predict the occurrence of cholangitis after Kasai operation. Our nomogram model integrates two distinct variables: neutrophil ratio post-operative to pre-operative ratio and alkaline phosphatase post-operative to pre-operative ratio, which serve as reliable predictors for the initial onset of cholangitis following Kasai surgery. This could significantly enhance clinical decision-making processes.

What is the implication, and what should change now?

- This research represents the inaugural effort to create a nomogram aimed at predicting cholangitis post-Kasai surgery, exhibiting commendable predictive efficacy. In the realm of precision medicine, this model has the potential to enhance clinical decision-making and optimize the management of patients diagnosed with BA.

Methods

Patients

The criteria for selecting participants for both the training and validation cohorts in this research were defined as follows: pediatric patients diagnosed with BA via intraoperative cholangiography and liver biopsy conducted during surgical intervention, who later received Kasai surgery. For the training cohort, a total of 80 children who underwent Kasai surgery for BA at Tianjin Children's Hospital from January 2017 to November 2023 were included. Each of these patients had undergone intraoperative cholangiography and liver biopsy to validate the BA diagnosis.

The criteria for exclusion in this investigation included the absence of complete preoperative or postoperative routine blood tests and liver function data, in addition to patients who were not available for follow-up. Upon the application of these criteria, a final cohort of 56 children was incorporated into the training dataset.

The diagnosis of cholangitis in patients was characterized by the occurrence of an unexplained fever (≥38 ℃) along with at least one additional clinical manifestation. These manifestations included recurrent jaundice or pale stools, a direct bilirubin (DBIL) level of 20 μmol/L or higher, a white blood cell count (WBC) of 10×10^9/L or more, or a C-reactive protein (CRP) measurement of 10 mg/L or greater (9-11).

This study was approved by the ethics committee of Tianjin Children's Hospital (No. 2022-SYYJCYJ-008) and informed consent was obtained from each participant's guardians. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

In the present investigation, we gathered data from pediatric patients diagnosed with BA who received Kasai surgery at Xi'an Children's Hospital during the period from January 2018 to November 2019. These pediatric subjects constituted the validation cohort for our predictive model. Initially, a total of 62 children were recruited for this

validation group. Nevertheless, following the application of specific exclusion criteria—such as incomplete or absent preoperative and postoperative hematological and liver function data, along with instances of patients being lost to follow-up—the final validation cohort comprised 54 children.

All children have undergone anti-reflux valve surgery, and the length of the Roux-en-Y limb is 40–45 cm. All children follow the same postoperative antibiotic and corticosteroid treatment regimens. The antibiotic treatment regimen: children are given sulperazon intravenously for 2 weeks after the operation to fight infection, then switched to oral cefixime for 2 weeks, and then oral south China moxazole for another 2 weeks. The corticosteroid application regimen: intravenous infusion of methylprednisolone at a dose of 10 mg/kg/d is given for 5 days after the operation, then the dose is gradually reduced. After 7 days, it is changed to oral prednisolone at a dose of 1 mg/kg/d, and stopped after 4 weeks. Clinical and laboratory serological information was obtained from the medical records of each patient. This dataset comprised the age of the patients at the time of surgery, their gender, and the serological markers, which are detailed in *Table 1*.

Preoperative serological data were obtained from the most recent tests conducted within a 3-day window prior to surgical intervention, which ensured the data's accuracy and relevance. Conversely, postoperative serological information was collected from tests carried out within one week following the surgery, thus reflecting early alterations in serological indicators. For the pediatric subjects included in the validation cohort, the interval to cholangitis was calculated with precision. Specifically, cholangitis time was defined as the period extending from the date of surgery to the initial occurrence of cholangitis. In instances where cholangitis did not develop by the conclusion of the follow-up duration, the time to cholangitis was established as the period between the surgical procedure and the end of the follow-up, measured accurately in days. This methodology provided a thorough evaluation of both the incidence of cholangitis and its timing in relation to the surgical event.

By employing the serological data obtained both before and after surgery, we calculated the postoperative-to-preoperative ratio (PPR) for each respective serological marker. This ratio acts as a quantitative indicator, signifying the alteration in serological levels observed between the preoperative and postoperative phases. Through the examination of these ratios, our objective is to enhance our comprehension of the serological responses elicited by surgical procedures in the patients being analyzed. The findings are presented in *Table 2*.

Establishment and evaluating performance of the nomogram

Within the training cohort, we utilized univariate logistic regression to investigate the association between several potential factors and the incidence of primary cholangitis. This preliminary analysis enabled us to discern variables that exhibited a noteworthy correlation with primary cholangitis, specifically those with P values below 0.1. Subsequently, these identified variables were selected as candidates for additional examination.

