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ORIGINAL RESEARCH

The Predictive Value of the Combination of Serum RBP4, ALP, IL-1β for Postoperative Recurrence of Intrahepatic Bile Duct Stones

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Objective: To investigate the predictive value of serum retinol-binding protein (RBP4), alkaline phosphatase (ALP), and interleukin (IL)-1β for postoperative recurrence of intrahepatic bile duct stones (IBDS).

Methods: This retrospective study included 320 patients with intrahepatic bile duct stones (IBDS) admitted to our hospital from May 2020 to May 2022, all of whom underwent laparoscopic choledocholithotomy combined with choledochoscopy. Patients were divided into a recurrence group and a non-recurrence group based on their postoperative status. Serum levels of RBP4 and IL-1β were measured by ELISA; liver function indicators including ALP were analyzed using a biochemical analyzer; levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were also detected by ELISA; toll-like receptor 4 (TLR4) and thyroid-stimulating hormone (TSH) were measured by radioimmunoassay.Pearson correlation analysis was performed to assess the relationships between serum RBP4, ALP, IL-1β and laboratory indicators. Multivariate logistic regression analysis was used to identify factors influencing postoperative recurrence of IBDS. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of serum RBP4, ALP, and IL-1β for IBDS recurrence after surgery.

Results: The levels of serum RBP4, ALP, IL-1β, TNF-α, TLR4, and TSH in the recurrence group were significantly higher than those in the non-recurrence group ($P < 0.05$). Pearson correlation analysis showed that serum RBP4, ALP, and IL-1β were all positively correlated with TNF-α, TLR4, and TSH ($P < 0.05$). Multivariate logistic regression analysis identified RBP4, ALP, IL-1β, TNF-α, TLR4, and TSH as independent risk factors for postoperative recurrence of IBDS ($P < 0.05$).According to ROC curve analysis showed that the area under the curve (AUC) for serum RBP4 in predicting postoperative recurrence of IBDS was 0.844, for serum ALP was 0.822, and for serum IL-1β was 0.732. The combined detection of RBP4, ALP, and IL-1β yielded an AUC of 0.892, which was superior to the predictive performance of each marker alone ($Z = 2.654$, $Z = 2.668$, $Z = 2.650$; all $P < 0.05$).

Conclusion: Serum levels of RBP4, ALP, and IL-1β are significantly elevated in patients with IBDS, and their combined detection can enhance the predictive value for postoperative recurrence of IBDS.

Keywords: retinol binding protein, alkaline phosphatase, Interleukin-1β, intrahepatic bile duct stones, recurrence, predictive value

Intrahepatic bile duct stones(IBDS) are primarily caused by biliary tract infections and bile stasis. Clinically, manifestations include abdominal pain and high fever. In severe cases, the condition may lead to septicemia or even septic shock, often accompanied by bile duct obstruction, presenting symptoms such as fatigue, nausea, and vomiting. If timely treatment is not provided, the disease may progress rapidly, leading to chronic and recurring episodes, seriously threaten the patient's life.[1,2] As a chronic disease and complex disease, IBDS can be challenging to manage, Most clinical treatments currently involve surgical methods, which have a high stone removal efficacy.[3] However, the risk of postoperative recurrence is also high, with most patients even requiring repeat surgeries, which affects their quality of life.[4] Therefore, it is particularly important to find indicators related to IBDS in clinical practice that can effectively predict postoperative recurrence in a timely manner. Retinol-binding protein (RBP4), as an adipokine, can transport vitamin A or retinol in the blood, and is mainly secreted by hepatocytes

