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		DLOGICAL SPECTRUM AND PREDICTO MALIGNANCY IN EXTRA HEPATIC BILL FRUCTION: A STUDY FROM CENTRAL IA	R ARY KEY WORDS: Extrahepatic bile duct obstruction, Bilirubin, Alkaline phosphatase			
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ABSTRACT	BACKGROUND: Etiology of extra hepatic biliary obstruction (EHBO) is often a diagnostic dilemma. Benign and malignant causes need to be differentiated as the treatment modality differs. So, we conducted a study to develop comprehensive clinical and biochemical predictors of malignancy in patients with EHBO. MATERIAL AND METHODS: Descriptive observational study of two hundred three patients diagnosed as EHBO was 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 to find predictors of malignancy. Diagnostic cut- off value was calculated using receiver operating characteristics curve to discriminate benign and malignant EHBO cases. RESULTS: On univariate analysis patients with malignant EHBO were older [57.61 ± 12.86 vs 49.93 ± 15.92 years(p value = 0.0002)], had more frequent hepatomegaly[61.33% vs 38.6%(p value <0.0001)], palpable gall bladder[91.49% vs. 8.51%(p value <0.001)], higher median serum bilirubin[15.05(9.155-22) vs. 6.2(2.45-11)mg/dl(p value <0.001)] and higher median serum alkaline phosphatase[519(338.5-725) vs. 327(211-434)IU/L(p value <0.001)]. Receiver operating characteristic curve identified total bilirubin of 8.18 mg/dL as the best cut-off value for predicting a malignant EHBO with a sensitivity of 81.0%, a specificity of 63.1% and a positive predictive value of 88.1% (area under the curve=0.777, 95% CI=0.669 to 0.795). Multivariate analysis showed age>41 years, serum alkaline phosphatase (>410 IU/L) and serum bilirubin >8.18 mg/dL to be independent predictors of malignancy. CONCLUSION: In patients with EHBO older age (>41 years), high serum bilirubin (>8.18 mg/dL) and high serum alkaline phosphatase (>410 IU/L) independently predict presence of malignancy.					
INTRODUCTION Extra Hepatic Biliary Obstruction (EHBO) is a condition in malignant biliary obstruction early diagnosis can pick up case at resectable stage. Therefore, it is important to diagnose						

which bile flow is obstructed starting from hepatic ducts up to the second part of the duodenum.¹ Jaundice due to biliary obstruction is be caused by a heterogeneous group of diseases that include both benign and malignant conditions.² Etiological spectrum of EHBO has not changed much in the last two decades. Malignant etiology is still more common than benign with carcinoma of gallbladder accounting for bulk of malignant obstruction in northern part of India, at the same time burden of CBD stone is increasing.³ The symptoms of EHBO include jaundice with or without abdominal pain, dark urine, pale stools, pruritis, weight loss, and anorexia. It is one of the common and potentially treatable forms of hepatobiliary disease. It may lead to dreaded complications like ascending cholangitis, liver abscesses and organ failure if diagnosis is delayed. Biochemically, it is characterized by elevated levels of serum alkaline phosphatase, GGT with or without elevation of direct bilirubin. Amino-transferase level may also be elevated in cholangitis.⁴Ultrasonography is firstline imaging modality, which can identify the gallstones, dilated biliary ducts, bile duct stones, masses in the abdomen, and the presence of peritoneal fluid. Ultrasound remains the first-line imaging tool for investigation of suspected biliary obstruction; however, recent advances in MRI have changed practice, and ERCP in patients with biliary disease is increasingly reserved for therapeutic purposes.⁵

Despite the advances in diagnosis and treatment modalities available, survival remains poor in malignant cases.⁶ However in benign cause like choledocholithiasis early diagnosis can be lifesaving in patients presenting with cholangitis. Likewise

and establish etiology so that appropriate treatment can be initiated.So the aim of the study was to develop comprehensive clinical and biochemical predictors of malignancy in extra-hepatic biliary obstruction. This is particularly helpful in resource limited country like India where both medical facilities and patient awareness are scarce.

MATERIALS AND METHODS

An observational descriptive study was conducted at Sri Aurobindo Medical College and Post Graduate Institute (SAMC PGI) department of Gastroenterology, Indore, Central India. SAMCPGI is a tertiary level teaching hospital engaged in both undergraduate and postgraduate teaching programs. The study included all patients of EHBO admitted from January 2020 to December 2022 in department of gastroenterology.