Subsequently, we developed a multivariate logistic regression model to evaluate the independent impact of each candidate variable on cholangitis. Variables that exhibited no significant contribution to the model, indicated by P values equal to or exceeding 0.05, were omitted from further analysis. The variables that demonstrated a robust and independent correlation with cholangitis were then utilized to create a more precise logistic regression model.

In order to enhance the clinical utility of our model, we constructed a nomogram utilizing the Xiantao Academic software. This nomogram assigns a weighted score to each variable based on its corresponding β-coefficient. By aggregating the scores associated with the specific values of the variables for an individual patient, we are able to efficiently and effectively estimate the patient's risk of developing cholangitis.

In conclusion, we assessed the predictive efficacy of our nomogram through two principal metrics: the area under the curve (AUC) and the calibration curve. The AUC serves as an indicator of the nomogram's overall accuracy in distinguishing between patients who are likely to develop cholangitis and those who are not. Conversely, the calibration curve evaluates the degree to which the predicted probabilities produced by the nomogram correspond with the actual observed outcomes. Collectively, these metrics enable us to evaluate the clinical applicability of our nomogram in forecasting the risk of cholangitis.

Statistical analysis

The statistical analysis was conducted utilizing SPSS version 27 (IBM Corp, New York, USA), R version 4.2.2

Table 1 Serological indicators before and after surgery and their abbreviations

Serological indicators	Abbreviations
Preoperative	
White blood cell pre-operation	WBC PRO
Neutrophil ratio pre-operation	NEU% PRO
Lymphocyte ratio pre-operation	LYM% PRO
Monocyte ratio pre-operation	MONO% PRO
Eosinophil ratio pre-operation	EO% PRO
Basophil ratio pre-operation	BASO% PRO
Neutrophil count pre-operation	NEU PRO
Lymphocyte count pre-operation	LYM PRO
Monocyte count pre-operation	MONO PRO
Eosinophil count pre-operation	EO PRO
Basophil count pre-operation	BASO PRO
Red blood cell pre-operation	RBC PRO
Hemoglobin pre-operation	HGB PRO
Hematocrit pre-operation	HCT PRO
Red blood cell volume pre-operation	RBCV PRO
Mean cell hemoglobin pre-operation	MCH PRO
Mean cell hemoglobin concentration pre-operation	MCHC PRO
Platelet pre-operation	PLT PRO
Mean volume pre-operation	MV PRO
Plateletcrit pre-operation	PCT PRO
Platelet distribution width pre-operation	PDW PRO
Total protein pre-operation	TP PRO
Albumin pre-operation	ALB PRO
Globulin pre-operation pre-operation	GLO PRO
Prealbumin pre-operation	PA PRO
Alanine aminotransferase pre-operation	ALT PRO
Alkaline phosphatase pre-operation	ALP PRO
Gamma-glutamyl transpeptidase pre-operation	GGT PRO
Cholinesterase pre-operation	ChE PRO
Leucine aminopeptidase pre-operation	LAP PRO
Adenosine deaminase pre-operation	ADA PRO
Total bilirubin pre-operation	TBIL PRO
Direct bilirubin pre-operation	DBIL PRO
Indirect bilirubin pre-operation	IBIL PRO
Aspartate aminotransferase pre-operation	AST PRO
Mitochondrial aspartate aminotransferase pre-operation	mAST PRO
Lactate dehydrogenase pre-operation	LDH PRO
Total bile acids pre-operation	TBA PRO
Postoperative	
White blood cell post-operation	WBC PO
Neutrophil ratio post-operation	NEU% PO
Lymphocyte ratio post-operation	LYM% PO
Monocyte ratio post-operation	MONO% PO
Eosinophil ratio post-operation	EO% PO
Basophil ratio post-operation	BASO% PO
Neutrophil count post-operation	NEU PO
Lymphocyte count post-operation	LYM PO
Monocyte count post-operation	MONO PO
Eosinophil count post-operation	EO PO
Basophil count post-operation	BASO PO
Red blood cell post-operation	RBC PO
Hemoglobin post-operation	HGB PO
Hematocrit post-operation	HCT PO
Red blood cell volume post-operation	RBCV PO
Mean cell hemoglobin post-operation	MCH PO
Mean cell hemoglobin concentration post-operation	MCHC PO
Platelet post-operation	PLT PO
Mean volume post-operation	MV PO
Plateletcrit post-operation	PCT PO
Platelet distribution width post-operation	PDW PO
Total protein post-operation	TP PO
Albumin post-operation	ALB PO
Globulin post-operation	GLO PO
Prealbumin post-operation	PA PO
Alanine aminotransferase post-operation	ALT PO
Alkaline phosphatase post-operation	ALP PO
Gamma-glutamyl transpeptidase post-operation	GGT PO