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and adipocytes. It can promote the transport of retinol through circulation to peripheral tissues, and studies have found that serum RBP4 is significantly elevated in the serum of patients with metabolic dysfunction-associated fatty liver disease.[5] Alkaline phosphatase (ALP) is a liver function indicator that can reflect bile stasis and can determine whether there is biliary obstruction in the body.[6] Interleukin (IL)-1β, as an inflammatory cytokine, is produced in large quantities when the body is infected by viruses, causing an inflammatory response in the liver tissue, thereby damaging the liver tissue.[7] The pathogenesis of IBDS has not yet been fully elucidated. Studies have shown that bile stasis and inflammatory exudates may contribute to its progression. Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), Toll-like receptor 4 (TLR4), and thyroid-stimulating hormone (TSH) are all associated with inflammatory exudates and bile stasis.[8,9] Based on this, there are currently few reports on the combination of serum RBP4, ALP, and IL-1β in predicting postoperative recurrence of IBDS. Therefore, this study aims to explore the predictive value of the combination of serum RBP4, ALP, and IL-1β for postoperative recurrence of IBDS.

Materials and Methods

General Information

This retrospective study included 320 patients with Intrahepatic Bile Duct Stones (IBDS) who were admitted to The Central Hospital of Yongzhou between May 2020 and May 2022. All patients underwent laparoscopic choledocholithotomy combined with choledochoscopy. The cohort consisted of 202 male and 118 female patients, with an age range of 40 to 65 years and a mean age of 52.78±5.36 years. The mean Body Mass Index (BMI) was 22.40±3.09 kg/m². Patients were divided into a recurrence group and a non-recurrence group based on postoperative outcomes. The patient selection process is illustrated in Figure 1. Inclusion criteria: (1) Met the diagnostic criteria for IBDS as previously described;[10]

