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ORIGINAL RESEARCH

A Composite Index for Distinguishing Benign and Malignant Obstructive Jaundice

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Objective: To explore a more effective and practical comprehensive index for differentiating benign from malignant obstructive jaundice by analyzing the clinical data of patients with benign obstructive jaundice (BJ) group and malignant obstructive jaundice (MJ) group.

Methods: A retrospective analysis was conducted on the clinical data of 339 patients with obstructive jaundice. The cases were divided into two data sets: training cohort and validation cohort. The cases were divided into two groups: malignant and benign obstructive jaundice group. Logistic regression analysis was used to build a prediction model for judging the nature of obstructive jaundice, and the prediction model was verified using the validation cohort.

Results: Multivariate analysis revealed that CEA, TBIL, and NLR were independent factors in malignant obstructive jaundice. A comprehensive index for differentiating benign from malignant obstructive jaundice was established based on these indicators. The sensitivity, specificity, and receiver operating characteristic curve of this model for differentiating benign from malignant obstructive jaundice were 79.57%, 93.26%, and 0.920, respectively.

Conclusion: The prediction model based on the comprehensive index of CEA, TBIL, and NLR has a higher accuracy in differentiating malignant obstructive jaundice.

Keywords: obstructive jaundice, comprehensive index, differentiation diagnosis

Introduction

Obstructive jaundice is one of the most common symptoms of benign and malignant diseases of the liver, gallbladder, and pancreas. Accurate differentiation of obstructive jaundice has important clinical significance.[1,2] Obstructive jaundice can be caused by various reasons and is mainly divided into benign and malignant lesions. Even with the advanced technology available today, some patients with obstructive jaundice are difficult to differentiate between good and bad at the early stage of diagnosis.[3,4] This makes it difficult to formulate treatment strategies and thus affects the therapeutic effect and prognosis of patients. Therefore, it is essential to determine the cause of obstructive jaundice in a timely, convenient, effective, and accurate manner for treatment.

Currently, imaging examinations and tumor markers are mainly used for diagnosis. Some patients with early-stage imaging examinations are difficult to detect or differentiate tumor properties. There have been many studies reporting the use of biochemical indicators to determine the nature of obstructive jaundice. Single indicators have certain diagnostic

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significance, such as carbohydrate antigen 19–9 (CA19-9), bilirubin, etc.;[3–8] combined use of multiple biochemical indicators significantly improves performance, such as CA19-9 combined with total bilirubin, CA9-9 combined with C-reaction protein (CRP), etc.[7–10] However, there is still no particularly effective method.

This study plans to collect the case data of obstructive jaundice patients hospitalized in our hospital in recent years and conduct a retrospective analysis study. According to the nature of the disease, the cases will be divided into groups of benign obstructive jaundice and malignant obstructive jaundice. Then, the serum tumor markers, blood routine test results, and liver function levels will be compared and analyzed between the two groups to explore the value of each indicator in differentiating benign from malignant obstructive jaundice diseases. It is hoped that a convenient and effective comprehensive model can be established to differentiate between benign and malignant obstructive jaundice.

Method

Patient

This study collected a total of 339 patients with obstructive jaundice who met the inclusion and exclusion criteria from January 2016 to December 2021 in the Department of Hepatobiliary Pancreatic Surgery, Guilin Medical College Hospital. All cases were diagnosed by laboratory, imaging examinations, surgical exploration, and postoperative pathological examinations. They were divided into two groups: benign obstructive jaundice (BJ) group and malignant obstructive jaundice (MJ) group. The cases were divided into two data sets: training cohort (randomly selected 80% of cases) and validation cohort (remaining 20% of cases). Each data set divided the cases into two groups: BJ group and MJ group. All patients signed informed consent forms. This study was approved by the ethics committee of Guilin Medical College Hospital (QTLL202172).