Table 1 (*continued*)

Table 1 (*continued*)

Serological indicators	Abbreviations
Cholinesterase post-operation	ChE PO
Leucine aminopeptidase post-operation	LAP PO
Adenosine deaminase post-operation	ADA PO
Total bilirubin post-operation	TBIL PO
Direct bilirubin post-operation	DBIL PO
Indirect bilirubin post-operation	IBIL PO
Aspartate aminotransferase post-operation	AST PO
Mitochondrial aspartate aminotransferase post-operation	mAST PO
Lactate dehydrogenase post-operation	LDH PO
Total bile acids post-operation	TBA PO

Table 2 Serological indicators ratio and their abbreviations

Serological indicators ratio	Abbreviations
White blood cell post-operative to pre-operative ratio	WBC PPR
Neutrophil ratio post-operative to pre-operative ratio	NEU% PPR
Eosinophil ratio post-operative to pre-operative ratio	EO% PPR
Neutrophil count post-operative to pre-operative ratio	NEU PPR
Monocyte count post-operative to pre-operative ratio	MONO PPR
Basophil count post-operative to pre-operative ratio	BASO PPR
Hemoglobin post-operative to pre-operative ratio	HGB PPR
Red blood cell volume post-operative to pre-operative ratio	RBCV PPR
Mean cell hemoglobin concentration post-operative to pre-operative ratio	MCHC PPR
Mean volume post-operative to pre-operative ratio	MV PPR
Platelet distribution width post-operative to pre-operative ratio	PDW PPR
Albumin post-operative to pre-operative ratio	ALB PPR
Prealbumin post-operative to pre-operative ratio	PA PPR
Alkaline phosphatase post-operative to pre-operative ratio	ALP PPR

Table 2 (*continued*)

Serological indicators ratio	Abbreviations
Cholinesterase post-operative to pre-operative ratio	ChE PPR
Adenosine deaminase post-operative to pre-operative ratio	ADA PPR
Direct bilirubin post-operative to pre-operative ratio	DBIL PPR
Aspartate aminotransferase post-operative to pre-operative ratio	AST PPR
Lactate dehydrogenase post-operative to pre-operative ratio	LDH PPR
Lymphocyte ratio post-operative to pre-operative ratio	LYM% PPR
Monocyte ratio post-operative to pre-operative ratio	MONO% PPR
Basophil ratio post-operative to pre-operative ratio	BASO% PPR
Lymphocyte count post-operative to pre-operative ratio	LYM PPR
Eosinophil count post-operative to pre-operative ratio	EO PPR
Red blood cell post-operative to pre-operative ratio	RBC PPR
Hematocrit post-operative to pre-operative ratio	HCT PPR
Mean cell hemoglobin post-operative to pre-operative ratio	MCH PPR
Platelet post-operative to pre-operative ratio	PLT PPR
Plateletcrit post-operative to pre-operative ratio	PCT PPR
Total protein post-operative to pre-operative ratio	TP PPR
Globulin post-operative to pre-operative ratio	GLO PPR
Alanine aminotransferase post-operative to pre-operative ratio	ALT PPR
Gamma-glutamyl transpeptidase post-operative to pre-operative ratio	GGT PPR
Leucine aminopeptidase post-operative to pre-operative ratio	LAP PPR
Total bilirubinpost-operative to pre-operative ratio	TBIL PPR
Indirect bilirubin post-operative to pre-operative ratio	IBIL PPR
Mitochondrial aspartate aminotransferase post-operative to pre-operative ratio	mAST PPR
Total bile acids post-operative to pre-operative ratio	TBA PPR

Table 3 Clinical and laboratory characteristics of the model design cohort

Characteristics	Group 1 (n=41)	Group 2 (n=15)	P value
Cholangitis time (days)	62 (32, 104)	–	–
Noncholangitis follow-up time (days)	–	556 (125, 1,338.5)	–
Sex			0.76
Male	20 (48.8)	8 (53.3)	
Female	21 (51.2)	7 (46.7)	
Age at operation (days)	66.7±24.8	59.5±19.4	0.32

Data are presented as median (interquartile range), n (%) or mean ± standard deviation. Group 1: children who develop cholangitis postoperatively. Group 2: children who did not develop cholangitis postoperatively.

(R Development Core Team), and Xiantao Academic software. A P value of less than 0.05 was established as the threshold for statistical significance

Results

Patient characteristic

The dataset utilized for this investigation included a total of 56 participants, divided into two separate cohorts based on the incidence of postoperative primary cholangitis. The first cohort, referred to as Group 1, consisted of 41 pediatric patients who experienced cholangitis following surgical intervention, comprising 20 males and 21 females. The average age at the time of surgery for this group was recorded at 66.7±24.8 days. Conversely, Group 2 was made up of 15 children who did not exhibit cholangitis after the operation, with a gender distribution of 8 males and 7 females, and an average surgical age of 59.5±19.4 days. The demographic details of these groups are presented in *Tables 3*,*4*.