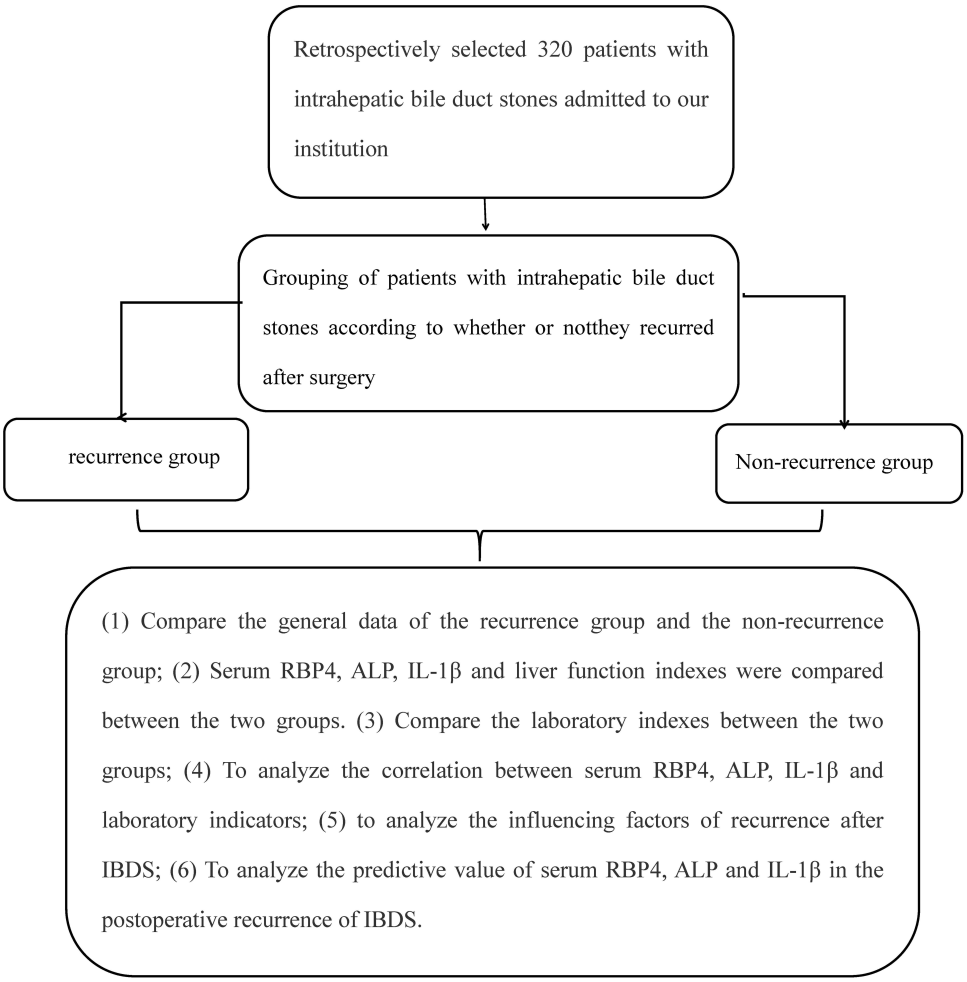

Figure 1 Flow chart of case collection.

(2) Diagnosis was confirmed by imaging and other examinations, with at least one test showing the presence of stones within the intrahepatic bile ducts, with or without proximal bile duct dilation; (3) All met the surgical indications; (4) Achieved complete stone clearance during surgery. Exclusion criteria: (1) Patients with severe active infectious diseases; (2) Patients with dysfunction of important organs; (3) Pregnant or breastfeeding women; (4) Patients with malignant tumors; (5) Patients with mental illness; (6) Patients with metabolic dysfunction-associated fatty liver disease. This study was approved by the hospital's ethics committee.

Methods

Detection of Serum RBP4 and IL-1β

On the morning following admission, 5 mL of fasting venous blood was collected from each patient. The samples were allowed to stand for 20 minutes at room temperature and then centrifuged at 3500 rpm for 10 minutes (centrifuge radius: 10 cm). After centrifugation, the serum was separated. Serum levels of RBP4 and IL-1β were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Shanghai Jianglai Biotech Co., Ltd., Shanghai, China). All samples and standards were run in duplicate. The absorbance was measured at 450 nm using a Multiskan FC microplate reader (Thermo Fisher Scientific, Waltham, MA, USA). A standard curve was generated to calculate the serum concentrations. All procedures were performed according to the manufacturer's instructions.

Detection of Liver Function Indicators

Serum from the separated samples was analyzed using a biochemical analyzer model 7600 (Nihon Denka Kogyo Co., Ltd., Japan) to detect alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin (ALB), and indirect bilirubin (IBIL).

Detection of Laboratory Indicators

Serum levels of Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured using ELISA. Toll-like receptor 4 (TLR4) and thyroid-stimulating hormone (TSH) levels were measured by radioimmunoassay.

Recurrence

Patients were followed for 24 months postoperatively through outpatient visits. Follow-up examinations were conducted every 6 months to monitor and record postoperative recurrence. Recurrence was defined as the new formation of stones within the intrahepatic bile ducts confirmed by imaging.

Data Collection

The following clinical and demographic data were collected for each patient: age, gender, BMI, smoking history, drinking history, history of diabetes, history of hypertension, history of hepatitis, duodenal periampullary diverticulum, stone location, common hepatic duct diameter, size of IBDS, number of stones, number of stone removal procedures, white blood cell count (WBC), and neutrophil count (NEU).

Observation Indicators

The analysis included the following comparisons and evaluations: (1) A comparison of general information and clinical characteristics between the recurrence and non-recurrence groups; (2) A comparison of serum levels of RBP4, ALP, IL-1β, and other liver function indicators between the two groups; (3) A comparison of other laboratory indicators (IL-6, TNF-α, TLR4, TSH) between the groups; (4) A correlation analysis between serum RBP4, ALP, IL-1β, and other laboratory indicators; (5) A multivariate analysis to identify independent risk factors for the postoperative recurrence of IBDS; and (6) An evaluation of the predictive value of serum RBP4, ALP, and IL-1β, both individually and in combination, for postoperative recurrence.

