

A novel prognostic model for diagnosing atypical bile duct hyperplasia in patients with intrahepatic lithiasis

Hongcheng Lu, MD^a, Hao Yang, MD^a, Linquan Wu, MD^{a,*}, Wenjun Liao, PhD^{a,*}, Xianping He, MD^a, Enliang Li, MD^a, Rongshou Wu, MD^b, Shidai Shi, MD^c, Zhilong Yang, MD^d

Abstract

There is no specific method for the preoperative diagnosis of atypical bile duct hyperplasia, which is a precursor of cholangiocarcinoma. This study aimed to create a new model for diagnosing atypical bile duct hyperplasia based on routine laboratory tests in patients with intrahepatic lithiasis.

The new diagnostic model was developed with a derivation cohort that included 375 patients with intrahepatic lithiasis. Clinical and pathological data were retrospectively collected. Prognostic factors were evaluated with univariate and logistic regression analyses. The validation cohort included 136 patients who were retrospectively screened to quantify the model's predictive value.

Age and Carbohydrate Antigen 19-9 (CA-199) were revealed to be diagnostic indicators of atypical bile duct hyperplasia in patients with intrahepatic lithiasis. The new diagnostic model was created with the formula: $-6.612 + (0.002 \times \text{CA-199}) + (0.072 \times \text{Age})$. The area under the receiver operating curve of the model was 0.721. With 0.25 as the cutoff point, the sensitivity and specificity of this model in the derivation cohort were 13.9% and 95.9%, respectively. In the validation cohort, these values were 28.5% and 88.7%, respectively. The novel model has an acceptable and stable ability to predict atypical hyperplasia in the intrahepatic bile duct.

This novel model provides a simple system for diagnosing atypical bile duct hyperplasia before surgery in patients with intrahepatic lithiasis.

Abbreviations: ABDH = Atypical bile duct hyperplasia, AFP = Alpha fetoprotein, ALB/TP = albumin/total protein., auROC = The area under the receiver operating curve, BillIN = Biliary intraepithelial neoplasia, CA-199 = Carbohydrate Antigen 19-9, CEA = Carcinoembryonic antigen, CTC = Circulating tumor cells, ctDNA = Circulating tumor DNA, DBIL/IBIL = direct bilirubin/indirect bilirubin, ICC = Intrahepatic cholangiocarcinoma, INR = International normalized ratio, IPN-B = Intraductal papillary neoplasm of the bile duct, RBC = Red blood cell counts, WBC = White blood cell counts.

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^a Second Affiliated Hospital of Nanchang University, Research Center of Hepatobiliary Disease, Nanchang, ^b The First Affiliated Hospital of Gannan Medical College, General Surgery, Ganzhou, ^c Ji'an People's Hospital, Hepatobiliary Surgery, Jian, ^d Jingdezhen People's Hospital, General Surgery, Jingdezhen, Jiangxi, China.

* Correspondence: Linquan Wu, Wenjun Liao, Second Affiliated Hospital of Nanchang University, Research Center of Hepatobiliary Disease. No. 1 Minde Road, Nanchang, Jiangxi, China (e-mail: wulqnc@163.com, liaowenjun120@163.com).

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1. Introduction

Intrahepatic cholangiocarcinoma (ICC), the second most common primary liver cancer in humans after hepatocellular carcinoma, is highly malignant and has an extremely poor prognosis.^[1–3] From 1973 to 2012, the reported incidence of ICC in the United States increased from 0.44 to 1.18 cases per 100,000 people, for an annual percentage change of 2.30%. Over the past decade, this trend has accelerated to an annual percentage change of 4.36%.^[4] Median overall survival is 4 months in patients with ICC.^[5] Early detection and timely intervention are of great importance in the clinical treatment of this disease. However, it remains difficult to detect ICC through preoperative evaluation. The incidence of unrecognized cholangiocarcinoma in patients undergoing surgery for hepatolithiasis is reported to be as high as 11.7%, and this percentage may be underestimated.^[6] Surgical resection is currently the main treatment for ICC. Unfortunately, the treatment effect is extremely poor.