Descriptive statistics are expressed as numerical values (percentages), mean ± standard deviation (mean ± SD), or median [interquartile range (IQR)] for data that do not follow a normal distribution. To identify statistically significant differences among groups for categorical data, the χ^2 test or Fisher's exact test was utilized. For continuous variables, methodologies such as analysis of variance (ANOVA), *t*-test, and Wilcoxon test were applied.

Univariate logistic regression analysis of variables significantly associated with cholangitis

In the dataset utilized for this investigation, a comprehensive total of 38 preoperative serological markers, 38 postoperative serological markers, along with their corresponding ratios were incorporated. However, the basophil ratio from postoperative to preoperative (BASO% PPR) and the basophil count from postoperative to preoperative ratio (BASO PPR) were omitted from the analysis due to the absence of data for certain patients, as the divisor yielded a value of zero. Consequently, 112 distinct indicators were analyzed through univariate logistic regression to ascertain variables that could be linked to the incidence of cholangitis following Kasai surgery. Variables exhibiting a P value below 0.1 during the univariate logistic regression (Table S1) were deemed to have a correlation with the outcome and were subsequently included in the multivariate logistic regression analysis. Five specific indicators were identified as being associated with the onset of cholangitis post-Kasai surgery: platelet post-operation (PLTPO), mean volume post-operation (MV PO), neutrophil ratio from postoperative to preoperative (NEU PPR), alkaline phosphatase ratio from postoperative to preoperative (ALP PPR), and mean volume pre-operation (MV PRO). Thus, the following indicators were retained for further multivariate logistic regression analysis: PLTPO [odds ratio (OR) =0.997; 95% confidence interval (CI): 0.992–1.001; P=0.09], MV PO (OR =0.568; 95% CI: 0.294–1.101; P=0.09), MV PRO (OR =0.594; 95% CI: 0.324–1.088; P=0.09), neutrophil ratio post-operative to pre-operative ratio (NEU% PPR) (OR =2.145; 95% CI: 0.916–5.020; P=0.08), and alkaline phosphatase post-operative to pre-operative ratio (ALP PPR) (OR =421.410; 95% CI: 4.453–39877.2457; P=0.009).

Establishment of the nomogram model

Employing the five indicators of PLT PO, MV PO, MV PRO, NEU% PPR, and ALP PPR, the outcomes derived from the multivariate logistic regression analysis are presented as follows: NEU% PPR exhibited an OR of 3.953 with a 95% CI ranging from 1.285 to 12.161 and a P value of 0.02. Conversely, MV PRO demonstrated an OR of 0.704, accompanied by a 95% CI of 0.418 to 1.185 and a P value of 0.19. Furthermore, PLT PO recorded an OR of 0.995, with a 95% CI between 0.989 and 1.001 and a P value of 0.11. Lastly, ALP PPR showed a significant

Table 4 Clinical and laboratory characteristics of the model design cohort

Characteristics	Group 1	Group 2	P
Preoperative			
WBC (10^9/L)	10.586±3.2736	10.837±3.056	0.80
NEU%	24.8 (15.2, 30.9)	16 (13.7, 20.2)	0.02
LYM%	62.6 (57.2, 70.6)	69.4 (61.05, 77.15)	0.14
PLT (10^9/L)	423.73±154.19	408.33±120.56	0.73
ALT (U/L)	114 (84, 208)	111 (90.5, 131)	0.28
GGT (U/L)	406 (207, 606)	366 (272, 716.5)	0.47
DBIL (μmol/L)	141.9 (111.4, 156.1)	120.6 (105.2, 154.75)	0.73
Postoperative			
WBC (10^9/L)	524.1±182.85	432.27±148.58	0.09
NEU%	12.92 (8.96, 15.14)	10.7 (10.125, 12.605)	0.39
LYM%	29.5 (24.7, 39.6)	32.7 (22.5, 43.45)	0.90
PLT (10^9/L)	59.04 (50.7, 63.1)	52.1 (44.95, 65.4)	0.51
ALT (U/L)	212 (144, 325)	187 (138, 268.5)	0.55
GGT (U/L)	510 (335, 748)	429 (341.5, 678)	0.76
DBIL (μmol/L)	116.5 (89.1, 145.2)	115.1 (79.05, 154.85)	0.93

Data are presented as mean ± standard deviation or median (interquartile range). Group 1: children who develop cholangitis postoperatively. Group 2: children who did not develop cholangitis postoperatively. ALT, alanine aminotransferase; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LYM%, lymphocyte ratio; NEU%, neutrophil ratio; PLT, platelet; WBC, white blood cell.

