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Predictive factors in the differential diagnosis of benign and malignant causes in patients undergoing endoscopic retrograde cholangiopancreatography for extrahepatic cholestasis

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Abstract. – OBJECTIVE: Diagnosing benign *vs.* malignant extrahepatic cholestasis is challenging despite the currently available advanced imaging and endoscopic techniques. This study aims to determine the predictive accuracy of initial biochemical data and bile duct dilatation findings in transabdominal ultrasound (US) to differentiate between benign and malignant disease in patients with extrahepatic cholestasis.

PATIENTS AND METHODS: We reviewed the case records of 814 patients who had undergone endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (in cases of unsuccessful ERCP) for extrahepatic cholestasis. The etiology of biliary obstruction was determined based on ERCP, endoscopic ultrasonography, radiology, cytology, biopsy, and/or clinical follow-up at one year. The patients were divided into benign and malignant groups according to the underlying etiology of biliary obstruction. A complete biochemical profile, transabdominal ultrasonography at presentation, and other demographic data were recorded.

RESULTS: Alkaline phosphatase (p = 0.002), aspartate aminotransferase (p = 0.038), and bilirubin levels were significantly higher in malignant patients. The mean age of patients with malignancy was 69.5 years, *vs.* 60.6 years in benign patients ($p < 0.001$). The likelihood of malignancy increased with the increased bilirubin levels (> 200 μmol/l: 30.0% sensitivity, 97.6% specificity). The total bilirubin level predicting malignancy as the best cut-off value was 111 mmol/L with optimum sensitivity and specificity (61.8% and 83.8%, respectively) and area under the curve = 0.756, ($p < 0.001$). Intrahepatic bile duct (IHBD) dilatation was significantly higher in malignant patients ($p < 0.001$).

CONCLUSIONS: A serum bilirubin level of 111 μmol/L or higher and the detection of IHBD dilatation on abdominal ultrasonography are important predictors in the differential diagnosis of benign and malignant causes of extrahepatic cholestasis

Key Words:
Endoscopic retrograde cholangiopancreatography (ERCP), Cholestasis, Predictive, Biliary stricture, Differential diagnosis.

Introduction

Obstructive jaundice is a clinical finding that can be caused by a wide variety of benign or malign disorders presenting with elevated bilirubin levels[1]. Extrahepatic cholestasis is caused by bile duct stenosis due to bile duct stones or stricture, with stricture often referring to malignancy. The presence or absence of abnormalities and the type of abnormalities in initial laboratory tests, including measurements of serum total and unconjugated bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), and game-glutamyltransferase (GGT), should help predict the diagnosis of extrahepatic cholestasis. A single noninvasive diagnostic test cannot accurately predict the presence of common bile duct (CBD) stones or strictures as a cause of extrahepatic cholestasis[2,3].

However, the predictive value of liver function tests may be affected by other diseases. Therefore, to identify the best predictive model, combining noninvasive biochemical tests and ultrasound (US) examination of the biliary tract can improve predictive accuracy and identify patients who require therapeutic endoscopic ret-

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rograde cholangiopancreatography (ERCP) presenting with clinical and laboratory signs of extrahepatic cholestasis[4]. Although the abdominal US shows the diameter of bile ducts and the level of obstruction in extrahepatic cholestasis, it rarely identifies the cause of obstruction as a tumor or stone[5]. Magnetic resonance cholangiopancreatography (MRCP) is a superior non-invasive imaging method for identifying biliary ductal anatomy and potentially obstructing lesions, but availability for patients requiring rapid diagnosis and treatment is limited[6]. Similar to MRCP, ERCP can be the initial screening procedure in the differential diagnosis of stones or stricture with therapeutic interventions in patients with extrahepatic cholestasis[7]. However, identifying the best non-invasive predictors should help to select the appropriate criteria for ERCP in suspected biliary stenosis and thus reduce unnecessary exploration, with its own associated risk of morbidity. To the best of our knowledge, combining serologic biochemical and US markers in predicting the differential diagnosis of extrahepatic cholestasis has not been evaluated to date.

The present study aimed to evaluate serologic biochemical and US markers in predicting the differential diagnosis of benign and malignant causes in patients undergoing ERCP for extrahepatic cholestasis.

Patients and Methods

The case records of patients who had undergone ERCP or percutaneous transhepatic cholangiography (PTC) (in cases of unsuccessful ERCP) for extrahepatic cholestasis during the 2017-2021 period were examined. Selected patients who had undergone interventional procedures (ERCP, PTC) were evaluated multimodally before or after interventional procedures with magnetic resonance imaging (MRI), computed tomography (CT), or endoscopic ultrasonography (EUS), including tissue sampling, to confirm the malignant or benign diagnosis of biliary strictures causing extrahepatic cholestasis.