Statistical Analysis

Data were processed using SPSS 25.0 software. Normally distributed measurement data were expressed as ($\bar{x} \pm s$), and the *t*-test was used for comparison. Categorical data were analyzed using the χ^2-test and expressed as n. Pearson's method

was used to analyze the correlation between serum RBP4, ALP, IL-1β, and laboratory indicators. Multivariate logistic regression analysis was used to analyze the influencing factors of postoperative recurrence of IBDS. The ROC curve was drawn to analyze the predictive value of serum RBP4, ALP, and IL-1β for postoperative recurrence of IBDS, and P<0.05 was considered statistically significant.

Results

Comparison of General Information Between the Two Groups

There were no significant differences in baseline demographic and clinical characteristics, such as age, gender, and BMI, between the recurrence and non-recurrence groups (all P > 0.05), as shown in Table 1.

Comparison of Serum RBP4, ALP, IL-1β, and Liver Function Indicators Between the Two Groups

The serum levels of RBP4, ALP, and IL-1β in the recurrence group were significantly higher than those in the non-recurrence group, with statistically significant differences (P < 0.05). There were no significant differences in other liver function indicators between the two groups (P > 0.05), as shown in Table 2.

Comparison of Laboratory Indicators Between the Two Groups

The levels of TNF-α, TLR4, and TSH in the recurrence group were significantly higher than those in the non-recurrence group, with statistically significant differences (P < 0.05). However, there was no significant difference in IL-6 levels between the two groups (P > 0.05), as shown in Table 3.

Table 1 Comparison of General Information Between the Two Groups

Item	Recurrence Group (n=48)	Non-Recurrence Group (n=272)	χ^2/t	*P*
Age (years)	53.26±5.32	52.69±5.37	0.679	0.498
Male/female	30/18	172/100	0.009	0.922
BMI (kg/m^2)	22.35±3.02	22.41±3.10	0.124	0.901
Drinking history	21 (43.75)	110 (40.44)	0.185	0.667
Smoking history	18 (37.50)	98 (36.03)	0.038	0.845
History of diabetes	15 (31.25)	67 (24.63)	0.938	0.333
History of hypertension	33 (68.75)	172 (63.24)	0.539	0.463
History of hepatitis	8 (16.67)	36 (13.24)	0.405	0.524
Periduodenal Diverticulum			0.003	0.954
Yes	4 (8.33)	22 (8.09)		
No	44 (91.67)	250 (91.91)		
Stone site			0.177	0.674
Left liver	36 (75.00)	196 (72.06)		
Right liver	12 (25.00)	76 (27.94)		
Diameter of common Hepatic duct (cm)	1.33±0.21	1.32±0.22	0.877	0.381
Size of intrahepatic bile Duct stones (mm)	9.50±2.05	9.34±1.89	0.534	0.594
Number of stones (pieces)	2.45±0.52	2.41±0.48	0.526	0.600
Number of stone Removals (times)	1.24±0.31	1.20±0.28	0.898	0.370
WBC ($\times 10^9/L$)	8.53±1.62	8.48±1.58	0.201	0.841
NEU ($\times 10^9/L$)	196.46±18.96	197.63±19.62	0.383	0.702

Abbreviations: BMI, Body Mass Index; WBC, White Blood Cell Count; NEU, Neutrophil Count; RBP4, Retinol-Binding Protein 4; ALP, Alkaline Phosphatase; IL-1β, Interleukin-1β; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TBIL, Total Bilirubin; ALB, Albumin; IBIL, Indirect Bilirubin.

