Factors Associated with Adverse Outcomes after Surgical Repair of Bile Duct Injury

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Abstract

**Background:** Bile duct injury management requires skill of experienced surgeons at referral centers. Multiple factors may alter their outcomes.

**Methods:** We retrospectively evaluated our results following bile duct injury surgery repair in from 01/2008 to 10/2015.

**Results:** 45 patients (62.2% female mean age 40.7 years) were evaluated. Most of them (57.8%) underwent open cholecystectomy as initial surgery. 80% of bile duct injury was diagnosed postoperatively. Median referral time was 3 weeks. Early repair was performed in 71.1%. Most common lesion was Amsterdam type D (44%) and Bismuth-Strasberg E4 (33%). Biliary leak occurred in 8.9%, bilioenteric stricture in 6.7% and recurrent cholangitis in 13.3% with one death. There was an 82.2% treatment success rate (McDonald classification). Risk factors for different biliary complications were: (univariate analysis) age > 46 years, previous bilioenteric repair, preoperative and postoperative high alkaline phosphatase, high Bismuth-Strasberg lesions and biliary stents. Age > 46 years was a significant risk factor in multivariate analysis.

**Conclusions:** There are possible risk factors that might influence efficacy and safety outcomes in bile duct repair surgery.

Keywords

Bile duct injury, Cholecystectomy, Biliary, Surgical repair, Hepaticojejunostomy, Complications

Introduction

Bile Duct Injury (BDI) during cholecystectomy is a complex and serious complication. The incidence of BDI following Laparoscopic Cholecystectomy (LC) and/ or Open Cholecystectomy (OC) ranges from 0.3-1.4%, depending on the study population and criteria used to define the injury [1-3]. BDI causes short and long-term morbidity, prolongs hospital stay, necessitates additional interventions and might impair quality of life [4,5].

The management of patients who suffered a BDI stands out as a surgical challenge, requiring the skills of experienced hepatobiliary surgeons at a tertiary referral center [6-9]. Several issues regarding the surgical management of BDI remain controversial. Advances in operative technique and postoperative care have resulted in

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a substantial decrease of morbidity associated with BDI repair. However, despite improvements in clinical management of patients undergoing BDI repair, postoperative complications remain frequent.

Previous studies have reported successful outcomes after BDI repair surgery in 75-98% of patients in major institutions [10-18]. Multiple factors may alter the outcome, including time of repair, associated sepsis, and vascular injury, level of injury and use of anastomotic stenting or transhepatic biliary tubes [10-15]. Outcome may be also altered whether patients are referred after a prior bilioenteric anastomosis compared with surgical management at a tertiary center [16]. Referral pattern and timing of referral might affect the outcome after BDI repair surgery [10,16-18]. Herein, we analyzed our surgical results for BDI repair in order to identify factors associated with their outcomes (morbidly and follow-up).

Methods

A retrospective review of medical records of patients who sustained a BDI (transection/stricture) between January 2008 and October 2015 referred to our unit was performed, given a previous approval of the institutional ethics and research committee. BDI repair surgery after total or major transection of the common bile duct, common hepatic duct or major segmental ducts was included in the study. Bilioenteric reconstruction surgery for postoperative bile duct strictures following LC and/or OC, bile duct exploration, or injury to the biliary tree in another surgery was also included. Minor leaks from cystic duct or gallbladder fossa, bile duct strictures from chronic pancreatitis, gallstones, sphincter of Oddi stenosis, or primary sclerosing cholangitis were excluded. Demographic data and laboratory preoperative parameters were recorded.

Preoperative management

Data gathered from the referral note included initial procedure performed (LC, OC or other) and moment in which BDI was diagnosed (preoperatively or postoperative). Referral was categorized as primary if no previous intervention was performed prior to referral and secondary if either any radiological, endoscopic or surgical procedure was performed prior to referral [18]. Time of referral was collected and time of repair was defined as early if BDI repair was carried out less than 6 weeks after first surgery and late if BDI repair was carried out more than 6 weeks after surgery [10,17,18]. Delayed repair was considered if BDI repaired 6 weeks after surgery and a previous surgical or endoscopical intervention was performed previously [17,18].

Classification of the injury

BDI were classified according to the initial lesion using Amsterdam Academical Medical Center classification [19] and combined Bismuth-Strasberg classification to determine level of injury [20,21]. Both classifications are displayed in Table 1.

Surgical management and technique

Patients underwent BDI repair when: i) Absence of biloma was documented by imaging techniques (ultrasound/computed tomography); ii) Adequate anatomical imaging was obtained by either magnetic resonance cholangiography and/or ERCP when feasible; iii) Absence of sepsis, cholangitis and organ failure.