Demographic characteristics, age, laboratory data, abdominal US imaging findings at the initial presentation, and final diagnoses were recorded. The final diagnosis was made by using histological tissue examination by interventional procedures (including ERCP brush cytology, EUS fine-needle aspiration, and biopsy with radiological or explorative surgery). In the presence of benign disease, clinical follow-up was performed at least twice with an interval of six months (consisting of cross-sectional imaging, ERCP, or EUS showing the absence of disease progression).

The patients were divided into benign and malignant groups according to the underlying pathology that caused extrahepatic cholestasis due to biliary strictures. In the benign disease group, the diagnosis of biliary stricture related to choledocholithiasis was made by the successful removal of the stone by ERCP. The laboratory data of the patients whose extrahepatic cholestasis cause was proven to be a stone by ERCP were followed up after the procedure to ensure diagnostic accuracy. Due to the methodology and design of our study, the population was not divided into the training set and the validation set. Only training was carried out in this study. This was the limitation of our study.

Statistical Analysis

JAMOVI software (https://www.jamovi.org) (version 2.3.16.0) was used for the statistical analysis of the data. The Shapiro-Wilk test was used to evaluate whether the data conformed to the normal distribution. The Student's *t*-test or Mann-Whitney U test was used to analyze continuous variables. The Chi-square test was used to analyze the categorical variables. Multiple logistic regression analysis was performed to identify independent predictors of malignancy. Receiver operating characteristic (ROC) analysis was performed to find the independent predictors' cut-off value that was significant for malignancy. Variables affecting malignancy were also found to have sensitivity, specificity, and negative and positive odds ratios. A two-way ANOVA was used to compare the mean differences between the groups that were split into two independent variables. A p-value of < 0.05 was considered statistically significant.

Results

A total of 814 patients with extrahepatic cholestasis were included in this study. Demographic data and bile duct imaging findings of US by etiology are shown in Table I. The mean age of patients with malignant disease (69.5 ± 15.2 years) was significantly higher than that of patients with benign disease (53 ± 18 years). Choledocholithiasis was the main benign cause

Table I. Demographic data of patients with extrahepatic cholestasis.

Number of patients	Benign disease (n = 671)	Malignant disease (n = 183)	*p*-value
Mean age (range), years	60.6 ± 19.0 (46-76)	69.5 ± 15.2 (61-81)	< 0.001
Male	273 (42.3%)	104 (46.8%)	0.053
Median total bilirubin (range), mmol/l	64.9 ± 59.8 (20.5-92.3)	165.9 ± 133.4 (66.7-236.0)	< 0.001
Median common bile duct diameter	11.0 ± 5.2 (8.0-12.0)	11.7 ± 5.0 (8.0-14.0)	0.097
Intrahepatic bile duct dilatation	84 (12.4%)	162 (89.0%)	< 0.001

of extrahepatic cholestasis. The most common malignant causes of extrahepatic cholestasis were cholangiocarcinoma and pancreatic head carcinoma. Other causes of extrahepatic cholestasis are shown in Table II.

Table III shows the laboratory data of patients with extrahepatic cholestasis. The mean serum values of bilirubin, ALP, GGT, and aspartate aminotransferase (AST) were significantly higher in patients with malignant diseases. In Figure 1, the ROC analysis shows that the total bilirubin level predicting malignancy with the best cut-off value was 111 mmol/L, with a sensitivity of 61.8% (54.3-68.8) and a specificity of 83.8% (80.6-86.3) [area under the curve (AUC) = 0.756, $p < 0.001$]. Table IV shows other laboratory tests, including ALT, AST, and AP, which had less sensitivity and specificity. Table V shows the sensitivity and specificity of different bilirubin levels in predicting malignancy in all patients with extrahepatic cholestasis.

As shown in Figure 2 and Table VI, grouping was done by taking the 6.5 cut-off value of the bilirubin level in the two-way ANOVA analysis, and the effect of both the bilirubin level ($f = 36.62$, $p < 0.001$) and the IHBD dilatation ($f = 578.03$, $p < 0.001$) was found to be significant. Additionally, the interaction level between the bilirubin level and IHBD dilatation was found to be statistically significant ($f = 23.23$, $p < 0.001$).

Table II. Underlying diagnoses of patients with extrahepatic cholestasis.