Table 2 Comparison of Serum RBP4, ALP, IL-1β and Liver Function Indexes Between the Two Groups

Norm	Recurrence Group (n=48)	Non-Recurrence Group (n=272)	t	P
RBP4 (mg/L)	9.98±1.35	7.25±1.28	13.512	<0.001
ALP (U/L)	176.25±32.25	137.65±30.26	8.067	<0.001
IL-1β (pg/mL)	19.68±2.35	13.26±2.03	19.711	<0.001
ALT (U/L)	21.32±3.54	20.96±3.62	0.637	0.524
AST (U/L)	19.65±5.34	19.53±5.30	0.144	0.885
TBIL (μmol/L)	23.58±3.65	22.96±3.26	1.193	0.234
ALB (g/L)	32.68±6.20	33.16±6.42	0.480	0.632
IBIL (μmol/L)	10.68±2.52	9.96±2.41	1.895	0.059

Abbreviations: RBP4, Retinol-binding protein 4; ALP, Alkaline phosphatase; IL-1β, Interleukin-1 beta; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; ALB, Albumin; IBIL:Indirect bilirubin.

Table 3 Comparison of Laboratory Indicators Between the Two Groups

Groups	Number of Examples	IL-6 (μg/L)	TNF-α (μg/L)	TLR4 (ng/mL)	TSH (mU/L)
Recurrence group	48	20.68±4.26	36.29±7.32	17.62±3.25	19.68±4.26
Non-recurrence group	272	19.69±3.89	29.65±6.59	12.86±2.38	13.42±3.52
t	–	1.602	11.880	12.029	10.989
P	–	0.110	<0.001	<0.001	<0.001

Abbreviations: IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-α; TLR4, Toll-like receptor 4; TSH, Thyroid-stimulating hormone.

Correlation Between Serum RBP4, ALP, IL-1β, and Laboratory Indicators

Pearson correlation analysis revealed that serum RBP4, ALP, and IL-1β were positively correlated with TNF-α, TLR4, and TSH (P<0.05), as shown in Table 4.

Analysis of Factors Influencing Postoperative Recurrence of IBDS

To identify independent risk factors for postoperative recurrence, a multivariate logistic regression analysis was performed. Postoperative recurrence of IBDS was set as the dependent variable (recurrence=1, no recurrence=0), while the serum levels of RBP4, ALP, IL-1β, TNF-α, TLR4, and TSH were included as independent variables. The analysis, using a forward stepwise selection method, showed that elevated levels of RBP4, ALP, IL-1β, TNF-α, TLR4, and TSH were independent risk factors for postoperative recurrence of IBDS (all P < 0.05), as shown in Table 5.

Table 4 Correlation of Serum RBP4, ALP, and IL-1β with Laboratory Indices

Norm	RBP4		ALP		IL-1β	
	r	*P*	*r*	*P*	*r*	*P*
TNF-α	0.486	<0.001	0.501	<0.001	0.510	<0.001
TLR4	0.479	<0.001	0.497	<0.001	0.532	<0.001
TSH	0.473	<0.001	0.513	<0.001	0.524	<0.001

Abbreviations: RBP4, Retinol-binding protein 4, ALP:Alkaline phosphatase; IL-1β, Interleukin-1 beta; TNF-α, Tumor necrosis factor-α; TLR4, Toll-like receptor 4; TSH, Thyroid-stimulating hormone.

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Table 5 Analysis of Factors Influencing Postoperative Recurrence of Intrahepatic Bile Duct Stones

Norm	β	SE	Wald χ^2	*P*	OR	95% CI
RBP4	0.701	0.252	7.730	0.005	2.015	1.230~3.302
ALP	0.719	0.341	4.449	0.035	2.053	1.052~4.005
IL-1β	0.453	0.209	4.698	0.030	1.573	1.044~2.369
TNF-α	1.240	0.369	11.299	<0.001	3.457	1.677~7.125
TLR4	1.134	0.342	10.994	<0.001	3.108	1.590~6.076
TSH	1.588	0.486	10.682	0.001	4.898	1.889~12.692

Abbreviations: RBP4, Retinol-binding protein 4; ALP, Alkaline phosphatase; IL-1β, Interleukin-1 beta; TNF-α, Tumor necrosis factor-α; TLR4, Toll-like receptor 4; TSH, Thyroid-stimulating hormone.