Inclusion and Exclusion Criteria

(1) Serum bilirubin levels were elevated, with the majority of increase in combined bilirubin (Direct Bilirubin).
(2) Patients had complete clinical examination data and a definitive diagnosis was made through pathological examination or follow-up imaging.
(3) Cases with incomplete serum testing were excluded.

Clinical Manifestation

All included cases received serological examinations upon admission, including complete blood count, liver function test, Carcinoembryonic antigen (CEA), Alpha fetoprotein (AFP), Carbohydrate antigen 125 (CA125), Carbohydrate antigen 153 (CA153), Carbohydrate antigen 19–9 (CA19-9) measurements, and Neutrophil to lymphocyte ratio (NLR) = neutrophil count/lymphocyte count.

Statistical Analysis

All data in this study were analyzed and processed using SPSS 28.0 statistical software. The normality of measurement data was first tested, and *T*-test was used for data that followed a normal distribution, while the rank sum test was used for data that did not follow a normal distribution. Count data was described by rate, and the chi-square test was used for group comparisons. The correlation between two independent samples was analyzed using Spearman's rank correlation coefficient (r). The normality of the sample data was determined using a normality test for measurement data. If the data were normally distributed, the mean ± standard deviation was used to represent the data, and an independent sample *t*-test was used for comparison between the two groups. If the data were not normally distributed, the median (25th percentile, 75th percentile) was used to represent the data, and a Wilcox test was used for comparison between the two groups. Categorical (qualitative) data were described statistically by frequency (percentage), and $\chi 2$ test or Fisher's exact test was used for comparison between groups.

Firstly, Logistic univariate analysis was conducted to identify significant differences in indicators between the two groups. Then multivariate analysis of malignant obstructive jaundice risk factors was performed. Finally, a comprehensive index for differentiating benign from malignant obstructive jaundice was established based on the logistic regression equation. The receiver operating characteristic curve (ROC) area under the curve (AUC), 95% confidence intervals (CI), cutoff values, sensitivity (Se), and specificity (Sp) were used to evaluate the effectiveness of the integrated index using a validation model.

The literature search was conducted using PubMed to compare the sensitivity and specificity of radiography and tumor markers in determining malignancy of obstructive jaundice.

The level of significance was set at 0.05 ($\alpha = 0.05$), and it was considered statistically significant when $P < 0.05$.

Results

General Baseline Data Analysis

This study included 339 cases of obstructive jaundice. The comparison of clinical data between the two groups is shown in Table 1. Table 2 showed the final diagnoses in this cohort of patients. Stone disease accounted for the majority of patients with obstructive jaundice caused by benign disease. The first and second causes of malignant obstructive jaundice are cholangiocarcinoma and pancreatic cancer, respectively.

Influencing Factors of Benign and Malignant Obstructive Jaundice

Variables with $P < 0.05$ in the above training groups were included in a binary logistic regression analysis, and the results showed that there were significant differences between the two groups for CEA, DBIL, ALT, and NLR ($P < 0.05$). Details are shown in Table 3.

Establishment of Predictive Model for Benign and Malignant Obstructive Jaundice

These $p < 0.01$ indicators were included in a logistic stepwise regression equation (Table 4) to establish a comprehensive index for differentiating benign from malignant obstructive jaundice:

$$p=\exp(-2.848+0.444*CEA+0.017*TBIL-0.208*NLR)/(1+\exp(-2.848+0.444*CEA+0.017*TBIL-0.208*NLR))$$

The likelihood ratio test of the model showed that the regression model had statistical significance ($\chi^2 = 19.827$, $P < 0.01$), and the goodness-of-fit test showed that the model fit was good ($\chi^2 = 177.995$, $P = 0.645$). The adjusted determination coefficient R2 was 0.467. DBMOJCI ≥ > 0.42195 was used to diagnose malignant obstructive jaundice, and the prediction results of the regression model for the diagnosis of malignant obstructive jaundice showed that the AUC of the regression model was 0.920 (95% CI: 0.881 to 0.949), with a sensitivity and specificity

