Original article

Predictors of Malignancy in Patients of Extra Hepatic Biliary Obstruction

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Abstract

Background: Etiology of extra hepatic biliary obstruction (EHBO) is often a diagnostic dilemma. To differentiate between benign and malignant causes is of utmost important. Therefore, we conduct a study to know the various predictors of malignancy in it. **Material and Methods:** 138 consecutive patients diagnosed as EHBO were included in the study. After detail history, examination and investigations patients were divided into benign and malignant groups. Univariate and multivariate logistic regression analysis was done. Receiver operating characteristics curve was drawn to determine the optimal diagnostic cut- off value for predicting malignancy. **Results:** On univariate analysis patients with malignant EHBO were older, had more loss of weight, cholestatic symptoms, presence of hepatomegaly, palpable gall bladder, higher mean serum bilirubin [18.45±8.09 vs 9.70±9.40 mg/dl (p value <0.001)] and higher mean serum alkaline phosphatase [517.38±234.01 vs 356.44±208.98 IU/L (p value <0.001)]. Area under curve showed cut off value for serum bilirubin of >16.5 mg/dl (sensitivity 61.9%, specificity 84.3% and 95% confidence interval 0.751-0.896) and of serum alkaline phosphatase of >455IU/L (sensitivity 52.4%, specificity 82.9% and 95% confidence interval 0.651-0.824) as a predictor of malignancy. Multivariate analysis showed palpable gall bladder and serum bilirubin > 16.5 mg/dl to be independent predictors of malignancy. **Conclusion:** In patients with EHBO palpable gall bladder, serum bilirubin > 16.5 mg/dl and serum alkaline phosphatase > 455 IU/ L are important discriminating factors for malignancy.

Keywords: *bile duct obstruction extrahepatic, bilirubin, alkaline phosphatase, malignancy, predictor*

Introduction

Extra hepatic biliary obstruction (EHBO) is an important cause of morbidity and mortality in the community and occurs when there is an obstruction to the passage of conjugated bilirubin from liver cell to intestine. The etiology of it is diverse and ascertaining the exact cause is necessary for specific management of these patients. To differentiate between benign and malignant cause of EHBO is not only challenging for medical professionals but also important for further management and prognosis of these patients. Inflammatory benign lesions sometimes present with same clinical and radiological findings as malignant lesions. Even with currently available advanced imaging and endoscopic techniques there is delay in its diagnosis. Also, preoperative biopsy confirmation of malignant etiology is not always possible because of the complex anatomy of the biliary system. Early diagnosis is of utmost important in malignant obstruction as lesion is resectable only in early stages [1-4]. A wide range of invasive and noninvasive diagnostic tests are available including Ultrasonography (USG), Contrast Enhanced Computed Tomography (CECT), Magnetic Resonance Cholangio Pancreatography (MRCP), Endoscopic Ultrasonography (EUS), Cholangioscopy, Cancer Antigen 19-9 (CA-19-9) etc. but no single clinical finding or investigation is ideal to differentiate between the two. Understanding the factors which help us to distinguish between the two will guide us in appropriate management of these patients. There is need to identify clinical and laboratory factors which predict

malignancy in patients with EHBO so that early diagnosis can be made. Thus, we conducted this study to know the clinical and biochemical predictive factors of malignancy in patients presenting with features of EHBO.

Materials and Methods

A retrospective cross-sectional study of 138 patients with a clinical diagnosis of EHBO was done in Sri Aurobindo Medical College and Post Graduate institute in the department of gastroenterology between January 2012 to December 2014. Consent was taken from patients and ethical approval to conduct the study was obtained from the ethical committee of Sri Aurobindo Medical College and PG Institute.

Demographic data was collected and all patients were subjected to detailed history and clinical examination. All patients of more than 18 year of age who had symptoms of extrahepatic obstructive jaundice confirmed with liver function test and abdominal sonography were included in the study. All patients with intrahepatic obstructive jaundice and with other etiologies of jaundice were excluded. Loss of weight more than 10% of body weight in less than 6 months was taken as significant. Liver span of more than 15 cm was taken as hepatomegaly. Laboratory investigations were done including hemogram, liver function test, renal function test, electrolytes, coagulation profile, ECG, X-ray Chest followed by abdominal ultrasonography, CECT of abdomen,