Benign disease	Patients n	Percentage %	Malignant disease	Patients n	Percentage %
Choledocholithiasis	540	90	Pancreatic ductal adenocarcinoma	87	40.7
Post-cholecystectomy stricture	24	4	Distal cholangiocarcinoma	48	22.4
Primary sclerosing cholangitis	9	1.5	Klatskin tumor	27	12.6
Chronic pancreatitis	8	1.4	Ampullary carcinoma	21	9.8
Choledochal cyst	6	1	Metastatic disease	14	6.6
Mirizzi syndrome	5	0.8	Gallbladder cancer	8	3.7
Hydatid cyst	4	0.7	Hepatocellular carcinoma	5	2.3
Caroli disease	2	0.3	Duodenal carcinoma	3	1.4
Fasciola hepatica	2	0.3	Lymphoma	1	0.5
Total	600		Total	214	

Table III. Laboratory data of patients with extrahepatic cholestasis.

Median values	Benign disease (n = 671)	Malignant disease (n = 183)	*p*-value
Median total bilirubin (range), mmol/l	64.9 ± 59.8 (20.5-92.3)	165.9 ± 133.4 (66.7-236.0)	< 0.001
Median direct bilirubin (range), mmol/l	47.8 ± 150.5 (10.2-63.2)	118.0 ± 100.9 (41.0-169.3)	< 0.001
ALP (IU/L)	237.5 ± 177.5 (127.0-298.0)	361.7 ± 248.8 (146.0-465.3)	0.002
GGT (IU/L)	402.7 ± 363.4 (159.5-524.0)	477.1 ± 470.5 (177.0-704.0)	0.088
AST (IU/L)	206.2 ± 300.7 (51.8-253.5)	166.5 ± 155.4 (62.0-190.0)	0.038
ALT (IU/L)	221.6 ± 236.9 (63.3-314.0)	187.21 ± 196.5 (60.0-208.3)	0.053

ALP, alkaline phosphatase; GGT, game-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

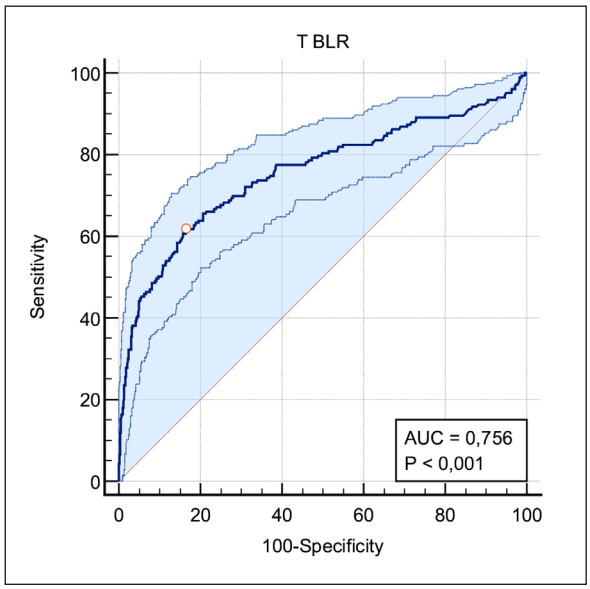

Figure 1. Receiver operating characteristic (ROC) curves for bilirubin and prediction of malignancy with area under the curve values for all patients with either benign or malignant causes of extrahepatic cholestasis.

Discussion

The present study revealed that bilirubin is the best predictive factor in discriminating between benign and malignant causes of extrahepatic cholestasis, although statistically significant differences were found in some biochemical parameters. Additionally, the results suggest that IHBD dilatation is an important discriminator between benign and malignant diseases.

An increased bilirubin level (> 110 mmol/L) was highly predictive for malignant causes of extrahepatic cholestasis, with a sensitivity of 61.8%, a specificity of 83.8%, and a positive likelihood ratio of 3.42. Furthermore, IHBD dilatation was significantly higher in malignant strictures than in benign strictures: 89.0% *vs.* 12.4%, respectively ($p < 0.001$). Previous studies[8,9] have shown similar findings when examining bilirubin levels and the biliary tract in malignant diseases, with serum bilirubin levels ≥ 85 µmol/l (sensitivity and specificity of 98.6% and 59.3%, respectively) and ≥ 75 µmol/l, which were highly predictive for malignant biliary strictures. In the same studies[8,9] on patients with extrahepatic cholestasis, IHBD dilatations were more frequently present in 73.8% and 93% of malignant strictures *vs.* 39.5% and 36% of benign strictures, respectively. A previous study[10] reported that there was no significant difference in the diameter of common bile duct dilatation between benign and malignant causes of extrahepatic cholestasis. Similarly, in our study, the CBD diameter did not reach a significant difference in patients with benign and malignant extrahepatic cholestasis, but IHBD dilatations were found significantly more frequently in malignancy.