Table 1 Comparison of General Clinical Data Between Two Groups of Patients

Variable_ Training	Group 0(n=178)	Group 1(n=93)	p_Training	Variable_ Validation	Group 0(n=40)	Group 1(n=28)	p_Validation
Age	62.5±14.01	65.67±10.03	0.121	Age	61.27±13.94	64.32±6.52	0.232
Sex			0.152	Sex			0.163
Male	89 (50%)	55 (59.14%)		Male	16 (40%)	16 (57.14%)	
Female	89 (50%)	38 (40.86%)		Female	24 (60%)	12 (42.86%)	
CEA	1.83 (1.29,2.62)	3.67 (2.26,5.86)	<0.001	CEA	1.9 (1.22,2.25)	3.51 (2.06,6.01)	<0.001
CA125	11.82 (9.28,19.02)	18.41 (11.85,38.53)	<0.001	CA125	12.31 (8.27,17.16)	19.95 (14.43,33)	0.001
CA199	64.28 (25.53,197.22)	175.11 (57.37,580.9)	<0.001	CA199	37.94 (12.88,132.15)	302.2 (49.26,1000)	0.001
AFP	2.36 (1.63,3.28)	2.8 (2.03,3.93)	0.003	AFP	2.24 (1.68,2.86)	2.33 (1.49,3.42)	0.636
TBIL	54.2 (33.65,88.09)	203.6 (111.1,273.2)	<0.001	TBIL	48.52 (30.14,89.06)	204.47 (128.5,303.1)	<0.001
TP	67.6±6.33	65.31±7.72	0.015	TP	67.74±6.48	65.2±7.95	0.151
ALT	128.9 (61.71,258.78)	96 (67,156.6)	0.016	ALT	127.06 (70.21,258.29)	68.5 (46,134.32)	0.02
AST	87.65 (49.72,195.81)	83.51 (58,128.3)	0.539	AST	95.64 (57.83,170.48)	69.7 (54.98,109.87)	0.154
NLR	5.85 (2.95,11.19)	3.36 (2.36,4.61)	<0.001	NLR	6.09 (3.88,13.4)	4.03 (2.82,6.48)	0.049

Notes: Group 1: benign obstructive jaundice group; Group 2: Malignant obstructive jaundice group.
Abbreviations: CEA, Carcinoembryonic antigen; AFP, alpha-fetoprotein; CA125, Carbohydrate antigen 125; CA153, Carbohydrate antigen 153; CA19-9, Carbohydrate antigen 19–9; TBIL, Total bilirubin; DBIL, Direct bilirubin; TP, total protein; ALT, alanine aminotransferase; AST, Aspartate transferase; NLR, Ratio of neutrophil to lymphocyte count.

Table 2 Underlying Diagnoses of Patients Presenting with Obstructive Jaundice

Diagnosis	Patients, n	Percentage of Total, %
Benign pathology	218	
Common bile duct stones	208	95.40
Duodenal papillary stenosis	3	1.38
Gallstones with cholecystitis	3	1.38
Congenital choledochal cyst	2	0.92
Chronic pancreatitis	2	0.92
Malignant pathology	121	
Extrahepatic cholangiocarcinoma	44	36.36
Pancreatic ductal adenocarcinoma	31	25.62
Duodenal adenocarcinoma	18	14.88
Hilar cholangiocarcinoma	16	13.22
Ampullary adenocarcinoma	7	5.79
Gallbladder cancer	3	2.48
Metastatic disease	2	1.65

Table 3 Multivariate Logistic Regression Analysis of Obstructive Jaundice Between Different Independent Variable Groups

Correlation Factor	B	S.E	Wald	*P*	Exp(B)
CEA	0.402	0.098	17.008	0.000	1.495
CA125	0.018	0.011	2.745	0.098	1.018
CA199	0.000	0.000	0.002	0.967	1.000
AFP	0.032	0.058	0.310	0.578	1.033
TBIL	0.018	0.003	39.296	0.000	1.018
TP	−0.002	0.031	0.006	0.939	0.998
ALT	−0.005	0.002	5.889	0.015	0.995
NLR	−0.225	0.057	15.583	0.000	0.798