OR of 4,014.727 with a 95% CI spanning from 5.583 to 2,887,192.1501 and a P value of 0.01, as illustrated in *Table 5*.

NEU% PPR and ALP PPR have been recognized as distinct prognostic factors for primary cholangitis subsequent to Kasai surgery, and these variables were utilized to develop a clinical nomogram model (refer to *Figure 1*). We use a specific patient case to demonstrate the application of *Figure 1*. For the 30th child in our cohort, the NEU% PPR is 2.558824, which is converted to a score of approximately 34 from the nomogram. The ALP PPR of the child is 0.510903, which is also converted to a score of approximately 34. The total score is 34+34=68. Through score conversion, the probability of developing cholangitis is 0.4 (40%). It is predicted that the probability of cholangitis after surgery for this child is low, and the child did not have an attack of cholangitis after the operation. The predicted result is consistent with the actual result of the child's cholangitis attack.

Validation of the model in predicting cholangitis

Utilizing the two identified risk factors from the training dataset alongside the predicted probability of cholangitis occurrence obtained from the model equation, a receiver operating characteristic (ROC) curve (illustrated in *Figure 2A*) was constructed. The AUC values were computed as follows: the NEU% PPR yielded an AUC of 0.706, the ALP PPR resulted in an AUC of 0.748, while the overall prediction model demonstrated a superior AUC of 0.829. Notably, the prediction probability derived from the model formula surpassed those based on the individual risk factors. The cut-off value of NEU% PPR is 1.7176, the cut-off value of ALP PPR is 0.5011, and the cut-off value of the model is 0.76201.

By utilizing the validation dataset, we estimated the likelihood of cholangitis occurrence as per the model's formula and subsequently produced a ROC curve (refer to *Figure 2B*). The AUC value obtained for the validation

Table 5 The results of the multivariate logistic regression model

Variables in each step of the multiple logistic regression analysis	B	SD	Wald	df	Significance	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Step 1a								
PLT PO	−0.002	0.020	0.013	1	0.91	0.998	0.960	1.037
MV PO	0.541	0.965	0.314	1	0.58	1.718	0.259	11.382
NEU% PPR	−1.271	0.558	5.184	1	0.02	0.280	0.094	0.838
ALP PPR	−8.484	3.368	6.344	1	0.01	0.000	0.000	0.152
PCT PO	6.237	19.978	0.097	1	0.76	511.487	0.000	5.178E*19
Constant	0.439	10.449	0.002	1	0.97	1.551	–	–
Step 2								
MV PO	0.644	0.482	1.784	1	0.18	1.903	0.740	4.894
NEU% PPR	−1.257	0.543	5.361	1	0.02	0.284	0.098	0.824
ALP PPR	−8.428	3.328	6.414	1	0.01	0.000	0.000	0.149
PCT PO	3.962	2.876	1.898	1	0.17	52.588	0.187	14,758.205
Constant	−0.659	5.280	0.016	1	0.90	0.517	–	–
Step 3								
NEU% PPR	−1.314	0.534	6.064	1	0.01	0.269	0.094	0.765
ALP PPR	−8.298	3.236	6.575	1	0.01	0.000	0.000	0.142
PCT POO	4.853	2.846	2.907	1	0.09	128.110	0.484	33,895.371
Constant	5.463	2.527	4.673	1	0.03	235.743	–	–

ALP PPR, alkaline phosphatase post-operative to pre-operative ratio; CI, confidence interval; df, degree of freedom; MV PO, mean volume post-operation; NEU% PPR, neutrophil ratio post-operative to pre-operative ratio; PCT PO, plateletcrit post-operation; PLT PO, platelet post-operation; SD, standard deviation.

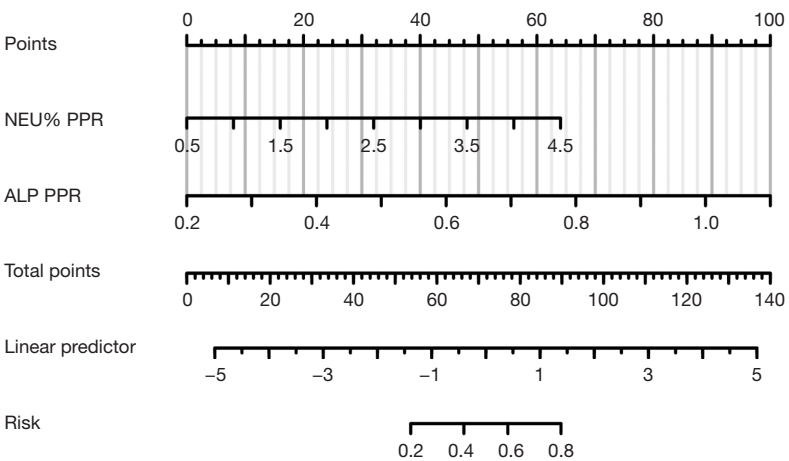

Figure 1 The clinical nomogram model based on NEU% PPR and ALP PPR for cholangitis following Kasai surgery. The nomogram was used by summing the points identified on the points scale for each factor. The total points projected on the bottom scales match the probability cholangitis occurrence of patient. ALP PPR, alkaline phosphatase post-operative to pre-operative ratio; NEU% PPR, neutrophil ratio post-operative to pre-operative ratio.

