

Risk Factors for Development of Biliary Stricture in Patients Presenting with Bile Leak after Cholecystectomy

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Background/Aims: This study was aimed at determining the factors associated with the development of benign biliary stricture (BBS) in patients who had sustained a bile duct injury (BDI) at cholecystectomy and developed bile leaks.

Methods: A retrospective analysis of 214 patients with BDI who were referred to our center between January 1989 and December 2009 was done. **Results:** One hundred fifty-three (71%) patients developed BBS (group I), and 61 (29%) were normal (group II). By univariate analysis, female gender ($p=0.02$), open cholecystectomy as the index operation ($p=0.0001$), delay in the referral from identification of injury ($p=0.04$), persistence of an external biliary fistula (EBF) beyond 4 weeks ($p=0.0001$), EBF output >400 mL ($p=0.01$), presence of jaundice ($p=0.0001$), raised serum total bilirubin level ($p=0.0001$), raised serum alkaline phosphatase level ($p=0.0001$), and complete BDI ($p=0.0001$) were associated with the development of BBS. Furthermore, open cholecystectomy as the index operation ($p=0.04$), delayed referral ($p=0.02$), persistent EBF ($p=0.03$), and complete BDI ($p=0.001$) were found to predict patient outcome in the multivariate analysis. **Conclusions:** For the majority of patients with BDI, the risk of developing BBS could have been predicted at the initial presentation. (*Gut Liver* 2013;7:352-356)

Key Words: Cholecystectomy; Bile ducts; Injuries

INTRODUCTION

Iatrogenic bile duct injury (BDI) is a major complication occurring in 0.2% to 0.3% of open cholecystectomies. With laparoscopic cholecystectomy, this incidence has risen to 0.5%.¹⁻³ The BDI can vary in severity from minor injuries like bile leaks

from the gall bladder bed to major injuries like complete transection of the common bile duct. Some of these injuries resolve while others develop benign biliary stricture (BBS). The 30% to 61% of patients with BDI eventually develop BBS requiring intervention.⁴⁻⁶ The differentiation between a major and a minor BDI is difficult⁴ at initial presentation making the prognostication difficult at presentation. Identification of the factors which predict the development of BBS at presentation is important in the overall management of BDI. The aim of the present study is to identify the factors associated with the development of BBS in patients who sustain BDI during cholecystectomy.

MATERIALS AND METHODS

This study is a retrospective analysis of a prospectively maintained data in a tertiary referral hospital in northern India. All patients referred to our department between January 1989 and December 2009 with postcholecystectomy BDI were considered for the study. Patients with complete bile duct ligation/clipping without bile leak and well formed BBS referred for definite repair were excluded.

At presentation, information regarding the cholecystectomy (preoperative symptoms, indication for cholecystectomy, preoperative evaluation, operative details, intraoperative complications, and postoperative events) was gathered by reviewing the medical records, interviewing the patient, and by discussing with the surgeon who operated whenever deemed necessary. All patients had an ultrasonography (USG) of abdomen. Contrast enhanced computed tomography of the abdomen, endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), fistulogram, and mebrofenin nuclear scintigraphy were carried out on a case to case basis. Patients were divided into four groups based on the initial presentation—

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external biliary fistula (EBF), biloma, bile peritonitis, and bile ascitis. Patients presented with controlled EBF were managed expectantly. Bile leaks and collections inside the abdomen were controlled with percutaneous drainage, percutaneous transhepatic biliary drainage (PTBD), ERC and stenting or laparotomy as required. All efforts were made to convert the internal bile leak into controlled EBF. BDI were classified into complete or partial depending on the operative details, findings on the fistulogram, mebrofenin scintigraphy, and ERC. All the patients who presented within 24 hours with complete operative information of bile duct transection were offered immediate repair (Roux-en-Y hepaticojejunostomy). Immediate surgical repair was not attempted in the rest of the patients. Patients with EBF were managed expectantly for a minimum period of 6 weeks to control the inflammation and infection prior to the planned definite management. Patients were evaluated with cholangiogram (ERC, PTC, or MRC) before the planned repair. We grouped patients into normal (group I) and BBS (group II) depending on the findings on liver function test (LFT), USG, mebrofenin nuclear scintigraphy, and/or cholangiogram. The criteria for group I were normal LFT, no dilatation of intrahepatic radicals on USG, normal mebrofenin scan and or normal cholangiogram. Definite repair of EBF was carried out in patients with EBF with no tendency for spontaneous closure and these patients were included in the BBS group for analysis.

Various factors at initial presentation in group I and group II were compared to determine the predictors for the development of BBS. Statistical analysis was done by SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as percentage, mean, median, and range. Univariate analysis was done by Student's t-test for continuous variables and chi-squared test for categorical variables. Multivariate analysis was done by logistic regression. Risk assessment was done by calculating the odds ratio.