Abbreviations: S.E, standard error; Wald, the value of the Waldka square; 95% CI, 95% confidence interval; CEA, Carcinoembryonic antigen; AFP, alpha-fetoprotein; CA125, Carbohydrate antigen 125; CA153, Carbohydrate antigen 153; CA19-9, Carbohydrate antigen 19–9; DBIL, Direct bilirubin; TP, total protein; ALT, alanine aminotransferase; NLR, Neutrophil/lymphocyte ratio.

Table 4 Factors Incorporated into Prediction Model for Benign and Malignant Obstructive Jaundice

Correlation Factor	B	S.E	Wald	*P*	Exp(B)
CEA	0.444	0.099	20.083	0.000	1.558
TBIL	0.017	0.003	45.716	0.000	1.017
NLR	−0.208	0.054	15.060	0.000	0.812
constant	−2.848	0.420	45.899	0.000	0.058

Abbreviations: S.E, standard error; Wald, the value of the Waldka square; 95% CI, 95% confidence interval; CEA, Carcinoembryonic antigen; DBIL, Direct bilirubin; NLR, Neutrophil/lymphocyte ratio.

of 79.57% and 93.26%, respectively, a positive predictive value of 95.74%, and a negative predictive value of 76.34%, as shown in Figure 1. We evaluated prediction performance evaluation and the clinical applicability of the model, as shown in Supplementary Figures 1 and 2.

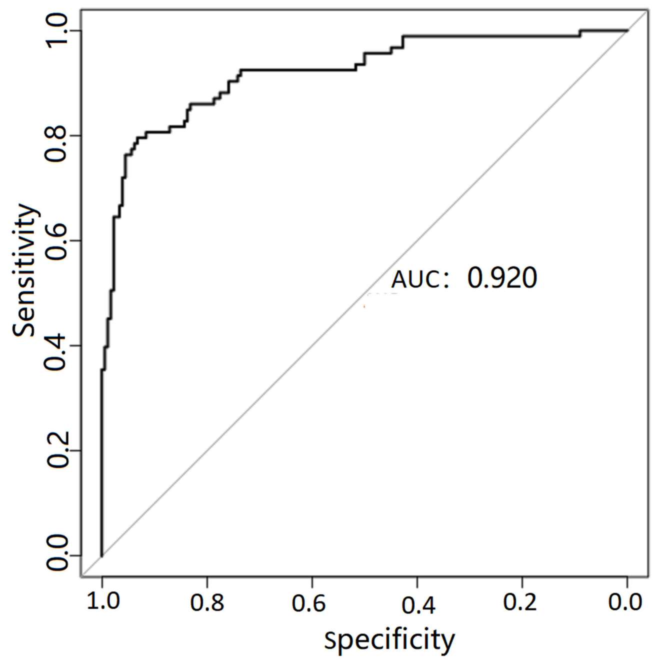

Figure 1 Diagnostic performance of predictive models. Area under the ROC curve was 0.920 (95% CI:0.881 to 0.949).The sensitivity and specificity were 79.57% and 93.26%, respectively. The positive predictive value was 95.74% and the negative predictive value was 76.34%.