Extrahepatic cholestasis is the cessation of bile flow due to obstruction of the biliary tract by stones or malignant lesions, which are diagnosed by dilatation of the IHBD and extrahepatic bile ducts on US, with sensitivity and specificity of 98.6% and 59.3%, respectively[11]. Experimental studies[12,13] have shown that there is a time lag between the dilation of IHBD and extrahepatic bile ducts. While the extrahepatic ducts dilate within 2-3 days of the onset of obstruction, IHBD dilatation takes about 1 week. Obstruction in extrahepatic cholestasis due to benign strictures, such as stones, shows fluctuation, whereas cholestasis in malignant strictures is progressive. Malignant strictures were more likely to cause IHBD dilatation than benign strictures (93% *vs.* 36%, respectively, $p = 0.002$)[9]. The chronic progressive cholestatic process of malignant diseases can explain why we observed IHBD dilatations more frequently in malignant strictures than in benign strictures in our study.

Table IV. Receiver operator characteristic test results predicting malignant biliary strictures.

Parameter median (range) values	Cut-off value (%)	Sensitivity	Sensitivity	+LR	-LR
Total bilirubin (umol/L)	111	61.8	83.8	3.42	0.02
ALP (IU/L)	136	59.7	83.3	3.58	0.48
GGT (IU/L)	246	80.6	53.7	1.74	0.36
ALT (IU/L)	68	45.8	81.5	2.47	0.66
AST (IU/L)	85	76.4	74.1	2.95	0.32

ALP, alkaline phosphatase; GGT, game-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table V. Bilirubin level and the likelihood of malignancy in all patients with either benign or malignant causes for extrahepatic cholestasis.

Total bilirubin level, umol/L	Sensitivity, %	95% confidence interval	Specificity, %	95% confidence interval	Positive likelihood ratio	Negative likelihood ratio
> **50**	79.23	72.6-84.9	52.61	48.8-56.4	1.67	0.39
> **100**	63.93	56.5-70.9	79.28	76.0-82.3	3.09	0.45
> **150**	45.36	38.0-52.9	93.74	91.6-95.5	7.25	0.58
> **200**	30.05	23.5-37.3	97.62	96.2-98.6	12.60	0.72

ALP, alkaline phosphatase; GGT, game-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

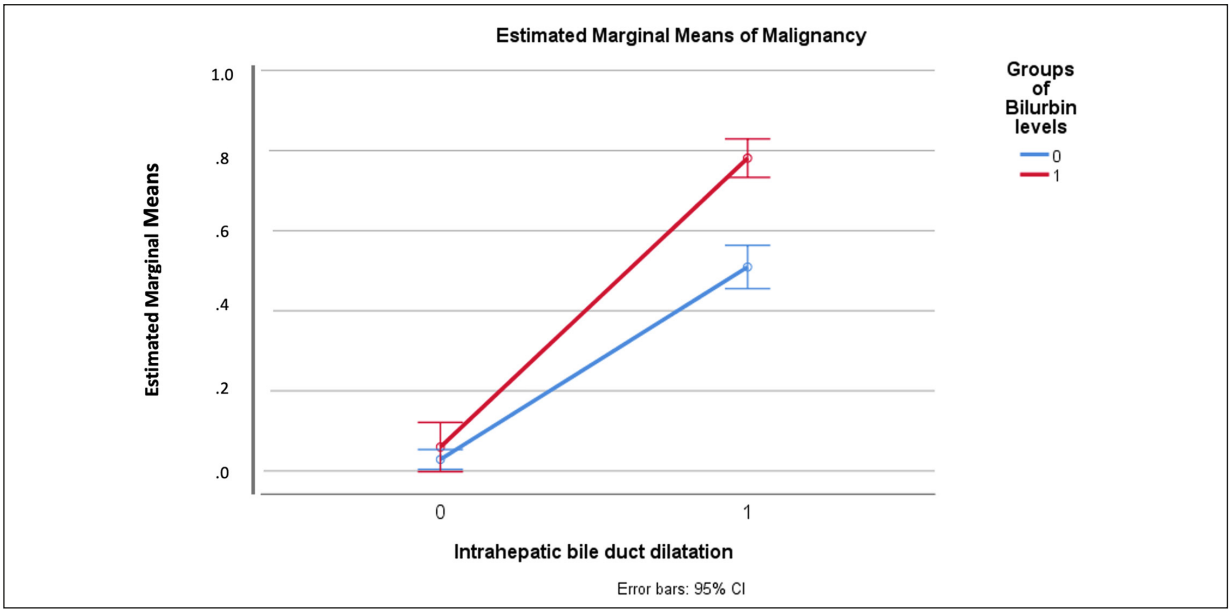

Figure 2. The plot of the mean malignancy score for each combination of groups of bilirubin and intrahepatic bile duct dilatation is plotted in a line graph.