RESULTS

Over a period of 21 years, 626 patients were referred with

postcholecystectomy BDI. Among them, 337 were referred with BBS for definite repair and were excluded from this analysis. Two hundred eighty-nine patients were referred with acute BDI with bile leak, of which two underwent immediate repair and hence excluded from the study. Of the remaining 287 patients, follow-up information was available in 214 and the data was analyzed. There were 141 (66%) females and 73 (34%) males. Median age was 40 years (range, 12 to 74 years). The median cholecystectomy referral interval was 19 days (range, 1 to 225 days).

1. Presentation

One hundred seventeen (55%) patients were referred after elective cholecystectomy, 17 (8%) after emergency cholecystectomy and in 80 (37%) patients the indication for cholecystectomy was not clear. One hundred forty-eight (69%) patients underwent open cholecystectomy (nine patients underwent a concomitant choledocholithotomy as well) and 66 (31%) underwent laparoscopic cholecystectomy. Ten patients were referred after laparoscopic converted to open cholecystectomy and were included in the laparoscopic group because it is presumed that the reason for conversion was an intraoperatively detected BDI. Cholecystectomy was recorded as difficult in 75 (35%) patients. BDI was detected intraoperatively in 25 (12%) patients and attempt to repair was done in 14 (7%). Eighty-six patients underwent intervention for BDI before referral to our centre. Among these, 46 patients had open surgical intervention, three had laparoscopic drainage, 25 had percutaneous radiological intervention, and 12 had endoscopic intervention.

The initial presentation in 214 patients with BDI is shown in Fig. 1. Median time for development of EBF was 1 day (range, 0 to 40 day), and the median fistula output was 400 mL/day (range, 15 to 1,000 mL/day). At presentation, 92 (42%) patients had jaundice, 61 (28%) had pallor and 79 (36%) had fever. Median hemoglobin was 10.2 g/dL (range, 4.8 to 15.0 gm%), median total leucocyte count was 9,800 cells/mm³ (range, 4,700 to 32,000 cells/mm³), median total bilirubin was 1.4 mg/dL (range, 0.2 to 27.4 mg%), median alkaline phosphatase was 349 IU/mL (range,

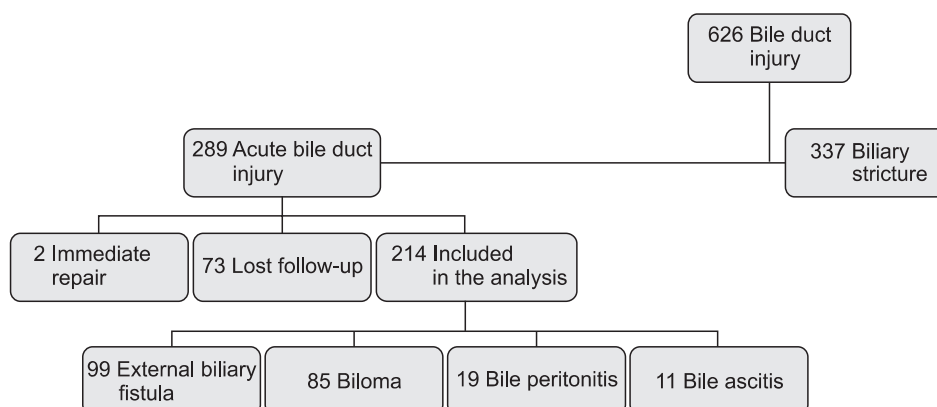


Fig. 1. Initial presentation of patients with bile duct injury.

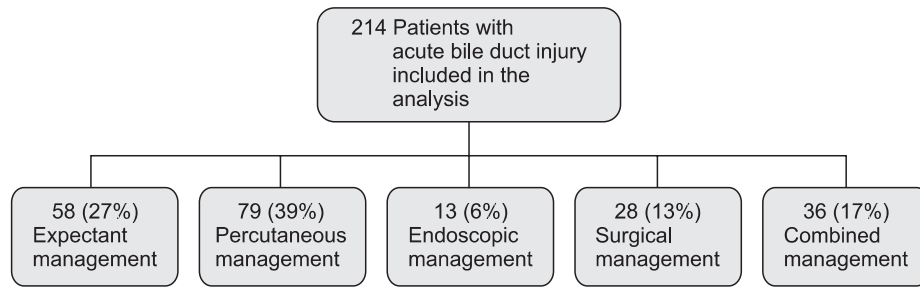


Fig. 2. Initial management and outcome of patients with acute bile duct injury.

