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• CLINICAL RESEARCH •

Biochemical and radiological predictors of malignant biliary strictures

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Abstract

AIM: Differentiation of benign biliary strictures (BBS) from malignant biliary strictures (MBS) remains difficult despite improvement in imaging and endoscopic techniques. The aim of this study was to identify the clinical, biochemical and or radiological predictors of malignant biliary strictures.

METHODS: We retrospectively reviewed all charts of patients who had biliary strictures (BS) on endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous cholangiography (PTC) in case of unsuccessful ERCP from March 1998 to August 2002. Patient characteristics, clinical features, biochemical, radiological and biopsy results were all recorded. Stricture etiology was determined based on cytology, biopsy or clinical follow-up. A receiver operator characteristic (ROC) curve was constructed to determine the optimal laboratory diagnostic criterion threshold in predicting MBS.

RESULTS: One hundred twenty six patients with biliary strictures were enrolled, of which 72 were malignant. The mean age for BBS was 53 years compared to 62.4 years for MBS (P=0.0006). Distal bile duct stricture was mainly due to a malignant process 48.6% *vs* 9% (P=0.001). Alkaline phosphates and AST levels were more significantly elevated in MBS (P=0.0002). ROC curve showed that a bilirubin level of 84 μmol/L or more was the most predictive of MBS with a sensitivity of 98.6%, specificity of 59.3% and a positive likelihood ratio of 2.42 (95% CI=0.649-0.810). Proximal biliary dilatation was more frequently encountered in MBS compared to BBS, 73.8% *vs* 39.5% (P=0.0001). Majority of BBS (87%) and MBS (78%) were managed endoscopically.

CONCLUSION: A serum bilirubin level of 84 μmol/L or greater is the best predictor of MBS. Older age, proximal biliary dilatation, higher levels of bilirubin, alkaline phosphatase, ALT and AST are all associated with MBS. ERCP is necessary to diagnose and treat benign and malignant biliary strictures.

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INTRODUCTION

Biliary stricture (BS) may result from an intra or extra-luminal benign or malignant process. Although history, laboratory investigations and imaging techniques may help to differentiate benign from malignant biliary strictures, it remains a clinical challenge. Endoscopic retrograde cholangiopancreatography (ERCP) has been considered the method of choice for the diagnosis of BS as a result of its accuracy in establishing the site and cholangiographic features of stricture[1]. Cytology specimens can be obtained, which has a sensitivity rate of only 35% but a specificity rate approaching 100% for the diagnosis of malignancy[2].

Recently, new imaging techniques with increased diagnostic yield have emerged. For instance, magnetic resonance cholangiopancreatography (MRCP) as a non-invasive method has similar or even better diagnostic yield with the advantage of avoiding complications of ERCP[1,3,4]. Also, with the advent of multislice CT (MS-CT), it has been possible to detect minute biliary and pancreatic tumours as well as small lymph nodes and vessels[5]. MS-CT cholangiography has become valuable in pre-operative evaluation and determining unresectability[6]. Therefore, CT has maintained as the method of choice for pancreatic and biliary tumours imaging[7,8]. Furthermore, intraductal ultrasonography (IDUS) has been valuable in the differentiation of MBS from BBS. It has increased the accuracy of ERC-tissue sampling, but it has not been suitable for staging lymphadenopathy-associated MBS[8].

The aim of this study was to identify the clinical, biochemical and or radiological predictors of malignant biliary strictures.

MATERIALS AND METHODS

All patients with biliary strictures from March 1998 to August 2002 who had ERCP or PTC in case of unsuccessful ERCP were included. Demographic characteristics, presenting features, laboratory data, imaging technique findings and management modalities were analyzed.

Definition of biliary strictures was suggested by cholangiographic features and it was supported by brush cytology, fine needle aspiration (FNA), the presence of mass or metastases by imaging and or clinical follow-up.

ERCP was performed by three experienced gastroenterologists using 4.2 mm channel duodenoscopes (Pentax or Olympus). All patients received diazepam and demerol as premedication. In addition, patients with biliary dilatation received cefuroxime prophylaxis. Endoscopic and cholangiographic findings were recorded.

Biopsy and brushing materials were obtained when feasible, strictures dilated with balloon or Soehendra dilator and large 10-12 F stent inserted.

Data collected were entered into the computer using Microsoft Excel. After all data were checked for completeness, statistical analysis was performed using Stat Pac gold analysis software and Microsoft Excel programs. Two-tailed P values of less than 0.05 were considered statistically significant. A receiver operator characteristic (ROC) curve was constructed

to determine the optimal laboratory diagnostic criterion threshold (*i.e.* total bilirubin, ALT, AST and alkaline phosphatase) in predicting a malignant biliary stricture. A ROC curve displayed the false positive rate on the x axis (specificity), and the true positive rate on the y axis (sensitivity) for varying test thresholds, thus plotting the performance of a diagnostic test[10]. The ideal cut-off criteria for the laboratory results were chosen by determining the point lying geometrically closest to an ideal test with 100% specificity and sensitivity[11].