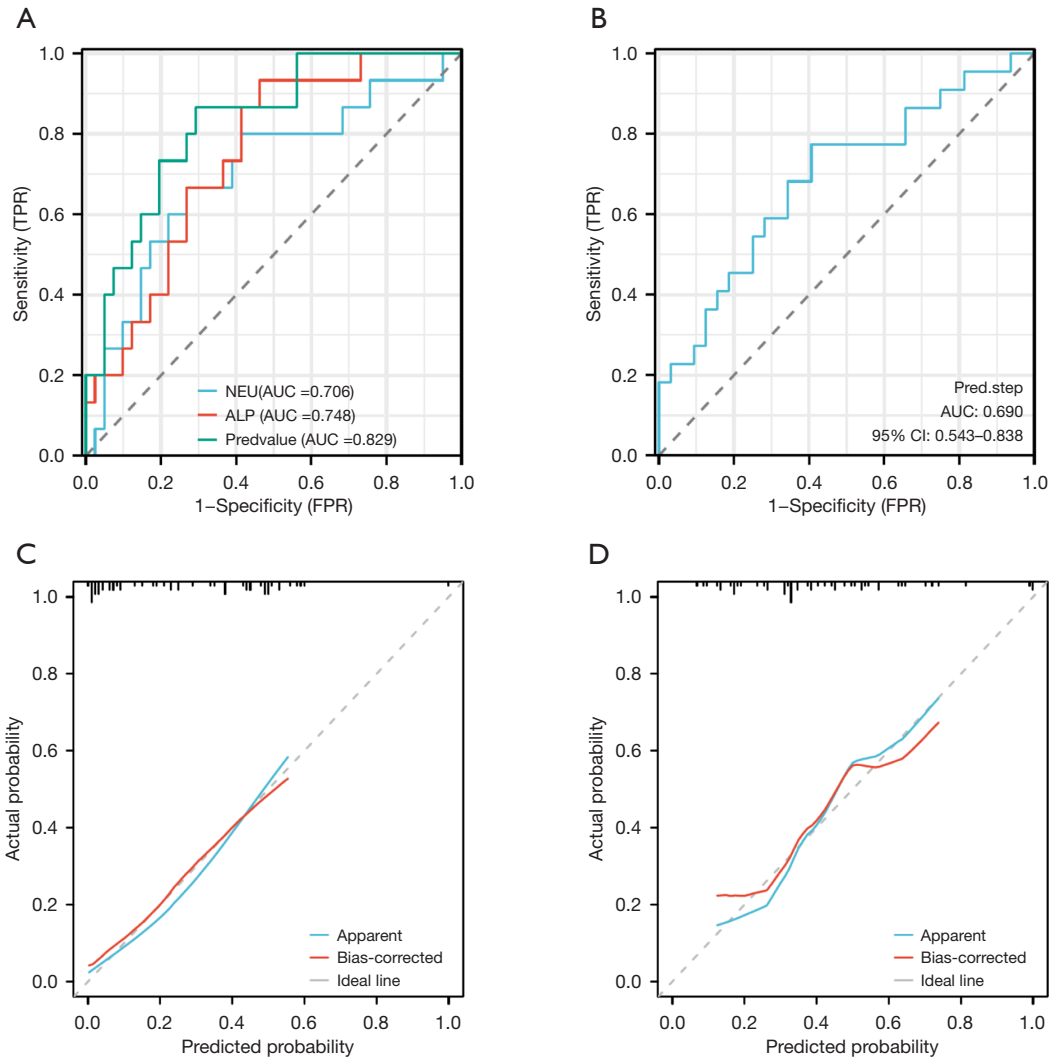

Figure 2 The ROC curves and calibration curves of the model training set and validation set. The ROC curve of the nomogram and comparison with NEU% PPR and ALP PPR (A). The ROC curve of the validation set (B). The nomogram-predicted probability of cholangitis in the training data set (C). The nomogram-predicted probability of cholangitis in the validation data set (D). ALP PPR, alkaline phosphatase post-operative to pre-operative ratio; AUC, area under the curve; CI, confidence interval; FPR, false positive rate; NEU% PPR, neutrophil ratio post-operative to pre-operative ratio; ROC, receiver operating characteristic; TPR, true positive rate.

dataset was 0.690.