Research on ICC is attracting increasing attention. Current research confirms that the pathogenesis of ICC is complex and involves multiple steps, with chronic inflammation of the bile duct epithelium an important part of the process. Recent studies have proposed 2 types of precancerous lesions of invasive ICC: biliary intraepithelial neoplasia (BillIN) and intraductal papillary

neoplasm of the bile duct (IPN-B). BillN progresses to tubular adenocarcinoma and IPN-B progresses to tubular adenocarcinoma or colloid carcinoma. BillN and IPN-B are significantly associated with chronic inflammatory biliary diseases. Biliary epithelial dysplasia and atypical hyperplasia are the necessary intermediate conditions before both BillN and IPN-B.^[7,8]

One of the most common causes of chronic cholangitis is hepatolithiasis.^[9] Hepatolithiasis is a common intrahepatic bile duct disease, mainly occurring in the Asia-Pacific region, including China, Japan, and South Korea, with an incidence between 3.1% and 21.2%. The condition is relatively rare in Western countries, where the incidence is about 1%.^[10] However, the incidence of hepatolithiasis in Western countries has risen in recent years, a finding that may be related to increased immigration from endemic areas.^[11] Hepatolithiasis can induce cholangitis and abnormal bile metabolism.^[10,11] The correlation between hepatolithiasis and cholangiocarcinoma is generally accepted; the reported prevalence of cholangiocarcinoma among patients with hepatolithiasis is 2.4%.^[11] The reported total incidence of cholangiocarcinoma in association with hepatolithiasis is 4% to 12%.^[12] It is possible that effective intervention in hepatolithiasis could reduce the incidence of ICC.

Precancerous lesions are difficult to detect preoperatively in patients with hepatolithiasis. In patients with precancerous lesions, simple lithotomy may not be appropriate and could have serious consequences. Initially extended hepatectomy is particularly important for hepatolithiasis patients with a high risk of developing ICC, because most patients with subsequent cholangiocarcinoma are not eligible for repeat surgical intervention.^[13] For patients without precancerous lesions or ICC, stone removal alone can achieve a curative effect. Hepatectomy or extended hepatectomy may not be necessary, especially for patients in poor condition after multiple operations. Unfortunately, there is no clinical guideline or standard for surgical treatment of hepatolithiasis with BillN or IPN-B, and no preoperative imaging test can diagnose BillN or IPN-B. Imaging tests currently available are not sufficient to make a definitive diagnosis of biliary epithelial dysplasia.

If patients with hepatolithiasis could be diagnosed with BillN or IPN-B before surgery and thus received timely intervention, the incidence of ICC could be greatly reduced. Therefore, the purpose of our study was to evaluate correlations between preoperative tests and postoperative pathologic results to establish a model for predicting the presence of biliary epithelial dysplasia in hepatolithiasis patients. Having such a model would help determine the risk of conversion to ICC and could guide clinicians in developing appropriate treatment plans.

2. Methods

2.1. Study design and patients

2.1.1. Derivation cohort. We retrospectively screened the records of 696 patients treated at Jingdezhen People's Hospital, Ji'an People's Hospital, the First Affiliated Hospital of Gannan Medical College, and Second Affiliated Hospital of Nanchang University in JiangXi Province from January 2011 to December 2016. Intrahepatic lithiasis was diagnosed in all patients preoperatively with magnetic resonance imaging, computed tomography, magnetic resonance cholangiography, or endoscopic retrograde cholangiography. Patients who did not undergo partial hepatectomy, those with incomplete clinical data, and those with other tumors before intrahepatic lithiasis were

excluded. Patients were divided into 3 groups according to postoperative pathological diagnosis: atypical bile duct hyperplasia (ABDH; atypical hyperplasia group), intrahepatic lithiasis or cholangitis (non-atypical hyperplasia group), and patients with incidentally found primary liver cancer. The 375 patients in the atypical hyperplasia and non-atypical hyperplasia groups were included in the analysis (Fig. 1).

2.1.2. Validation cohort. The validation cohort included 136 patients treated from January 2017 to December 2017 at the Second Affiliated Hospital of Nanchang University. The retrospective review of these patients used the same screening criteria as for the derivation cohort to validate the performance of the diagnostic model.

This study had been proved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University.