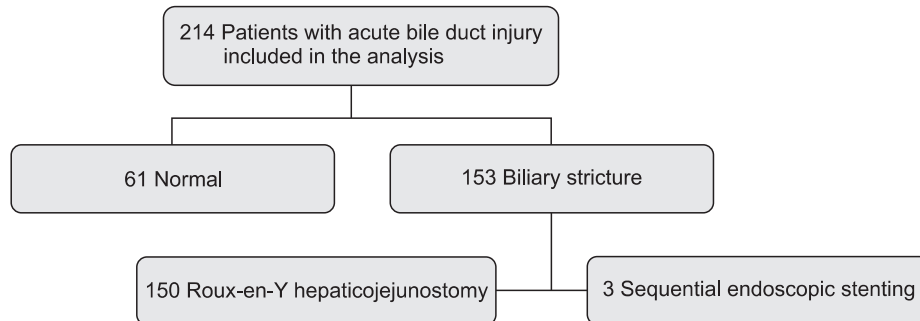


Fig. 3. Final outcome of patients with acute bile duct injury.

37 to 2,330 IU/mL), and median prothrombin time was 14 seconds (range, 9 to 68 seconds).

2. Initial management

In all patients, the initial management focused on controlling the bile extravasation and treating sepsis. Fistulogram was done in 49 (23%) patients through EBF demonstrating BDI in 28 (57%) patients. The study was inconclusive in the rest. Mebrofenin nuclear scintigraphy was done in 85 (40%) patients to demonstrate the bile flow into the gastrointestinal tract if any and 42 (20%) patients were found to have activity in the gastrointestinal tract on mebrofenin scan denoting a partial BDI. ERC was done in 72 (33%) patients which revealed complete BDI in 32 (44%) patients, partial BDI in 38 (53%), and normal cholangiogram in two (3%) patients. Contrast leak from the cystic duct was demonstrated in 20/38 patients and common bile duct stones were found in 4/38 patients. All 38 patients with partial BDI underwent stenting. PTBD was required in 22 (10%) patients to manage cholangitis or bile leak. Forty-six (21%) patients required operation: 27 (59%) patients underwent open lavage, three had laparoscopic lavage, and nine had tube hepaticostomy/T-tube drainage. Based on these investigations, overall 83 (39%) patients were found to have partial BDI, 114 (53%) had complete BDI and BDI could not be classified in 17 (8%) patients. The initial management of patients with BDI is shown in Fig. 2.

3. Follow-up

The EBF resolved in 129 (60%) patients with in 4 weeks of intervention for bile leak, and in 85 (40%) patients EBF persisted. During median follow-up period of 15 months (range, 6 to 98 months), 61 (29%) patients were defined as normal final

outcome and the remaining 153 (71%) patients developed BBS (type I in 3, type II in 51, type III in 50, type IV in 10, and type V stricture in 12 patients) with median follow-up duration of 2 months (range, 1 to 68 months). Three patients underwent sequential endoscopic dilatation and stenting and the remaining 150 patients underwent Roux-en-Y hepaticojejunostomy. Of the 150 patients 18 underwent repair in the presence of persistent EBF. The outcome of patients with acute BDI is summarized in Fig. 3.

Various factors associated with the development of BBS were analyzed to find out the risk factors for the development of BBS and the results are given in Table 1.

DISCUSSION

In patients with BDI, treating the sepsis and controlling the bile leak is the priority at presentation. As BBS is the most important sequelae of BDI, further strategies are directed to detect the development of BBS and its definite management. Identifying the high risk group for the development of BBS in the post injury setting would help in planning the evaluation and management in patients with BDI. Although several factors at presentation are presumed to be associated with the development of BBS, the available evidence from the published literature widely varies⁴ because of the less number of patients studied. In our study we tried to identify the factors at initial presentation of BDI that predict the risk of future BBS. The development of BBS was higher (71%) in our series compared to others which included patients with BDI presenting with minor bile leaks.^{5,6} This is possibly due to a referral bias as most of the minor BDI would have resulted in a referral to the gastroenterologist/en-

Table 1. Factors Associated with the Development of Biliary Stricture in Patients with Postcholecystectomy Bile Duct Injury (n=214)