Predictive Value of Serum RBP4, ALP, and IL-1β for Postoperative Recurrence of IBDS

Using the recurrence group as the positive control and the non-recurrence group as the negative control.Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of serum RBP4, ALP, and IL-1β for postoperative recurrence. The results showed that the area under the curve (AUC) for serum RBP4 in predicting postoperative recurrence of IBDS was 0.844, for serum ALP it was 0.822, and for serum IL-1β it was 0.732. A model combining all three markers yielded a significantly higher AUC of 0.892, which was superior to their individual predictive values (Z=2.654, Z=2.668, Z=2.650, respectively; all P < 0.05), as shown in Figure 2 and Table 6.

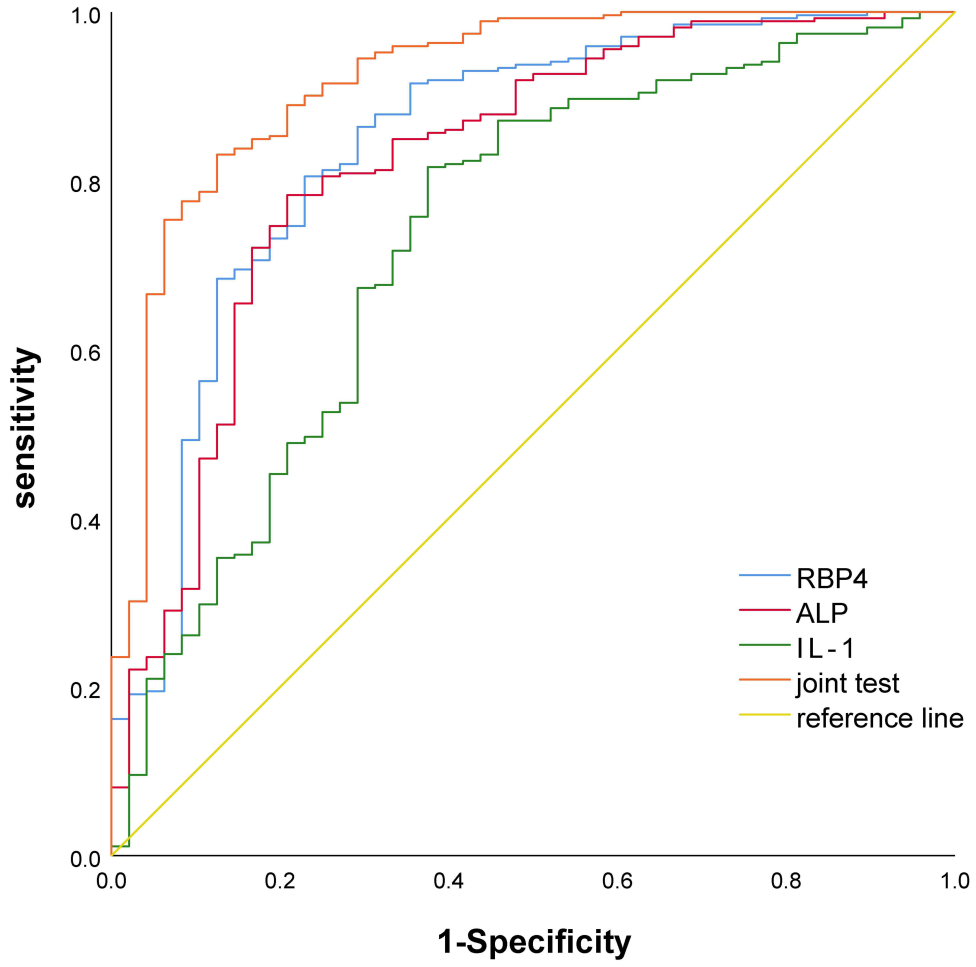

Figure 2 Predictive value of serum RBP4, ALP, and IL-1β for postoperative recurrence of intrahepatic bile duct stones.