2.2. Data collection

Six hundred ninety six patients were diagnosed with intrahepatic lithiasis and underwent surgical treatment. The following patients were excluded from analysis: those who had not undergone partial hepatectomy, those with incomplete clinical data, those with other tumors, and those diagnosed with malignant tumor after surgery. Finally, 375 patients who underwent partial hepatectomy were included in the analysis. Two reviewers (HC Lu and H Yang) independently collected presurgical clinical data from hospital records and integrated the final results with input from a third author (XP He). Clinical data included sex, age, white and red blood cell counts, neutrophil ratio, hemoglobin, total protein (TP), albumin (ALB), aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin (DBIL), indirect bilirubin (IBIL), alkaline phosphatase, γ glutamyl transferase, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA-199), international normalized ratio (INR), prothrombin time, DBIL/IBIL, and ALB/TP. The diagnosis of atypical bile duct hyperplasia was based on pathological examination; postoperative pathological data were retrospectively collected.

2.3. Statistical analysis

All routinely available demographic and biochemical variables, were regarded as potential predictors. In univariate statistical analyses, we used the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables. All results are presented as frequencies and percentages or means and standard deviations. Logistic regression models were fitted with a backward stepwise selection method (pe: .05 and pr: .06), using baseline factors (age, neutrophil ratio, ALB, CEA, CA-199, and DBIL/IBIL) that had been shown in univariate analyses to be risk factors associated with the diagnosis of ABDH. The goodness-of-fit of the diagnostic model was assessed with the Hosmer-Lemeshow test. A collinearity test was used to detect the collinearity of the variables in the regression model. The area under the receiver operating curve (auROC) of the diagnostic model was calculated to evaluate the model's performance. In addition, the discriminative power, which is the ability of the model to distinguish high-risk patients from low-risk patients, was used to evaluate the model's performance in the derivation cohort. In the validation cohort, an external population of patients was enrolled to validate the model's performance. The sensitivity and specificity of the diagnostic model for predicting abnormal hyperplasia in the