The standard surgical treatment was an end-to-side 40-60 cm hepaticojejunostomy with cephalic dissection until healthy gross macroscopic biliary duct was reached and cannulation of right and left hepatic ducts for identification purposes was performed. Division of the hilar plate was performed when needed. Independent anastomosis of the right and left duct were performed if no biliary junction was available. Intrahepatic anastomosis by partial resection of segment IV was performed if no extrahepatic ducts were identified. All anastomosis were performed with either 4-0 and/or 5-0 hydrolyzable monofilament sutures [22]. A transhepatic silastic catheter (8 Fr) was introduced to the ductal lumen, exteriorized through the hepatic dome and abdominal wall while

<table>
<thead>
<tr>
<th>Amsterdam Academical Medical Center</th>
<th>Bismuth-Strasberg</th>
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<tr>
<td>Type</td>
<td>Description</td>
</tr>
<tr>
<td>A</td>
<td>Cystic duct leaks or leakage from aberrant or peripheral hepatic radicles</td>
</tr>
<tr>
<td>B</td>
<td>Major bile duct leaks with or without concomitant biliary strictures</td>
</tr>
<tr>
<td>C</td>
<td>Bile duct strictures without bile leakage</td>
</tr>
<tr>
<td>D</td>
<td>Complete transection of the duct with or without excision of some portion of the biliary tree</td>
</tr>
<tr>
<td>E</td>
<td>Involvement of aberrant right hepatic duct alone or with concomitant stricture of the common hepatic duct</td>
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</table>
distal tip of the catheter was placed in the intestinal lumen in selected cases according to previously published recommendations [15]. In some instances, a transanastomotic silastic tubes (neither transhepatic nor jejunal loop exit) stenting the remnant bile ducts were placed. Jejunal limb was anastomosed side-to-end with the bile duct, in standard fashion using 3-0 hydrolysable monofilament suture. Two closed suction drains were left in place until absence of biliary leak was determined following patient oral intake and they were closed and kept in place one month afterwards. The same attending surgeon performed all procedures.

**Outcome**

Morbidity was divided in biliary and nonbiliary complications using Clavien-Dindo classification of surgical complications [23]. Patient follow-up were stratified according to MacDonald’s classification outcome of BDI repair [24]. This classification grades results from A to D according to liver function tests, clinical symptoms including cholangitis and treatment revision. Grades A and B are considered treatment success.

**Statistical analysis**

Continuous variables statistics are described by mean, standard deviation and range; and categorical variables in frequencies and percentage. Univariate analysis was carried out using student T-test and/or U Mann-Whitney test if variables were parametric and non-parametric accordingly. Chi-square and/or Fisher exact test were used for univariate categorical analysis and binary logistic regression for multivariate analysis. A p-value less than 0.05 was considered statistically significant. SPSS software v.21 (Chicago, IL, USA) was used for statistical analysis.

### Results

**Patient characteristics, management, presentation and preparation**

Forty-five (n = 45) patients were included in the study. Mean age was 40.7 ± 15.3 years (14-79 range) with a median age of 45 years. Twenty-eight (62.2%) were female and 17 were male. Female/male ratio of 1.64. OC was the initial surgery in 26 patients (57.8%), 17 patients (37.8%) underwent LC and two patients (4.4%) other initial procedures (liver/bile duct trauma in 1 patient and one liver tumor resection, both open procedures).

Nine (20%) BDI were recognized during initial surgery and 80% (n = 36) were diagnosed postoperatively. Thirteen patients (28.9%) were primary referred (no previous intervention) and 32 patients (71.1%) were secondary referred. The most common procedure prior to referral was relaparotomy, drainage without repair in 18 patients (40%). Fifteen patients (33.3%) underwent a second relaparotomy after initial surgery and six patients (13.3%) underwent two additional relaparotomies (Table 2).

Median time of referral to our service was 3 weeks with a mean time of 10.4 ± 37.4 weeks (0-250 range). Thirteen patients (28.9%) were referred and underwent biliary reconstruction within one week of referral. Twenty-eight patients (62.2%) had their reconstruction performed during same admission of initial surgery. Early repair was performed in 32 patients (71.1%), late repair in seven patients (15.6%) and delayed repair in six patients (13.3%).

Biochemical parameters at referral and admission to our service evidenced that 22% of patients (n = 10) had hemoglobin < 10 gr/dl (mean 11.4 ± 2.06 gr/dl) and 11 patients (24.4%) had leukocytosis > 12 × 10^9/L and/or < 4 × 10^9/L (mean 10.6 ± 4.7 × 10^9/L). Twenty-six patients (57.8%) had jaundice (serum total bilirubin > 2.5 mg/dl). Two patients (4.4%) were cirrhotic. Abnormal values of serum ALP (> 129 IU/L) were observed in 38 (84.4%) (Table 3).

### Table 2: Procedures performed in patients.

<table>
<thead>
<tr>
<th>Procedures performed prior BDI repair (secondary referral) (n = 32, 100%)</th>
<th>BDI repair type (n = 45, 100%)</th>
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<tbody>
<tr>
<td>Relaparotomy, drainage but without repair (n = 18) (56.2%)</td>
<td>Single end-to-side hepaticojejunostomy (n = 38, 84%)</td>
</tr>
<tr>
<td>ERCP (n = 11, 34.3%)</td>
<td>Separate two end-to-side hepaticojejunostomy (n = 5, 11.1%)</td>
</tr>
<tr>
<td>Relaparotomy, repair and drainage (n = 3) (9.3%)</td>
<td>Intrahepatic bile duct anastomosis (n = 2, 4, 4%)</td>
</tr>
</tbody>
</table>

BDI: Bile Duct Injury; ERCP: Endoscopic Retrograde Cholangiopancreatography.