The calibration curves for both the training and validation datasets are presented in *Figure 2C,2D*. The findings indicate that the probabilities predicted by the model for cholangitis closely matched the observed probabilities, thereby reflecting an alignment between the predictions and the actual incidence of cholangitis. Furthermore, the results suggest that the nomogram's ability to discriminate cholangitis predictions is likely applicable to diverse populations and holds potential for integration into clinical practice.

Considering the occurrence of primary cholangitis at various intervals post-Kasai surgery, we employed the Kaplan-Meier (KM) method to assess two independent predictors (*Figure 3A,3B*). Patients were categorized into low and high NEU% PPR groups based on the median value (P=0.14, HR =0.63), and a similar classification was applied to the ALP PPR groups (P=0.006, HR =0.40). The

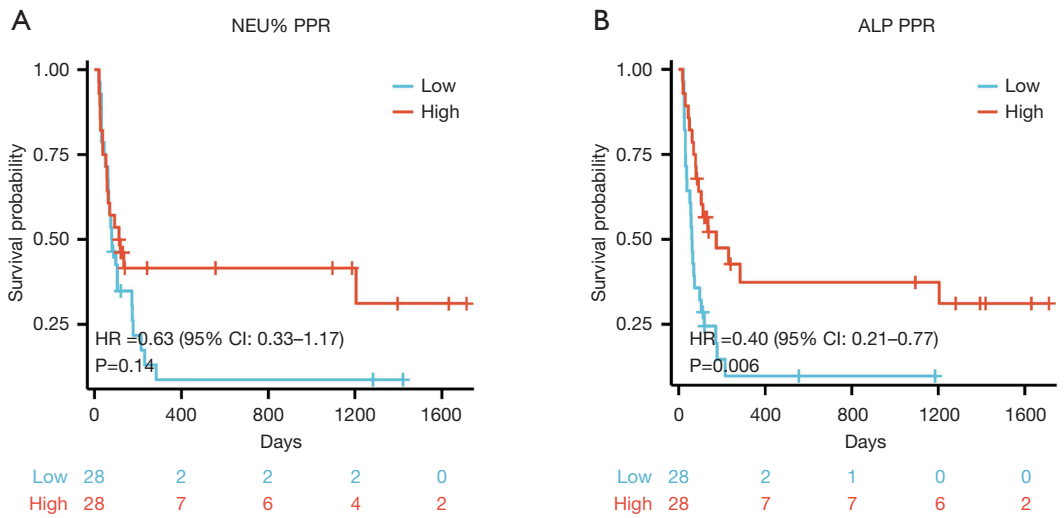

Figure 3 The Kaplan-Meier analysis in NEU% PPR and ALP PPR. The Kaplan-Meier analysis in NEU% PPR (A). The Kaplan-Meier analysis in ALP PPR (B). ALP PPR, alkaline phosphatase post-operative to pre-operative ratio; CI, confidence interval; HR, hazard ratio; NEU% PPR, neutrophil ratio post-operative to pre-operative ratio.

frequency of cholangitis was notably lower in the low ALP PPR group in comparison to the high ALP PPR group, with this disparity becoming more pronounced over time.

Discussion

Cholangitis that arises after Kasai surgery is a crucial determinant of the prognosis for BA, frequently manifesting within the initial year following the operation (12,13). Preventive strategies aimed at mitigating cholangitis following Kasai surgery encompass the implementation of anti-reflux techniques during the surgical procedure, the administration of steroids in the postoperative period, and the provision of prophylactic antibiotics. Nevertheless, there remains an ongoing debate concerning the effectiveness of intraoperative anti-reflux interventions and the use of postoperative steroids in significantly decreasing the incidence of postoperative cholangitis (14-20). Prophylactic administration of oral antibiotics is essential in managing postoperative cholangitis (21-23). Nevertheless, prolonged administration of antibiotics has the potential to disturb the microbiota within the body, resulting in various complications. Should it be feasible to anticipate the onset of cholangitis following Kasai surgery proactively, administering prophylactic antibiotics to children identified as being at elevated risk for developing cholangitis could prove beneficial. Consequently, the development of a predictive model for cholangitis post-Kasai surgery is of paramount importance.

In this retrospective investigation, we gathered data from 56 pediatric patients who underwent Kasai surgery at Tianjin Children's Hospital. We compiled a total of 114 serological markers and derived indicators, all sourced from standard blood tests and biochemical analyses routinely conducted during hospitalization. These indicators can be acquired in a cost-effective, efficient, rapid, and non-invasive manner in most healthcare facilities, thereby significantly reducing the barriers for general practitioners in utilizing our model. The comparison of preoperative and postoperative indicators provides insights into the patient's prognosis following surgery and may serve as a predictive tool for the initial occurrence of postoperative cholangitis. Additionally, we employed an independent external dataset as a validation cohort, which reinforces the reliability of our validation process.