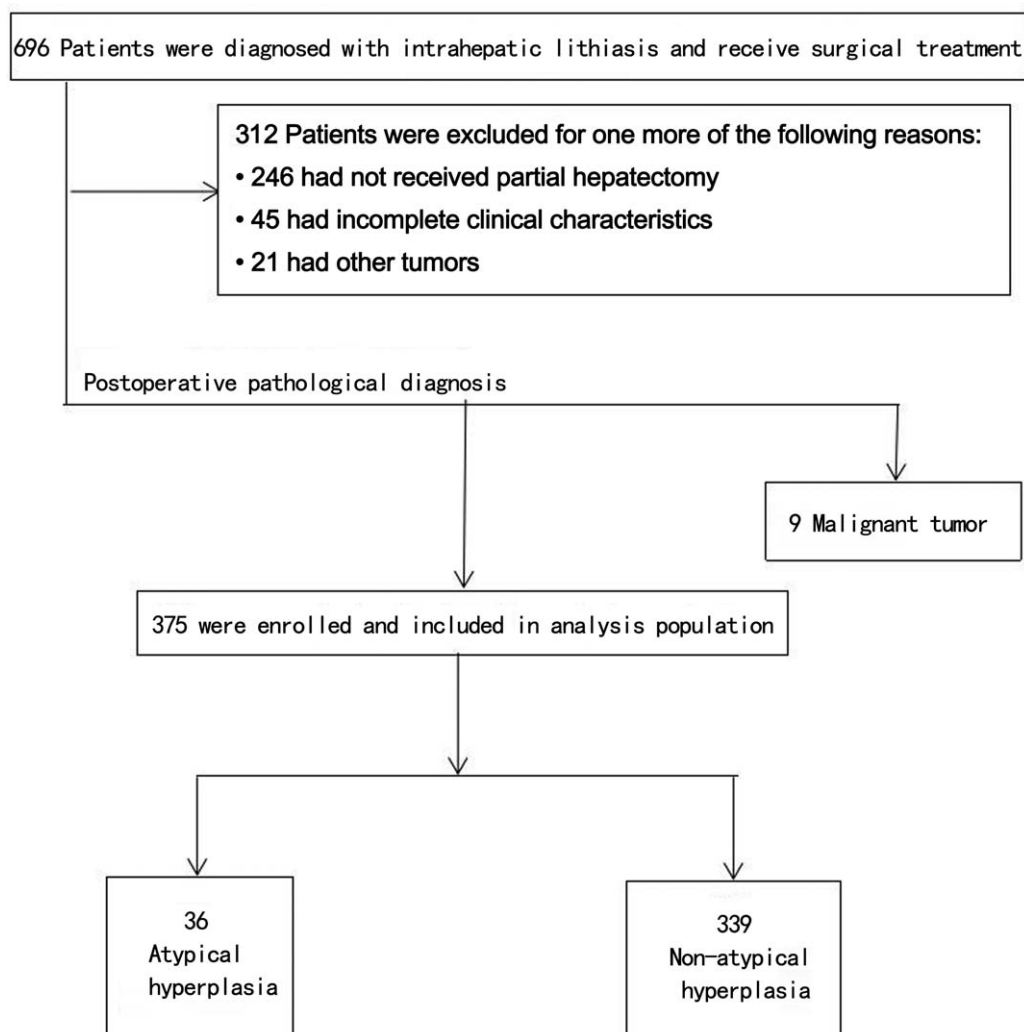


Figure 1. Screening, enrolment and classification of patients according to the postoperative pathological diagnosis.

intrahepatic bile duct were calculated with the formula that was created in the derivation phase.

Statistical analyses were performed with STATA software (version 12.0; Stata Corporation LP, College Station, TX). Differences were considered significant at $P < .05$.

3. Results

3.1. Patients characteristics

Demographic and laboratory characteristics of all enrolled patients are summarized in Table 1. The derivation cohort included 375 patients divided into 2 groups: the atypical hyperplasia group and the non-atypical hyperplasia group. The atypical hyperplasia group consisted of 36 patients, of whom 15 (41%) were male; the mean age in the atypical hyperplasia group was 59 years. The non-atypical hyperplasia group included 339 patients, of whom 93 (27%) were male; the mean age in the non-atypical hyperplasia group was 53 years. Patients in the atypical hyperplasia group were significantly older than those in the non-atypical hyperplasia group (59.28 vs 53.16 years, $P < .001$) and had higher neutrophil ratio (0.67 vs 0.61, $P = .02$),

lower albumin (37.35 vs 38.44, $P = .03$), higher CEA (2.12 vs 1.40, $P = .005$), higher CA-199 (205.96 vs 107.40, $P = .02$), and higher DBIL/IBIL (0.64 vs 0.61, $P = .03$). Parameters that showed significant differences between groups were used for model construction (see Table 1). In the validation cohort, the atypical hyperplasia group included 21 patients, of whom 10 (47%) were male. The mean age in the atypical hyperplasia group was 61 years. The non-atypical hyperplasia group included 115 patients, of whom 45 (39%) were male. The mean age in the non-atypical hyperplasia group was 56 years. Comparing the atypical hyperplasia group with non-atypical hyperplasia group in the validation cohort, only age (61.76 vs 56.55 years) was significantly different (see Table 2).

3.2. Model development for atypical hyperplasia in the intrahepatic bile duct

The multivariable analysis included a total of six variables that were significant in univariate analyses: age, neutrophil ratio, ALB, CEA, CA-199, and DBIL/IBIL. After a backward stepwise selection method ($pe: .05$ and $pr: .06$), 2 variables remained in the model: age and CA-199. Multivariable analysis indicated that age

Table 1**Characteristics of patients in the derivation.**

Characteristic	Atypical hyperplasia (n = 36)	Non-atypical hyperplasia (n = 339)	P value
Male (no.)	41.67% (15)	27.43% (93)	.073
Age (years)	59.28 ± 8.28	53.16 ± 10.22	.0004*
WBC (10 ⁹ /L)	6.87 ± 3.64	6.41 ± 3.45	.706
Neutrophil ratio	0.67 ± 0.16	0.61 ± 0.16	.019*
RBC (10 ¹² /L)	3.93 ± 0.40	3.95 ± 0.51	.894
Hemoglobin (g/L)	115.91 ± 14.93	116.09 ± 17.30	.847
Total protein (g/L)	64.79 ± 7.02	65.08 ± 6.39	.721
Albumin (g/L)	37.35 ± 3.08	38.44 ± 3.76	.027*
Aspartate aminotransferase (U/L)	65.89 ± 92.36	62.55 ± 100.19	.960
Alanine aminotransferase (U/L)	59.94 ± 71.25	66.22 ± 90.50	.855
Total bilirubin (umol/L)	33.56 ± 32.26	27.64 ± 31.99	.375
Direct bilirubin (umol/L)	24.14 ± 26.62	19.38 ± 26.88	.291
Indirect bilirubin (umol/L)	9.25 ± 6.28	8.25 ± 6.25	.363
alkaline phosphatase (U/L)	202.69 ± 163.76	213.28 ± 187.20	.765
γ-Glutamyl transferase (U/L)	273.01 ± 283.99	224.22 ± 238.70	.529
AFP (ng/ml)	2.83 ± 1.43	3.33 ± 3.22	.187
CEA (ng/ml)	2.12 ± 2.50	1.40 ± 1.02	.005*
CA-199 (U/ml)	205.96 ± 279.70	107.40 ± 206.06	.020*
INR	0.99 ± 0.18	0.98 ± 0.29	.934
Prothrombin time (sec)	11.14 ± 1.70	11.20 ± 4.80	.985
DBIL/IBIL	0.64 ± 0.14	0.61 ± 0.13	.027*
ALB/TP	0.58 ± 0.04	0.59 ± 0.04	.228