Magnetic Resonance Cholangio Pancreatogram and Endoscopic Retrograde Cholangio Pancreatography (ERCP). CECT was performed in all patients using Somatom definition AS (Siemens) 64 slice and MRI/MRCP was performed using Magnetom symphony 1.5 Tesla (Siemens). Diagnosis of malignancy was established by histopathology or cytology. Diagnostic material for histopathology was obtained during ERCP from the ampulla or percutaneous CT biopsy while diagnostic material for fine needle aspiration cytology (FNAC) was obtained from endoscopic biliary brush cytology, EUS guided FNAC or by percutaneous ultrasonography or CT guided FNAC. Histopathological and cytological slides were examined by single experienced histopathologist. Patients were then divided into benign and malignant groups. Therapeutic ERCP with sphincterotomy and endoscopic stone removal was done in cases of choledocholithiasis. Patients with resectable malignancies were referred for surgery and those with unresectable malignancies i.e. those with distant metastasis or vascular invasion had undergone palliative biliary stenting. In addition to therapeutic endoscopic management patients with cholangitis were also managed with IV fluids and IV antibiotics. Antibiotics were modified later according to bile culture and sensitivity report.

Statistical analysis

The data were expressed as mean ± standard deviation unless otherwise noted. Comparison of continuous variables was carried out using unpaired student's t test. Chi-square test was applied to compare between the categorical variable. Statistical tests were based on 2- tailed probability.

Receiver operating characteristics (ROC) curves were used to assess the predictors of malignancy through the analysis of area under the curve ROC curve (AUROC). AUROC ranges from 0 to 1. An AUROC above 0.8 indicates excellent diagnostic accuracy and between 0.7 to 0.8 is generally considered useful. Multivariate logistic regression was also done. All data was stored in Microsoft excel format and was analyzed by using IBM SPSS version 20.0 software (SPSS, Chicago, Illinois, USA). A p value < 0.05 was considered significant.

Results

Baseline characteristic of cases and controls are shown in **Table I** and etiological spectrum of EHBO are shown in **Table II**. Out of 138 patients with EHBO, there were 63 females and 75 males. Out of these 73 patients had malignant etiology and 65 patients had benign etiology. Mean age of patients with malignant etiology was higher as compared to patients with benign etiology (p<0.001). No significant sex difference was found between the two groups.

Pain in abdomen and fever were equally common in benign and malignant EHBO patients. Loss of weight and cholestatic symptoms were significantly more common in patients with malignant etiology as compared to benign ones. (p value 0.002 and 0.030 respectively) Presence of hepatomegaly was more common in patients of malignant EHBO as compared with patients with benign EHBO (p <0.001). Gall bladder was palpable more frequently in patients with malignant etiology as compared to patients with benign EHBO (p< 0.001).

Mean serum bilirubin was significantly higher in patients with malignant EHBO as compared to benign EHBO (p<0.001)]. Similarly, mean serum alkaline phosphatase (SAP) was significantly higher in malignant EHBO as compared to benign EHBO (p<0.001). There was no significant difference in mean aspartate aminotransferase (AST) and mean alanine aminotransferase (ALT) in the two groups. Area under the curve values for serum bilirubin and SAP as a predictor for malignancy were assessed and both were found to be highly significant (p value < 0.001) (**Table III, Figure I**). Cut off value as a predictor for malignancy for serum bilirubin >16.5 gm/dl had sensitivity of 61.9% and specificity of 84.3% (p value < 0.001, 95% confidence interval 0.751-0.896) and SAP of > 455 IU/L had sensitivity of 52.4% and specificity of 82.9% (p value < 0.001, 95% confidence interval 0.651-0.824).