Table VI. Two-way ANOVA test results of interaction between bilirubin and IHBD dilatation.

Dependent Variable: MALIGN						
Source	Type III sum of squares	df	Mean square	F	Sig.	Partial eta squared
Intercept	62,556	1	62,556	760,259	0.000	0.473
Group_bilirubin *IHBD Dilatation	1,911	1	1,911	23,231	0.000	0.027
Group_bilirubin	3,013	1	3,013	36,620	0.000	0.041
IHBD Dilatation	47,561	1	47,561	578,025	0.000	0.406
Error	69,693	847	0.082			
Total	182,000	851				
Corrected Total	143,076	850				

R Squared = 0.513 (Adjusted R Squared = 0.511).

A possible reason why bilirubin levels are low in benign diseases is the earlier diagnosis of patients with stones due to clinical pain and cholangitis. Consequently, bilirubin levels at admission were lower in these patients than in patients with a malignancy. Extrahepatic bile duct dilatations resulting from stone obstruction allow trapped stones to move within the duct and lead to tem-

porary bile flow, which prevents an excessive increase in bilirubin and IHBD dilatations. Additionally, in biliary strictures without choledocholithiasis, such as inflammatory strictures, the degree of stricture changes according to the active and calm periods of inflammation, which enables periodic bile flow. In a retrospective study[14] of 1,026 patients with obstructive jaundice, bilirubin levels of 100 or greater were found to be the best predictive value for malignancy. In the same study[14], although increased bilirubin levels were an important predictor of malignancy, its sensitivity was shown to decrease with the increase of bilirubin (> 100 μmol/l: 71.9% sensitivity and > 250 μmol/l: 31.9% sensitivity). Similarly, our study found that sensitivity decreased with the elevation of bilirubin levels (> 100 μmol/l: 63.93% sensitivity and > 200 μmol/l: 30.5% sensitivity)

We do not suggest using bilirubin alone to predict malignant biliary strictures in extrahepatic cholestasis. For this purpose, when we combined and examined the interaction between bilirubin and IHBD dilatation in our study, we reached much higher predictions for malignancy than for bilirubin alone. We suggest that these combination findings will eliminate the sensitivity disadvantage that decreases with increased bilirubin and provide greater value than previous studies in predicting the differentiation of malignant-benign cholestasis.

The literature describes some accepted modalities that are used to assess the characterization of strictures with advanced radiological imaging methods, such as MRI, CT, positron emission tomography and EUS. MRI has the best values for characterizing biliary strictures in these imaging methods, with a sensitivity of 95% and a specificity of 97%. Although the data presented in these studies[15-18] do not represent a comprehensive review of the literature, our results seem to be comparable to other imaging methods in the prediction of malignant biliary strictures in patients with cholestasis, with a sensitivity of 61.8%, a specificity of 83.8%, and a positive likelihood ratio of 3.42. A comparison of our results with other modalities demonstrated its usefulness for clinical use. The assessment of increased bilirubin levels and the imaging of IHBD dilatations together will be effective for clinicians. Imaging of IHBD dilatations, together with determining high bilirubin levels in primary care, will provide a quick decision on the patient's referral to the tertiary level to exclude malignancy and further investigation. Thus, it will prevent wasting time.

Conclusions

A bilirubin level > 110 is the best predictor in patients with malignant extrahepatic cholestasis. Additionally, optimum predictions were achieved with the combination of IHBD dilatations. Although these findings cannot replace advanced imaging methods in differential diagnosis, they highlight the need for a multidimensional evaluation of these patients.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Informed Consent
Informed written consent was obtained from all participants.

Authors' Contribution
O.Y contributed to study conception, design and writing; O.Y, MA.E, contributed to material preparation, data collection and analysis, MA.E contributed to study supervision and study design, OY, MA.E contributed to editing and critical review, final version of the manuscript was read and approved by all authors.

Data Availability
The data associated with the current study are available from the corresponding author upon reasonable request.

Ethics Approval
All the study was based on hospital data obtained consulting clinical records. For this reason, ethical disclosure was not required in our institution.

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