AFP = alpha fetoprotein, ALB/TP = albumin/total protein, CA-199 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, DBIL/IBIL = direct bilirubin/indirect bilirubin, INR = international normalized ratio, RBC = red blood cell counts, WBC = white blood cell counts.

and CA-199 were the most important factors for identifying patients with ABDH (95% CI: -9.021 to -4.203) (see online Supplementary Table 1, <http://links.lww.com/MD/C937>). The diagnostic model for identifying patients with atypical hyperplasia of the intrahepatic bile duct used the following formula:

$$Z = -6.612 + (0.002 \times \text{CA-199}) + (0.072 \times \text{Age})$$

3.3. Correlation between age and CA-199

Because only 2 variables remained in the model, we tested whether there was a correlation between age and CA-199 level by making age an independent variable and CA-199 a dependent variable in linear regression analysis. The resulting variance inflation factor was 1.00, indicating that age and CA-199 were not linearly dependent, but were 2 independent factors that

Table 2**Characteristics of patients in the validation.**

Characteristic	Atypical hyperplasia (n = 21)	Non-atypical hyperplasia (n = 115)	P value
Male (no.)	47.62% (10)	39.13% (45)	.466
Age (years)	61.76 ± 7.83	56.55 ± 10.89	.032*
WBC (10 ⁹ /L)	7.17 ± 4.43	7.43 ± 5.83	.726
Neutrophil ratio	0.67 ± 0.12	0.69 ± 0.13	.793
RBC (10 ¹² /L)	3.97 ± 0.43	4.12 ± 0.55	.214
Hemoglobin (g/L)	119.57 ± 12.83	120.01 ± 16.30	.638
Total protein (g/L)	68.19 ± 6.39	68.75 ± 7.61	.632
Albumin (g/L)	37.88 ± 3.81	39.20 ± 4.88	.226
Aspartate aminotransferase (U/L)	81.49 ± 122.17	66.12 ± 97.16	.959
Alanine aminotransferase (U/L)	86.75 ± 127.97	77.91 ± 108.36	.505
Total bilirubin (umol/L)	39.44 ± 44.70	44.51 ± 58.91	.849
Direct bilirubin (μmol/L)	18.42 ± 26.85	21.67 ± 35.90	.863
Indirect bilirubin (μmol/L)	21.02 ± 18.48	22.83 ± 23.89	.833
alkaline phosphatase (U/L)	259.37 ± 228.47	234.78 ± 196.45	.414
γ-Glutamyl transferase (U/L)	275.31 ± 241.37	243.98 ± 278.08	.256
AFP (ng/ml)	2.79 ± 1.70	2.81 ± 2.37	.958
CEA (ng/ml)	1.59 ± 0.79	1.67 ± 1.08	.814
CA-199 (U/ml)	230.03 ± 290.33	128.56 ± 208.58	.071
INR	1.02 ± 0.10	1.03 ± 0.14	.894
Prothrombin time (sec)	11.91 ± 1.16	11.90 ± 1.56	.783
DBIL/IBIL	0.34 ± 0.15	0.34 ± 0.16	.816
ALB/TP	0.56 ± 0.06	0.57 ± 0.05	.279

AFP = alpha fetoprotein, ALB/TP = albumin/total protein, CA-199 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, DBIL/IBIL = direct bilirubin/indirect bilirubin, INR = international normalized ratio, RBC = red blood cell counts, WBC = white blood cell counts.