All patients of EHBO attending outpatient, inpatient or emergency department of our hospital were included in our study. Demographic data was collected and all patients were subjected to detailed history and clinical examination. Liver span of more than 16 cm was taken as hepatomegaly.⁷ Laboratory investigations were done including hemogram, liver function test, coagulation profile, renal function test, electrolytes, Electro cardiogram, X-ray Chest followed by abdominal ultrasonography, Contrast enhanced Computed Tomography (CECT) of abdomen, Magnetic Resonance CholangioPancreatogram and Endoscopic Retrograde Cholangio Pancreatography (ERCP). CECT was performed in

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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 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. Those patient with very large stone were referred for surgical exploration of CBD and stone removal. 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 (Piperacillin Tazobactum and Metrogyl). Antibiotics were modified later according to bile culture and sensitivity report. In case of routine ERCP procedure we used ceftriaxone to decrease the chances of bacteremia.

Data was collected from individual patient's medical records using a pretested structured data collection format. Collected data was checked for completeness, cleaned, coded, entered and analyzed with SPSS version 25, Chicago, Illinois, USA. The association of the variables which were quantitative were analyzed using Mann-Whitney Test and Independent t test. The association of the variables which were qualitative in nature were analyzed using Chi-Square test. Receiver operating characteristic curve was used to find cut off point, sensitivity, specificity, positive predictive value and negative predictive value of age, duration, serum bilirubin, ALP and CBD diameter for predicting malignancy. Univariate and multivariate logistic regression was used to find out risk factors of malignancy. P value <0.05 was considered as a statistically significant. Ethical clearance was obtained from SAMCPGI Institution Review Board (IRB).

RESULTS

Two hundred three patients of EHBO were included, 103 of those had benign cause while 100 had malignant etiology. The main causes of benign were related to stone disease (choledocholithiasis) while malignant was carcinoma gall bladder followed by periampullary carcinoma. Other causes of EHBO are shown in (figure 1).

The mean age of patients with Malignant etiology was (57.61 ± 12.86) and was significantly higher than that of patients with Benign etiology (49.93 ± 15.92) (P=0.0002). Hepatomegaly was present in 42 patients with malignant etiology compared to 11 with benign etiology (P<0.0001). Forty three patients with malignant etiology had palpable gall bladder compared to 4 patients in benign category (P<0.0001). Alkaline phosphatase and serum bilirubin were higher in malignant EHBO (compared to benign EHBO (P<0.0001).There were no significant gender differences (Table 1).

ROC analysis (table 2) identified total bilirubin of 8.18 mg/dL as the best cut-off value for predicting a malignant EHBO with a sensitivity of 81.0%, a specificity of 63.1% and a positive predictive value of 68.1% (area under the curve=0.777, SE=0.0335, 95% CI=0.706 to 0.826) and alkaline phosphatase of 410 IU/L as the best cut-off value for predicting a malignant EHBO with a sensitivity of 68.69%, a specificity of 72.82% and a positive predictive value of 70.8% (area under the curve=0.735, SE=0.0362, 95% CI=(0.669 to 0.795) (Figure 2,3).On the other hand, ROC analysis for age, duration and CBD diameter had a poor sensitivity and specificity.

The univariate analysis revealed that age, serum bilirubin, serum alkaline phosphatase, CBD diameter, hepatomegaly www.worldwidejournals.com and palpable gall bladder were associated with malignant EHBO. In the multivariate analysis (table 3), three independent factors were found to be associated with malignant EHBO: Age (OR: 1.040; 95% CI 1.010-1.070; p=0.0091), Serum bilirubin (OR: 1.051; 95% CI 1.006-1.098; p=0.022), Serum alkaline phosphatase (OR: 1.003; 95% CI 1.001-1.005; p=0.001).

DISCUSSION

The differentiation between benign and malignant biliary obstruction can be difficult but is of utmost importance in regard to prognosis and planning optimal therapy. In our study, benign causes of EHBO were found in 50.74% patients and 49.26% had malignant etiology. Most common benign cause was choledocholithiasis and malignant was carcinoma gall bladder. This study correlates with study from Amritsar which has showed benign lesions in 52% and malignant in 52% of cases, with choledocholithiasis as the commonest biliary obstruction and peri-ampullary carcinoma as malignant obstruction.⁹ A large prospective study from North India, over a 10-year period which showed that malignant obstruction was more common than benign (75.3% vs. 24.7%). Carcinoma of the gallbladder (CA GB) and common bile duct (CBD) stone were the most common causes in the malignant and benign categories, respectively. This can be explained by the fact that carcinoma gall bladder is more common in northern part of India.¹¹