RESULTS

One hundred twenty six patients were included, 54 of those had a BBS while 72 had a MBS. The main causes of BBS were related to stone disease (choledocholithiasis, Mirizzi syndrome or postcholecystectomy). In 22 patients the cause could not be identified. Cholangiocarcinoma and pancreatic head carcinoma were the most common causes of MBS. Other causes of BS are shown in Table 1.

The mean age of patients with MBS (62.4±11.7 years) was significantly higher than that of patients with BBS (53±18 years) (P=0.0006). Fifty percent of BBS were proximal (P=0.01) and approximately 50% of MBS were distal (P<0.001). There were no significant gender differences (Table 2). Jaundice was found in more than 80% of patients with BBS and MBS, and right upper quadrant (RUQ) pain in 50% of patients. Anorexia, weight loss and fever were less common and no significant differences were observed when both groups were compared (Table 3).

Table 1 Causes of biliary strictures (n=126)

Benign	*n*	%	Malignant	*n*	%
Choledocholithiasis	12	22	Cholangiocarcinoma	31	43
Mirizzi syndrome	7	13	Pancreatic head CA	23	32
Postcholecystectomy	6	11	Ampullary CA	5	7
Sclerosing cholangitis	3	5.5	Gallbladder CA	5	7
Choledochal cyst	2	3.7	Metastatic CA	4	5.5
Chronic pancreatitis	1	1.9	Hepatocellular CA	2	2.7
Juxtapapillary diverticulum	1	1.9	Lymphoma	2	2.7
Non-specified	22	40.7			
TOTAL	54		TOTAL	72	

Table 2 Demographic data of patients with biliary strictures (n=126)

	Benign	Malignant	*P* value
Number of patients	54 (%)	72 (%)	
Mean age	53±18	62.4±11.7	0.0006
Males	25 (46)	41 (56.9)	0.2255
Females	29 (54)	31 (43.1)	0.2255
Sites of biliary stricture			
Proximal	27 (50)	20 (27.7)	0.0107
Middle	22 (41)	17 (23.6)	0.0394
Distal	5 (9)	35 (48.6)	<0.001

Table 3 Presenting symptoms of patients with biliary strictures (n=126)

	Benign *n*=54 (%)	Malignant *n*=72 (%)	*P* value
Jaundice	44 (81)	61 (84.7)	0.5884
RUQ pain	27 (50)	38 (52.8)	0.7561
Weight loss	4 (7)	11 (15.3)	0.1326
Fever	3 (5)	7 (9.7)	0.3066
Anorexia	4 (7)	7 (9.7)	0.5843

Mean serum values of bilirubin, alkaline phosphatase, ALT and AST were significantly higher in patients with MBS. However GGT levels were not significantly different in both groups (Table 4).

As shown in Table 5 and Figure 1, ROC analysis identified total bilirubin of 84 umol/L as the best cut-off value for predicting a malignant biliary stricture with a sensitivity of 98.6%, a specificity of 59.3% and a positive likelihood ratio of 2.42 (area under the curve=0.735, SE=0.044, 95% CI=0.649-0.810). On the other hand, ROC analysis showed that other laboratory tests including ALT, AST and alkaline phosphates to have a poor sensitivity and specificity.

Proximal biliary dilatation was more frequently encountered in MBS compared to BBS, 73.8% *vs* 39.5% (P=0.0001). Majority of patients, 87% of BBS and 78% of MBS were treated endoscopically.

Table 4 Laboratory data of patients with biliary strictures (n=126)

	Benign *n*=54	Malignant *n*=72	*P* value
Total bilirubin (umol/L)	142.6±98.4	184.61±120.8	0.0389
Direct bilirubin (umol/L)	102.4±95.3	138.10±98.5	0.0433
Alkaline phosphatase (IU/L)	108.5±48.5	145.50±57.5	0.0002
GGT (IU/L)	397.0±496.5	436.50±325.1	0.591
ALT (IU/L)	52.7±38.3	66.94±35.6	0.0339
AST (IU/L)	76.5±43.2	107.80±45.7	0.0002

Table 5 Receiver operator characteristic (ROC) test results in predicting malignant biliary strictures

Parameter	Cut-off value	Sensitivity (%)	Specificity (%)	+LR	-LR
Total bilirubin (umol/L)	84	98.6	59.3	2.42	0.02
Direct bilirubin (umol/L)	63	91.7	61.1	2.36	0.14
Alkaline phosphatase (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

+LR=positive likelihood ratio; -LR=negative likelihood ratio.