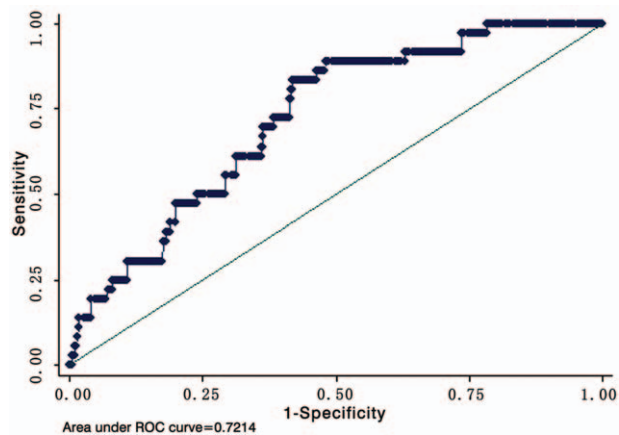


Figure 2. The receiver operating characteristic curve of the model for predicting the diagnosis of patients with abnormal hyperplasia in the intrahepatic bile duct.

together helped predict diagnosis. Therefore, it was reasonable to keep both factors in the model.

3.4. Goodness-of-fit test and the auROC

The goodness-of-fit of the diagnostic model was evaluated with the Hosmer–Lemeshow test with 10 observation groups. The Hosmer–Lemeshow test showed $P = .646$, indicating that there was no significant difference between the predicted diagnosis and actual diagnosis. The area under the receiver operating characteristic (auROC) of the model for predicting the diagnosis of patients with abnormal hyperplasia in the intrahepatic bile duct was .721 (see Fig. 2), indicating that the new model had a moderate discrimination ability.

3.5. Model performance

3.5.1. Derivation cohort. The derivation cohort included 375 patients, among whom 36 were diagnosed with atypical hyperplasia of the intrahepatic bile duct. The remaining 339 patients did not have atypical hyperplasia of the intrahepatic bile duct. We choose .25 as the cutoff in this model because it provided excellent diagnostic specificity with acceptable diagnostic sensitivity. The sensitivity and specificity of the diagnostic model were 13.9% (5/36) and 95.9% (325/339), respectively (see online Supplementary Table 2, <http://links.lww.com/MD/C937>).

3.5.2. Validation cohort. In the validation cohort, 136 patients were collected to assess the discriminating power of the diagnostic model using the above formula. P values were calculated for each individual patient. Patients were considered to have atypical hyperplasia of the intrahepatic bile duct when the p value was $> .25$ and were considered to have a normal intrahepatic bile duct when the p value was $< .25$. The p values of 19 patients were greater than .25; 115 patients had p values below .25. Among the 19 patients who were considered to have ABDH according to the diagnostic model, 6 actually had ABDH. Among the 115 patients who were considered not to have ABDH according to the diagnostic model, 102 actually had a normal intrahepatic bile duct. Therefore, the sensitivity and specificity of the model in the validation cohort were 28.5% and 88.7%, respectively (see Supplementary Table 3, <http://links.lww.com/MD/C937>).

4. Discussion

ICC is an aggressive malignancy and is the second most common primary hepatobiliary cancer, after hepatocellular cancer. Although advanced surgical techniques and radiation therapy have recently been proposed, the survival of patients with cholangiocarcinoma remains poor.^[14] The above clinical characteristics highlight the need for more efforts in the prevention and early detection of ICC.^[15] Tissue dysplasia plays an important role in tumor development. Esophageal dysplasia and gastric epithelial dysplasia have been confirmed to have important relationships with esophageal cancer^[16] and gastric carcinogenesis^[17], respectively. Intrahepatic bile duct hyperplasia, especially atypical hyperplasia, is also considered an important precursor of cholangiocarcinoma.^[18] However, there is currently no specific method of diagnosing ABDH before surgery. Our study provides a solution to this problem with a novel, simple, prognostic model to diagnose ABDH preoperatively in patients with intrahepatic stones, allowing early intervention in these high-risk patients to reduce the incidence of ICC.