Multiple logistic regression analysis to predict malignancy was done, it showed that palpable gall bladder and S.Bilirubin> 16.5 mg/dl were independent predictors of malignancy(p value, CI) (**Table IV**)
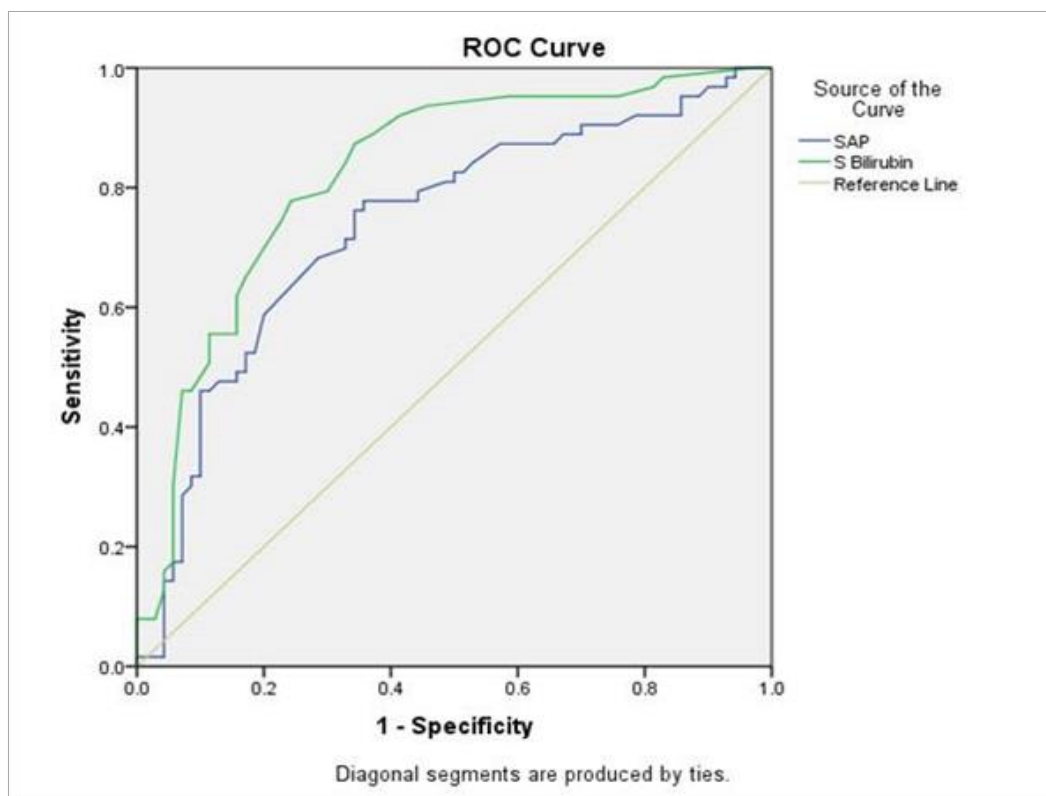

Figure I: Receiver operating characteristic curves for bilirubin and alkaline phosphatase

Table I: Clinical and laboratory characteristics of patients with benign and malignant EHBO

	Benign		Malignant		P-Value
Demography					
N	73		65		
Sex	F	M	F	M	
	34	39	29	36	0.818
Mean Age (years)	48.52±15.25		57.51±12.70		<0.001
Symptoms/Signs					
Pain in abdomen	56(76.71%)		32(49.23%)		0.105
Fever	34(46.57%)		22(33.85%)		0.407
Loss of weight	17(23.29%)		51 (78.46%)		0.002
Cholestatic Symptoms	13(17.80%)		41(63.08%)		0.030
Hepatomegaly	12 (16.44%)		30(46.15%)		<0.001
Gall bladder palpable	2(2.74%)		31(68.89%)		<0.001
Lab values					
Mean serum bilirubin (mg/dl)	9.70 + 9.40		18.45 + 8.09		<0.001
Mean SAP (IU/L)	356.44 + 208. 98		517.38 + 234.01		<0.001
Mean AST (IU/L)	162.77 + 160.32		206.68 + 148.23		0.098
Mean ALT (IU/L)	229.96 + 469.24		208.78 + 148.42		0.731

Note- All continuous data are expressed as mean+ standard deviation and categorical data are expressed as values or percentages. F- Female, M- Male, SAP – Serum Alkaline phosphatase, AST- Aspartate aminotransferase, ALT- Alanine aminotransferase

Table II: Aetiological spectrum of EHBO

Causes of EHBO	No. of patients	Percentage
Benign EHBO:		
Choledocholithiasis	58	79.45
Benign CBD stricture	4	5.48
Hydatid cyst with biliary communication	3	4.12
Choledochal cyst	3	4.12
Portal biliopathy	2	2.74
Amoebic liver abscess with biliary communication	2	2.74
Chronic pancreatitis	1	1.37
Malignant EHBO:		
Carcinoma gall bladder	20	30.77
Periampullary Carcinoma	17	26.15
Cholangio Carcinoma	15	23.08
Carcinoma head pancreas	10	15.38
Neuro Endorinal Tumor	1	1.54
Disseminated lymphoma	1	1.54
Metastatic lymphadenopathy	1	1.54

EHBO-Extra hepatic biliary obstruction, CBD- Common bile duct

Table III: Area under curve analysis of serum bilirubin and serum alkaline phosphatase for predicting malignancy.