Table 6 Value of Serum RBP4, ALP, and IL-1β in Predicting Recurrence of Intrahepatic Bile Duct Stones After Surgery

Items	AUC	95% CI	Sensitivity (%)	Specificity (%)	Truncation Value
RBP4	0.844	0.776~0.911	74.53	82.53	8.627 mg/L
ALP	0.822	0.752~0.893	77.69	80.32	160.358 U/L
IL-1β	0.732	0.649~0.815	78.63	78.35	17.124 pg/mL
Joint test	0.920	0.874~0.967	93.65	78.06	–

Abbreviations: RBP4, Retinol-binding protein 4; ALP, Alkaline phosphatase; IL-1β, Interleukin-1 beta.

Discussion

The pathogenesis of Intrahepatic Bile Duct Stones (IBDS) is complex, characterized by a long disease course and challenges in achieving a complete cure. Residual stones and high recurrence rates are common. Stone formation is primarily related to bile stasis and local infection within the biliary system. Other contributing factors may include inflammatory exudates, immune dysfunction, and bacterial colonization.[11] Furthermore, IBDS are complex and often accompanied by bile duct stricture and biliary cirrhosis. Clinical treatment primarily focuses on removing stones and controlling ongoing infections to reduce the recurrence of stones and prevent malignant transformation. However, even after surgery, some patients still have residual stones or recurrence of stones.[12,13] Therefore, predicting indicators for postoperative recurrence of IBDS and early intervention can effectively improve patient prognosis.

Lipid transport proteins are a family that can bind and transport small lipophilic proteins, and RBP4 is an important member of this family. RBP4 is a protein secreted by hepatocytes and adipocytes, capable of binding and transporting vitamin A. Vitamin A, in turn, participates in the body's inflammatory response and oxidative damage.[14] RBP4 is most highly expressed in the liver, where the majority of vitamin A is stored in the form of retinyl esters. To mobilize vitamin A, retinyl esters are hydrolyzed into retinol, which then binds to RBP4 in hepatocytes and is transported to tissues through binding with specific membrane receptors.[14] RBP4 can induce insulin resistance, upregulate the inflammatory cytokine TNF-α, and stimulate lipolysis in adipocytes, leading to fatty liver degeneration.[15] Animal experiments have shown that intravenous injection of RBP4 in mice can activate NADPH oxidase 2 and nuclear factor-kappa B (NF-κB), promoting reactive oxygen species accumulation and significantly enhancing M1 polarization of Kupffer cells, which exacerbates lipid accumulation in the liver tissues of mice, while the levels of pro-inflammatory cytokines in the serum also significantly increase.[16] Our study found that serum RBP4 levels were significantly higher in the recurrence group, indicating that RBP4 may play a role in the recurrence of IBDS. It is hypothesized that elevated RBP4 levels may activate the NF-κB signaling pathway,further stimulating the expression of pro-inflammatory cytokine such as TNF-α, thereby promoting the recurrence of IBDS.

ALP (Alkaline Phosphatase) is a phosphomonoesterase enzyme widely distributed in the liver and bones of the human body. It is excreted from the liver into the bile ducts. When liver lesions occur, they stimulate hepatocytes to excessively synthesize ALP, which then refluxes into the bloodstream, causing elevated ALP levels.[17] ALP is primarily excreted through the bile ducts and liver, but obstructive jaundice can reduce the efficiency of its excretion, leading to elevated levels when common bile duct stones form, causing ALP to reflux into the bloodstream.[18] While some studies suggest ALP may have anti-inflammatory roles in specific contexts, such as upregulating miR-146a to reduce TNF-α expression in LPS-induced liver injury,[19] its elevation in clinical practice is a well-established marker of cholestasis and biliary damage. Indeed, previous studies have shown that serum ALP is significantly elevated in patients with common bile duct stones, and it can serve as a predictive indicator.[20] The results of this study showed that serum ALP levels were significantly higher in the recurrence group compared to the non-recurrence group, suggesting that ALP may be involved in the recurrence of IBDS. This may be because elevated ALP levels reflect ongoing or recurrent subclinical biliary obstruction and associated mucosal injury. Sustained elevation can impair the restoration of mucosal integrity, making postoperative recurrence more likely.