Validation

The Hosmer-Lemeshow Goodness-of-Fit Test was performed on the model in the validation set with a chi-square value of 46.714, p = 0. 0.645. And adjusted the determination coefficient R2=0.467. Malignant obstructive jaundice was diagnosed with p≥0.42195, and the prediction results of the regression model were shown as follows. The area under the training set ROC curve was 0.848 [0.748, 0.948], as shown in Figure 2. Sensitivity and specificity were 0.90 and 0.79. The false negative rate was 0.100, the false positive rate was 0.2083, the concordance rate was 0.8235, Kappa was

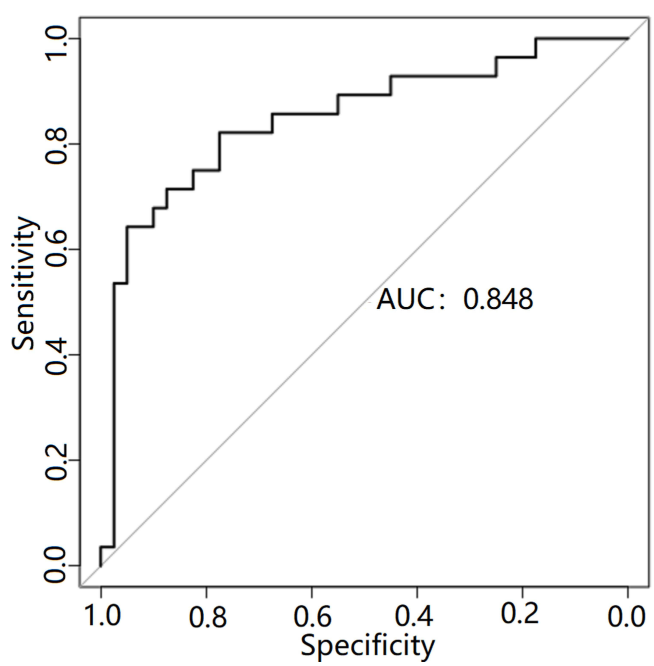

Figure 2 Validation of predictive models. The area under the validation set ROC curve was as 0.848 (95% CI:0.748, 0.948). Sensitivity and specificity were 0.90 and 0.79.

Table 5 Sensitivity and Specificity of Evaluation Model Compared with Other Assessment Modalities

Method	Patients	Sensitivity (%)	Specificity (%)	AUC
Prediction model (p)	339			
>0.487		76.34	95.51	0.92
>0.69639		64.52	97.19	
>0.83		50.54	98.31	
>0.93042		35.48	100	
Bilirubin, mmol/l				
>85 (Al-Mofleh 2004)	126	98.6	59.3	0.74
>100 (Giuseppe G 2011)	1026	71.9	88.0	0.82
>250 (Giuseppe G 2011)		31.9	98.0	
CA19-9, U/mL				
>32 (La Greca G 2012)	102	82.3	45.0	0.71
>70.5 (Morris-Stiff G 2009)	248	82.1	85.9	0.87
>100 (La Greca G 2012)	102	68.6	64.7	
>90, After biliary drainage (Marrelli D 2009)	128	61	95	
CA199/Tbile (La Greca G 2012)	102	49	78.4	
CA199/CRP (La Greca G 2012)	102	76.5	68.6	
CA199, multiplier (Liu W20 18)	508	67.8	80.7	0.815
CA199/Tbile (Liu W20 18)		69.96	82.71	0.889
Combined CA199 and Tbile (Liu W20 18)			93.2	80.5
Combine multiple indicators (Ince AT 2008)	225	88.5	45.7	

0.6194, the positive predictive value was 0.6428, the negative predictive value was 0.9500, the corrected index was 0.6916, the positive likelihood ratio was 4.3200, and the negative likelihood ratio was 0.1263.

Comparative Analysis

We will compare the diagnostic performance of the model we established with other assessment modalities reported in previous literature, as shown in Table 5.