Partial hepatectomy is a safe and effective procedure for hepatolithiasis, allowing definitive treatment of the disease and prevention of cancer.^[19,20] Studies have confirmed that aggressive hepatectomy is effective in treating intrahepatic stones and may minimize the deleterious consequences of subsequent cholangiocarcinoma.^[21] However, in patients without ABDH, expanded liver resection is not only unnecessary, but also increases surgical risk and surgical complications, especially in patients who undergo multiple biliary tract surgeries and those with cirrhosis. For patients with ABDH, partial hepatectomy often fails to eradicate the lesion and may allow progression to ICC. Therefore, it is important to find the correct approach in treating the disease. For high-risk patients with ABDH, expanded hepatectomy is the recommended surgical procedure. For low-risk patients, reducing the extent of hepatectomy and retaining as much liver tissue as possible is more beneficial. Our results provide a novel diagnostic model that uses simple clinical data to predict ABDH and could help distinguish patients with ABDH, who should undergo aggressive surgery, from patients with intrahepatic stones.

Routine laboratory tests often directly or indirectly reflect information on related diseases in the patient's body. However, the information provided by these results is vague and does not provide accurate information for ABDH diagnosis. Using logistic regression, we collected variables that can be determined from basic laboratory tests and clinical history alone and tried to elucidate the relationship between ABDH and this information. Our results are a good combination of these commonly used clinical indicators, and provide a simple equation for ABDH prediction, allowing effective surgical decision-making preoperatively.

The current study did not confirm the pathogenesis of bile duct hyperplasia; cholelithiasis and intrahepatic bile duct hyperplasia are both risk factors for ICC and chronic inflammation from hepatolithiasis may cause hepatobiliary cancer.^[22,23] ABDH, a precancerous condition of hepatobiliary cell carcinoma, has been reported to be more common among older patients.^[18] This finding is in line with the results of our study, which indicated that age was an important factor for identifying patients with ABDH. According to logistic regression analysis, CA-199 also indicated the presence of ABDH. Therefore, the model is based on 2

objective variables: age and CA-199. In model development, the collinearity test confirmed that there was no correlation between age and CA-199 level. Goodness-of-fit testing confirmed the rationality of the model using age and the CA-199 level.

The optimal way to validate a diagnostic model is to assess its performance in an independent patient cohort.^[24] We used a cohort of patients with intrahepatic stones treated at a single hospital from January 2017 to December 2017. The model performed decently in the validation cohort compared with the derivation cohort (sensitivity: 28.5%, specificity: 88.7% vs sensitivity: 13.8%, specificity: 95.8%). The model had a comparable discrimination ability in the validation cohort, demonstrating that this model had an acceptable and stable discrimination ability in diagnosing atypical hyperplasia in the intrahepatic bile duct and indicating that this model is valuable for identifying ABDH.

Early diagnosis and intervention are regarded as an effective treatment for tumors, including ICC. Various techniques have been used clinically to detect tumor information, including CTC and ctDNA detection.^[25,26] However, the price of these tests is so high that many patients cannot afford them, especially in developing countries. In areas with poor economic and health conditions, the morbidity associated with hepatolithiasis and ICC is higher than in developed countries. Therefore, these high-risk patients have more need for tumor screening. Our results could solve this problem. CA-199 is a routine, inexpensive test. Our equation combines age and CA-199 to predict ICC in patients with hepatolithiasis. This is an inexpensive, acceptable, and useful method.

Because this study had a limited number of cases, the current diagnostic efficiency is not very satisfactory. However, because there is a lack of specific diagnostic methods for ABDH, this novel model still has potential clinical application for diagnosing ABDH. With further research in the future, we believe this model will have better diagnostic performance and stability.

In summary, this study indicated that preoperative age and CA-199 level were important factors for diagnosing patients with ABDH. This novel diagnostic model for ABDH uses 2 clinical variables in patients with intrahepatic stones to predict patients at high risk of ABDH. Compared with the pathological examination, preoperative blood testing is cheaper, widely available, and routinely performed in clinical practice. This model may provide a useful tool in the preoperative diagnosis and early intervention for ABDH, which could reduce the incidence of ICC in patients with intrahepatic stones.

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Author contributions

Conceptualization: Hongcheng Lu, Linqun Wu.

Data curation: Hao Yang, Xianping He, Rongshou Wu, Shidai Shi, Zhilong Yang.

Formal analysis: Hongcheng Lu, Hao Yang.

Investigation: Hao Yang, Xianping He, Rongshou Wu, Shidai Shi, Zhilong Yang.

Methodology: Wenjun Liao.

Software: Hongcheng Lu

Supervision: Wenjun Liao

Validation: Enliang Li.

Writing – original draft: Hongcheng Lu.

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