IL-1β, as a pro-inflammatory cytokine, is mainly secreted by activated macrophages and released by fibroblasts and endothelial cells. It is a member of the interleukin family and exacerbates the inflammatory response in the body, increasing the degree of tissue and cellular damage.[21] While some experimental models have explored complex signaling pathways, such as using IL-1β pre-treatment to modulate the COX-2/PGE2 pathway and alleviate cholestatic liver damage,[22], its predominant role in clinical pathology is pro-inflammatory. Studies have shown that serum IL-1β is significantly elevated in patients with

gallstones, and its high expression promotes the accumulation of lipids in macrophages and the expression of inflammatory mediators, which is suppressed when IL-1β levels decrease.[23] The results of this study showed that serum IL-1β levels were significantly higher in the recurrence group than in the non-recurrence group, consistent with previous studies. This suggests that IL-1β may be involved in postoperative recurrence of IBDS. The possible mechanism is that elevated IL-1β levels can induce various inflammatory responses, promote infiltration of inflammatory cells, release reactive oxygen species, exacerbate mucosal injury, and cause biliary mucosal ulcers, thereby leading to postoperative recurrence in patients.

TNF-α is another key pro-inflammatory cytokine mainly secreted by mononuclear macrophages. It acts synergistically with cytokines like IL-1β to amplify the local inflammatory response in the body.[24] As a member of the innate immune receptor family, TLR4 recognizes pathogenic and damage-associated molecular patterns, mediating inflammatory responses to tissue damage. The role of TSH (thyroid-stimulating hormone) is less clear, but some evidence suggests that thyroid dysfunction can affect the sphincter of Oddi, potentially influencing bile flow and contributing to stone formation.[25] Our study found that serum TNF-α, TLR4, and TSH levels were significantly higher in the recurrence group than in the non-recurrence group, indicating that postoperative recurrence was associated with a persistent inflammatory and metabolic dysregulation. Pearson correlation analysis revealed that serum RBP4, ALP, and IL-1β were positively correlated with TNF-α, TLR4, and TSH, suggesting that these factors are interconnected and may contribute synergistically to the recurrence of IBDS. Confirming this, multivariate logistic regression analysis showed that RBP4, ALP, IL-1β, TNF-α, TLR4, and TSH were independent risk factors for the postoperative recurrence of IBDS, indicating that monitoring the levels of these indicators could effectively assess the patient's risk. The ROC curve analysis showed that the AUC for serum RBP4, ALP, and IL-1β in predicting the postoperative recurrence of IBDS were 0.844, 0.822, and 0.732, respectively. The combined AUC for predicting postoperative recurrence was 0.892, which was better than using the three indicators individually. This suggests that combined detection can effectively improve the predictive value for postoperative recurrence of IBDS, providing a reference for clinicians in formulating treatment strategies.

In conclusion, the serum levels of RBP4, ALP, and IL-1β in patients with IBDS were significantly elevated, and the combined detection of these three factors can improve the predictive value for postoperative recurrence of IBDS. This study has some limitations. First, as a retrospective study, there may be inherent selection and information biases. Second, this was a single-center study with a relatively small sample size. Therefore, larger, multi-center prospective studies are needed to further validate these findings.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

This study involving human participants was conducted in accordance with the ethical standards of the Medical Ethics Committee of The Central Hospital of Yongzhou and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients (or their legal guardians), who all signed the informed consent form prior to their inclusion in the study.

Consent for Publication

All authors give consent for publication.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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