In this research, we have effectively established the inaugural clinical prediction model specifically designed for primary cholangitis in pediatric patients with BA who have received Kasai surgery. Importantly, this model has been crafted for ease of use and uncomplicated implementation, thereby promoting its applicability in clinical environments. The independent predictors identified within this model include NEU% PPR and ALP PPR. NEU%, recognized as one of the most frequently utilized serological markers in clinical practice, is extensively employed in evaluating prognostic outcomes across a range of diseases (24-28). The

NEU% PPR assesses the degree of variation in neutrophil percentage following surgery compared to baseline pre-surgery levels, offering valuable insights into the fluctuations of granulocytes throughout the perioperative phase. This measure could potentially act as a predictor for the risk of postoperative inflammation to some extent.

The NEU% is recognized as one of the most prevalent biomarkers associated with inflammation (29). During bacterial infections, the NEU% exhibits a considerable rise, and it is recognized as the most sensitive and earliest indicator of inflammation. This parameter can be utilized to assess the effectiveness of treatment interventions (30). Yamaguchi has proposed that the earliest biomarker indicative of cholangitis is the NEU%, which demonstrates a certain predictive capability regarding the prognosis of this condition (31). The alteration in NEU% before and after surgical intervention serves as an indicator of its predictive capacity regarding prognosis, suggesting that NEU% may act as a viable prognostic marker for cholangitis following Kasai surgery.

ALP is an important variable assessed during liver function evaluations in clinical settings. The hepatic form of ALP is predominantly localized within the hepatic canaliculi (32). Increased levels of ALP are a typical indication of cholestasis, primarily resulting from dysfunctional bile secretion in the canaliculi (33). The research indicates that ALP levels are markedly elevated in pediatric patients diagnosed with BA (34), demonstrating its strong predictive capacity for the diagnosis of BA. Furthermore, when utilized in conjunction with serological markers like gamma-glutamyl transpeptidase (GGT), ALP considerably improves the diagnostic accuracy for the early detection of BA (35-37). Recent studies indicate that preoperative ALP levels may serve as a predictive marker for postoperative outcomes in pediatric patients undergoing Kasai surgery (38).

In the present investigation, we identified, for the first time, the prognostic significance of the ALP PPR in relation to cholangitis. Fluctuations in alkaline phosphatase concentrations serve as a proxy for the extent of biliary stasis, with a decline in these levels signifying mitigation in the severity of biliary stasis. Furthermore, the ALP PPR has been previously employed in clinical models to forecast outcomes in liver cancer, hepatic fibrosis, and liver failure (39-43). Current reports indicate that ALP serves as an important predictor in clinical models for the diagnosis of BA (36,37). To a certain degree, the ALP PPR functions as a proxy indicator for the modifications in bile duct patency that occur from the preoperative to postoperative phase. This suggests alterations in the flow dynamics within smaller bile ducts, which may allow for the prediction of postoperative cholangitis risk. Furthermore, it is identified as a significant independent risk factor not only during the construction of predictive models but also in the subsequent KM analysis. In this analysis, the incidence of cholangitis is notably lower in patients within the low ALP PPR cohort when compared to those in the high ALP PPR cohort. Over time, the disparity in cholangitis occurrence between these two cohorts becomes increasingly pronounced. Consequently, the ALP PPR may represent a clinically significant determinant related to the development of cholangitis following Kasai surgery.

Although our investigation offers valuable insights into the diagnostic implications of nomograms in BA, several recognized limitations warrant consideration. To begin with, the model was developed retrospectively, which may inadvertently lead to selection bias. Furthermore, the relatively small sample size of our study underscores the need for additional research encompassing a larger cohort. Notwithstanding these constraints, we are pioneers in examining the relationship between the occurrence of cholangitis following Kasai surgery and NEU% PPR along with ALP PPR. Furthermore, this research represents the inaugural effort to create a nomogram aimed at predicting cholangitis post-Kasai surgery, exhibiting commendable predictive efficacy. In the realm of precision medicine, this model has the potential to enhance clinical decision-making and optimize the management of patients diagnosed with BA.

Conclusions

Our nomogram model integrates two distinct variables: NEU% PPR and ALP PPR, which serve as reliable predictors for the initial onset of cholangitis following Kasai surgery. This could significantly enhance clinical decision-making processes.

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None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee of Tianjin Children's Hospital (No. 2022-SYYJCYJ-008) and informed consent was obtained from each participant's guardians. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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