Variable	Group I normal (n=61)	Group II benign biliary stricture (n=153)	Univariate analysis, p-value	Multivariate analysis, p-value	OR (95% CI)
Sex, female	33 (54)	108 (70)	0.02	0.07	1.2 (1-1.5)
Open cholecystectomy	28 (46)	120 (78)	0.0001	0.04	1.6 (1.2-2.1)
Emergency cholecystectomy	8 (17)	9 (10)	0.237	-	-
Difficult cholecystectomy	26	49	0.486	-	-
Intraoperative detection of bile duct injury	9 (19)	16 (15)	0.586	-	-
Intraoperative repair of bile duct injury	6 (10)	8 (5)	0.203	-	-
Prereferral procedure	26 (43)	60 (39)	0.646	-	-
Presentation					
EBF	37 (62)	104 (68)	0.381	-	-
Biloma	31 (51)	66 (43)	0.308	-	-
Bile ascites	5 (8)	10 (7)	0.645	-	-
Bile peritonitis	3 (5)	16 (10)	0.198	-	-
Referral delay, day	13 (0-225)	21 (0-730)	0.04	0.02	2.1 (1.1-3.9)
External biliary fistula output, mL/day	200 (20-800)	400 (15-1,000)	0.01	0.11	2.7 (1.1-6.9)
Jaundice at presentation	15 (25)	77 (52)	0.0001	0.46	3.3 (1.6-6.4)
Bilirubin, mg%	0.9 (0.1-8.3)	1.6 (0.1-27)	0.0001	0.5	2.1 (1.1-4.1)
Serum alkaline phosphatase, IU/mL	246 (37-1,339)	385 (69-2,330)	0.0001	0.25	2.4 (1.2-4.7)
Complete bile duct injury	7 (11)	107 (77)	0.0001	0.001	24.3 (10.1-58.9)
Persistent (>4 wk) external biliary fistula	12 (21)	73 (50)	0.0001	0.03	1.3 (1.1-1.6)

Data are presented as number (%) or median (range). Factors significant on univariate analysis were taken for multivariate analysis. A $p < 0.05$ was considered significant.

OR, odds ratio; CI, confidence interval; EBF, external biliary fistula.

doscopist.

In our experience, women with BDI were at higher risk for development of BBS than men. A Swiss survey which was done to identify the risk factors for BDI found that male gender was an independent risk factor for BDI during laparoscopic cholecystectomy (LC).⁷ In our patients difficult cholecystectomy was documented in 75 (35%) patients and this was not predictive of development of BBS.

About one third of injuries can be recognized intraoperatively during LC.^{8,9} Though 69% of injuries referred to us were following open cholecystectomy, injury was identified intraoperatively in 25 (12%) patients only and in 14 of 25 (56%) an attempt was made to repair the injury by the surgeon before referral. Stewart and Way¹⁰ found that intraoperative repair by primary surgeon was successful in only 20% of injuries. The proportion of major injuries among all BDI ranges from 30% to 61%.³⁻⁶ Even after identifying the BDI, 40% of primary surgeons attempt to manage the patients themselves delaying referral to the tertiary care center. Referral delay of more than 3 weeks was predictive of major injury and subsequent formation of stricture in our experience. This delay along with the tendency for minor BDI to resolve spontaneously might have contributed to the higher proportion of major BDI and BBS in our series.

The reported incidence of BDI is higher during laparoscopic

cholecystectomy compared to open cholecystectomy.^{1,4,11} But in our series, open cholecystectomy is found to be a risk factor for BBS. This might be due to the preferential option of open cholecystectomy for difficult cases of gall stone disease by peripheral surgeons. Laparoscopic cholecystectomy became common in this region only after 2005. As this series included patients operated from 1988, majority of cholecystectomies were open and were performed by peripheral surgeons. As laparoscopic cholecystectomies are performed in hospitals with more expertise and facilities, the incidence of BDI as well as the proportion of patients referred after BDI following laparoscopic cholecystectomy might be lesser. This has been observed previously by our group as well as by other groups from India.^{12,13} But this scenario is likely to change as more and more cholecystectomies are being performed laparoscopically.

In our study, the mode of presentation of bile leak (EBF, biloma, biliary ascites, and biliary peritonitis) did not predict the development of BBS. The mode of presentation of BDI to a referral centre depends on the time of recognition and the early management offered before referral. Adequately managed patients usually present with controlled EBF and biliary peritonitis usually indicates failure to recognize BDI and inadequate early management. High EBF output and the persistence of EBF were found to be risk factors for the development of BBS. Both these

factors indicate major BDI. The incidence of jaundice at presentation in patients with BDI ranges from 15% to 49%.^{13,14} The overall incidence of jaundice at presentation in our series was 42%. Biliary obstruction in patients with bile leak as evidenced by the presence of jaundice, raised serum bilirubin and/or alkaline phosphatase was found to be a risk factor for the formation of BBS in our series. The development of biliary obstruction in patients with EBF mostly indicates formation of stricture. The risk of development of BBS was higher in patients with complete BDI and this can be explained logically. Still 6% of our patients who had experienced complete bile duct injury did not develop benign biliary stricture. Similar finding was observed by others also.¹⁵

All BDI should be referred to expert centers for proper evaluation and management. Surgeons who opt to manage BDI by themselves should be aware of the risk factors for the development of BBS even if the sepsis and the bile leak are controlled. In majority of patients who sustain BDI, the risk of development of BBS can be predicted at the initial presentation. Identification of a risk group for BBS at initial presentation would help in selecting patients for intense follow-up.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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