Discussion

Our study has found that several biochemical indicators, including CEA, CA125, CA153, CA19-9, and AFP, have diagnostic value for distinguishing malignant from benign obstructive jaundice. The sensitivity and specificity of these indicators are similar to those reported in previous studies.[6,11,12] However, the sensitivity of CEA is only about 40%, while its specificity is nearly 90%.[6,8,12] Serum CA199 levels significantly increase in patients with malignant obstructive jaundice, but its use alone does not accurately diagnose obstructive jaundice.[5–8] The use of bile duct drainage before and after CA199 levels can improve diagnostic accuracy, but it remains at around 70%.[11] The diagnostic specificity of changes in CA199 levels after bile duct drainage is as high as 95%, but the sensitivity is only 61%.[13]

Bilirubin is an important biochemical indicator for diagnosing obstructive jaundice, and its level is different in patients with malignant and benign obstructive jaundice. Our results are consistent with previous studies.[3–5] In patients with obstructive jaundice, the serum bilirubin level is significantly higher in those with malignant disease than in those with benign disease.[5] Garcea et al[3] found that the serum bilirubin level was significantly higher in patients with malignant obstructive jaundice than in those with benign obstructive jaundice (>100 μmol/L), and when the serum bilirubin threshold was set at 84 μmol/L, it had the best sensitivity (71.9%) and specificity (86.9%) for malignant obstructive jaundice. Almofleh et al[4] found that when the serum bilirubin threshold was adjusted to 84 μmol/L, it had a high sensitivity (>95%) for predicting malignant obstructive stenosis, but a low specificity (<60%). Our results were slightly different; the sensitivity was less than 80%, but the specificity was greater than 70%. This may be due to the inclusion of all cases of biliary stricture in Almofleh I A's study, which focused solely on biliary stricture.

Overall, combining multiple biochemical indicators can improve the diagnostic accuracy of obstructive jaundice. In our study, a Logistic regression model was developed by combining serum CEA, TBIL, the NLR values to predict malignant obstructive jaundice, which had better diagnostic performance than single indicators or combinations of other indicators. Our validation group showed that the AUC of the prediction model for malignant obstructive jaundice was close to 0.9, indicating good diagnostic performance. The diagnostic performance of the prediction model was better than some previously reported indicators.[7–10] In terms of high specificity, our comprehensive index had a significant advantage over Garcea et al's study on single bilirubin indicators.[3] Some studies have found that combining bilirubin levels with survivin and CA199 can improve diagnostic ability.[7] La Greca et al[9] found that the sensitivity of using the ratio of serum CA19-9 to bilirubin (≥0.88) to CA19-9 increases multiplied by the increase in bilirubin (≥4.5) was less than 50%, and the specificity and accuracy were less than 80%; our study suggested that the diagnostic performance of CA19-9 and the increase in CA19-9 multiplied by the increase in bilirubin was poor compared to their results; however, our prediction model had similar specificity and better accuracy than their indicators.

The clinical significance of this predictive model is that the combined index of the predictive model can be used as a non-invasive, rapidly available screening tool to distinguish benign and malignant obstructive jaundice before the patient has a clear pathological result. This early identification is critical for timely triage, treatment planning, and potentially improving patient outcomes.

There are several limitations to our study. Firstly, it is a retrospective study and may suffer from selection bias. Secondly, our sample size is not large enough. Thirdly, most patients did not have routinely measured CRP at admission, so CRP was not included in our study. These limitations require further prospective, multicenter research for practical application.

Conclusion

A prediction model that combines serum CEA, DBIL, and NLR had higher diagnostic accuracy for malignant obstructive jaundice.

Abbreviations

AFP, Alpha fetoprotein; CA125, Carbohydrate antigen 125; CA153, Carbohydrate antigen 153; CA19-9, carbohydrate antigen 19-9; AUC, area under the curve; CEA, Carcinoembryonic antigen; CI, confidence intervals; BJ, benign obstructive jaundice; DBIL, Direct Bilirubin; NLR, Neutrophil to lymphocyte ratio; MJ, malignant obstructive jaundice; ROC, The receiver operating characteristic curve; Se, sensitivity; Sp, specificity; TBIL, total bilirubin.

Data Sharing Statement

The datasets of current study are available from the corresponding author (Jiangfa Li) on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Affiliated Hospital of Guilin Medical University (QTLL202172). All patients signed informed consent forms. This study complies with the Declaration of Helsinki.

Consent for Publication

All authors consented to publication.

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This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-4248230/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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