Variables Interval	AUC	p-Value	95% Confidence
S. Bilirubin > 16.5 mg/dl	0.824	<0.001	0.751-0.896
SAP > 455 IU/L	0.738	<0.001	0.651-0.824

AUC: Area under curve, SAP – Serum Alkaline Phosphatase

Table IV: Multivariate regression analysis of variables to predict malignancy

Variable	OR	CI	*p* Value
Age >45 years	2.364	0.899-6.218	0.081
Palpable gall bladder	20.893	4.152-105.129	<0.001
Serum bilirubin > 16.5 mg/dl	2.972	1.133-7.799	0.027
SAP > 455 IU/L	2.476	0.897-6.831	0.080

OR: Odds Ratio, CI – Confidence Interval, GB – Gall Bladder, SAP- Serum Alkaline Phosphatase

Discussion

The result of our study showed that patients with malignant EHBO have significant higher S. bilirubin and SAP as compared to patients with benign EHBO. Findings of our study are supported by other previous studies which has studied role of S. bilirubin and SAP to predict malignancy in patients with EHBO [5,6]. Malignant lesions tend to have complete obstruction compared to benign one [6] and increasing degree of biliary tract dilatation may allow stone to disimpact leading to ball valve effect that may prevent any further increase in bilirubin level [7]. This may be the probable reason for high levels of S. bilirubin and SAP in malignant EHBO. Also, patients with stone disease tend to present earlier due to associated pain or sepsis [7].

Area under the curve analysis showed S. bilirubin > 16.5 mg/dl and SAP > 455 IU/L were predictors of malignancy. Previous study done by Saluja et al.[6] has found S. bilirubin cut off of 8.4 mg/dl (AUC – 0.807) and SAP cut off of 478 IU/L (AUC- 0.624) as a predictor of malignancy. Also, other studies have found different cut off for S. bilirubin predicting malignant EHBO [8-10].

In our study patients with malignant EHBO were older as compared to patients with benign EHBO. Similar observations has been made by most of the previous studies [11-14] except one done by Kim et al.[15] Presence of cholestatic symptoms, weight loss, hepatomegaly and palpable gall bladder was more common in patients with malignant EHBO as compared to benign EHBO. In previous studies also loss of weight and cholestatic symptoms were more common in malignant EHBO [6,12,14,16]. Higher frequency of cholestatic symptoms could be explained by high severity of obstruction with malignant EHBO while higher degree of weight loss is because of the catabolic state seen in patients with malignancy. Gall bladder was palpable mostly in malignant group thus supporting the curvoisier's law as gallstones are formed over an extended period of time, resulting in a shrunken, fibrotic gall bladder which does not distend easily [12,13,17,18].

So to conclude though it is difficult to differentiate between benign and malignant EHBO various clinical and laboratory parameters can help us to predict them. In our study we comprehensively studied all the clinical and biochemical parameters to know their predictive accuracy for malignancy in patients with malignant EHBO. Patients with malignant EHBO had higher age, presence of significant loss of weight, cholestatic symptoms and palpable gall bladder. Serum bilirubin and SAP seems to be adequate laboratory parameters to predict malignancy in these patients. Patients with malignant EHBO had higher serum bilirubin and SAP as compared to benign EHBO. Serum bilirubin > 16.5 mg/dl and palpable gall bladder are independent predictors of malignancy. Based upon our results as well as previous studies on this issue it appears that no single clinical, laboratory or imaging is ideal to differentiate malignant and benign EHBO. A multimodal approach should be used in the assessment of such patients to predict malignancy.

List of abbreviations

EHBO: Extra Hepatic Biliary Obstruction
USG: Ultrasonography
CECT: Contrast Enhanced Computed Tomography
MRCP: Magnetic Resonance Cholangio Pancreatography
EUS: Endoscopic Ultrasound
CA-19-9: Cancer Antigen 19-9
ERCP: Endoscopic Retrograde Cholangio Pancreatography
FNAC: Fine Needle Aspiration Cytology
ROC: Receiver Operating Charachteristic
AUROC: Area under the ROC curve
SAP: Serum Alkaline Phosphatase
AST: Aspartate Amino Transferase
ALT: Alanine Amino Transferase

Data Availability

Readers can access the data underlying the findings of the study through online repositories

Conflicts of Interest

"The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper."

Funding Statement

Authors' contributions

"PM analyzed and interpreted the patient data He has also written the manuscript. MTN has conceptualized the study and has helped in writing the manuscript. All authors read and approved the final manuscript."

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