Our study showed that the mean age with malignant EHBO etiology was more than benign which is consistent with studies from Nigeria, Tanzania and other region which showed the same result.^{11,12} Majority of malignant EHBO patient had hepatomegaly and palpable gall bladder thus supporting the Courvoisier's law as gallstones are formed over an extended period of time, resulting in a shrunken, fibrotic gall bladder which does not distend easily.^{13,14}

The result of our study showed that patients with malignant EHBO have significant higher serum 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 serum bilirubin and SAP to predict malignancy in patients with EHBO. 15,16,17 Malignant lesions tend to have complete obstruction compared to benign one 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. This may be the probable reason for high levels of serum bilirubin and SAP in malignant EHBO. Also patients with stone disease tend to present earlier due to associated pain or sepsis. Area under the curve analysis showed serum bilirubin > 8.18 mg/dl and SAP > 410 IU/L were predictors of malignancy. Previous study done by Saluja et al. 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.¹⁸ Other studies have also found different cut off for serum bilirubin predicting malignant EHBO.¹

So to conclude it's difficult to identify between benign and malignant cause of EHBO. Clinical and laboratory parameters guide us to predict the etiology of EHBO. In our study we comprehensively studied clinical and biochemical variables to know their predictability for malignancy in patients with malignant EHBO. Patients with malignant EHBO had higher age, hepatomegaly and palpable gall bladder. Serum bilirubin and SAP seems to be acceptable laboratory parameters to predict malignancy in these patients. Patients with malignant EHBO had elevated serum bilirubin and SAP as compared to benign EHBO. Serum bilirubin >8.18mg/dl, Alkaline phosphatase >410IU/ml and age>41 years are independent predictors of malignancy. Based upon our results as well as earlier studies on this issue it appears that no single clinical, laboratory or imaging is ideal to differentiate malignant and benign EHBO. A multimodal approach is required in the assessment of such patients to predict malignancy.

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Table 1:-Association of parameters with benign and malignant.

Parameters	Benign	Malignant	Total	P value		
Gender						
Female	51 (53.68%)	44 (46.32%)	95 (100%)	0.431†		
Male	52 (48.15%)	56 (51.85%)	108 (100%)			
Hepatomega ly	11 (20.75%)	42 (79.25%)	53 (100%)	<0.001		
Palpable gall bladder	4 (8.51%)	43 (91.49%)	47 (100%)	<0.001		
Age(years)	49.93 ± 15.92	57.61 ± 12.86	53.71 ± 14.96	0.0002‡		
Duration(mo nths)	1(0.585- 3)	2(1-3)	2(0.67-3)	0.102§		
S.Bilirubin (mg/dL)	6.2(2.45- 11)	15.05(9.1 55-22)	10(4.35-19)	<.0001§		
SAP(IU/L)	327(211- 434)	519(338.5 -725)	398.5(234- 565.75)	<.0001§		
CBD(cms)	1.4(1.1- 1.6)	1.5(1.2- 1.85)	1.5(1.2-1.7)	0.014§		

‡ Independent t test, § Mann Whitney test, * Fisher's exact test, † Chi square test. SAP- Serum alkaline phosphatase, CBDcommon bile duct.

Table 2 : Area under curve analysis of serum bilirubin and serum alkaline phosphatase for predicting malignancy

VARIABLES	AUC	PVALUE	95% CI
S.BILIRUBIN>8. 18 mg/dl	0.770	<0.001	0.706-0.826
SAP > 410 IU/L	0.735	<0.001	0.669-0.795

AUC – Area under curve, SAP – Serum Alkaline Phosphatase, CI-Confidence interval

Table 3: Multivariate regression analysis of variables to predict malignancy

VARIABLES	OR	CI	p VALUE
Age >41 years	6.577	< 0.001	0.001
Serum bilirubin >8.18 mg/dl	2.821	<0.001	0.011
SAP > 410 IU/L	2.640	< 0.001	0.017
Hepatomegaly	1.217	< 0.001	0.713
Palpable gall bladder	3.067	<0.001	0.138
CBD diameter(>1.9cm)	2.665	0.861- 8.245	0.089

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



Figure 1: Distribution of etiology of study subjects.



Figure 2: Receiver operating characteristic curve of serum bilirubin for predicting malignancy.



Figure 3: Receiver operating characteristic curve of serum alkaline phosphatase for predicting malignancy.

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