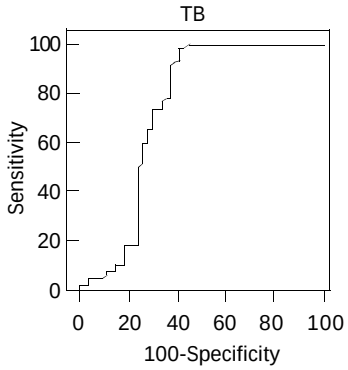

Figure 1 ROC analysis of total bilirubin.

DISCUSSION

The differentiation between benign and malignant biliary strictures can be difficult but is of obvious importance in regard to prognosis and planning optimal therapy.

In our study, majority of patients with BS presented with obstructive jaundice and half had right upper quadrant pain. Other less frequent symptoms included anorexia, weight loss and fever. In contrast to Tandon *et al*[12], who have encountered more anorexia and weight loss in MBS, we found no significant difference between MBS and BBS. This could be due to the early stage at presentation in our patients.

In our study, although statistically significant differences were found in most biochemical parameters, bilirubin was the best predictor of malignant biliary stricture. A serum bilirubin level of 84 μmol/L or greater was highly predictive of malignant biliary stricture with a sensitivity of 98.6%, a specificity of 59.3% and a positive likelihood ratio of 2.42. Furthermore, proximal biliary dilatation was more frequently encountered in MBS compared to BBS, 73.8% *vs* 39.5% (P=0.0001). Similarly, in a prospective study of 29 patients, Bain *et al*. have shown that a bilirubin of level of 75 μmol/L or greater or a stricture length of greater than 14 mm was highly predictive of malignant biliary stricture. In the same study, intrahepatic duct dilatation was present in 93% of malignant strictures versus 36% of BBS (P=0.002)[13].

In our study, we found that distal bile duct strictures were mainly due to a malignant process, 48.6% *vs* 9% in BBS (P<0.001), which is contrary to other studies. This is probably because we have rarely encountered BBS secondary to chronic pancreatitis which is commonly present with distal benign BS (we had only one patient).

ERCP remains to be an important imaging technique in the diagnosis and treatment of obstructive jaundice[14]. The yield of ERCP in differentiating MBS from BBS can be further improved with tissue sampling. Sensitivity of biliary fluid and brushing cytology is unsatisfactorily low. It can be improved by combining fine needle aspiration biopsy with intraductal forceps biopsy. This method has been known as triple tissue sampling[15,16]. Despite the triple tissue sampling, the sensitivity and negative predictive value have not exceeded 62% and 39%, respectively[16]. Furthermore, brushing cytology yield could be improved by stricture brushing after a 10 F dilatation of malignant stricture[17]. Similar observation on improvement of bile cytology has been reported earlier by Mohandas *et al*[18]. Evaluation of cytology specimens for aneuploidy and tumour markers, CA 19-9 and CEA might also increase the diagnostic yield[19].

Recently, intraductal ultrasonography (IDUS) has been evaluated in the differential diagnosis of MBS from BBS with conflicting results. While Gress *et al*. have not found reliable differentiation criteria[20], Inui *et al*. and Tamada *et al*., who used special biliary and pancreatic probes, have provided encouraging results[21,22]. However, its accuracy is still not exceeding 80%. IDUS has been reported to be superior to conventional endoscopic ultrasonography in terms of diagnostic accuracy, and prediction of tumour respectability[23].

Treatment of BS depends on the etiology, benign or malignant, magnitude of damage in post-surgical injuries and prediction of respectability of MBS. Endoscopic management of BBS has been considered the primary method before the decision of surgical intervention[24]. Major bile duct injuries require surgical construction. After initial evaluation of anatomy by direct cholangiogram and inserting a biliary drain, surgical reconstruction with Roux-en-Y hepaticojejunostomy has been associated with an overall success rate exceeding 90%[25]. It has been considered as the best treatment modality of BBS[26]. On the other hand Born *et al*. have considered endoscopic or percutaneous management as an adequate short and long-term alternative to surgery[27].

The decision of therapeutic modality for biliary or pancreatic tumours depends on the evaluation of respectability. It is important to determine preoperatively the spread of MBS. These events may help decide the appropriate treatment for each condition. Surgery has to be considered for the management of resectable tumours. However, at the time when the diagnosis of MBS has been established, it is often late for curable resection[28]. Therefore, endoscopic approach remains the method of choice for palliation. Majority of our patients (78%) had endoscopic palliation.

In a large series with 505 patients, Costamagna *et al*. strongly suggested ERCP in the diagnosis and palliation of all patients with suspected MBS[29]. ERCP has been considered as the optimal technique for diagnosis and palliation of MBS[30].

In conclusion, a serum bilirubin level of 84 μmol/L or greater is the best predictor of MBS. Older age, proximal biliary dilatation, higher levels of bilirubin, alkaline phosphates, ALT and AST are all associated with MBS. ERCP is the best imaging technique in demonstrating stricture and biliary dilatation, and remains the method of choice in managing BBS and MBS.

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