### Table 3: Biochemical parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Admission</th>
<th>One month after surgery</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>4.3 ± 5.3</td>
<td>1.84 ± 2.11</td>
<td>0.091</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>3.2 ± 4.3</td>
<td>1.28 ± 1.59</td>
<td>0.046</td>
</tr>
<tr>
<td>Indirect bilirubin (mg/dl)</td>
<td>1.06 ± 1.32</td>
<td>0.52 ± 0.51</td>
<td>0.342</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>346.1 ± 268.5</td>
<td>277.9 ± 187.9</td>
<td>0.009</td>
</tr>
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</table>

*Statistical significance by U Mann-Whitney test: (p < 0.05).
Follow-up

Forty-four patients were followed with a mean follow-up of 24.4 ± 28.8 months (1-93 range). Nine patients (20.4%) had jaundice (total bilirubin > 2.5 mg/dl) one month after surgery and 22 patients (50%) had higher (> 129 IU/L) abnormal serum ALP. There was a statistically significant decrease of bilirubin and ALP lower (> 129 IU/L) abnormal serum ALP. There was a statistically significant decrease of bilirubin and ALP one month after surgery (Table 3). Three patients developed biliary complications: stricture, cholangitis and recurrent cholangitis for sub-analysis. Older patients (> 45 years of age, based on median age) were statistically significantly associated with overall (46 ± 14 vs. 35 ± 12 years, p = 0.02), biliary complications (47 ± 12 vs. 35 ± 3 years, p = 0.01) and biliary leak (58 ± 7 vs. 37 ± 13 years, p = 0.01) as well. Female patients were prone to suffer more cholangitis bouts than male patients were (p = 0.05). Previous biliary leak was significant associated with high preoperative values of ALP. High Bismuth-Strasberg lesions (E3-E5) were significantly associated with occurrence of biliary complications but not associated with a specific biliary complication itself. The use of silastic transanastomotic/transhepatic stents was associated with biliary complications, (stricture and cholangitis, either recurrent or postoperative specifically) and a statistical trend to overall complications (p = 0.06). Biliary leak was significantly associated with high preoperative values of ALP. Successful outcome was stratified according to McDonald classification (Table 5). There was an 82.2% treatment success rate (grade A and B) and 17.8% treatment failures (Grade C and D).

Risk factors influencing BDI repair morbidity

Univariate analysis: Univariate analysis was performed in 44 patients with long-term follow-up in order to obtain possible association and risk factors that might influence BDI repair morbidity. For analysis purpose, morbidity was stratified as biliary and overall complications. Biliary complications were further divided in biliary leak, bilioenteric stricture, cholangitis and recurrent cholangitis for sub-analysis. Older patients (> 45 years of age, based on median age) were statistically significantly associated with overall (46 ± 14 vs. 35 ± 12 years, p = 0.02), biliary complications (47 ± 12 vs. 35 ± 3 years, p = 0.01) and biliary leak (58 ± 7 vs. 37 ± 13 years, p = 0.01) as well. Female patients were prone to suffer more cholangitis bouts than male patients were (p = 0.05). Previous biliary leak was significantly associated with high preoperative values of ALP. High Bismuth-Strasberg lesions (E3-E5) were significantly associated with occurrence of biliary complications but not associated with a specific biliary complication itself. The use of silastic transanastomotic/transhepatic stents was associated with biliary complications, (stricture and cholangitis, either recurrent or postoperative specifically) and a statistical trend to overall complications (p = 0.06). Biliary leak was significantly associated with high preoperative values of ALP. Successful outcome was stratified according to McDonald classification (Table 5). There was an 82.2% treatment success rate (grade A and B) and 17.8% treatment failures (Grade C and D).
Multivariate analysis: Binary logistic regression was performed for overall and biliary complications. There was not statistical significance in any of the variables examined by overall complication and specific biliary complications (leak, stricture and cholangitis). Age > 46 years was identified as a risk factor to grouped biliary complications by logistic regression analysis (Table 7).

Discussion

The main goal of BDI repair surgery is provide adequate biliary excretion without causing postoperative symptomatology and/or significant liver function derangement. Since milestone publications by Lillemoe and colleagues [6,7], in which treatment success following BDI repair (normal/mild abnormal liver function tests and no symptoms) was 90.8%, different treatment success have been reported, varying from 78% [9] to a 93% [11] with percentages in between [15]. Efficacy and safety outcomes in hepatobiliary surgery and BDI repair surgery traditionally include overall morbidity and specific biliary morbidity such as anastomotic biliary leak, cholangitis and stricture. Complication rate in BDI surgery varies from 15% to 43% [7,9,13,16,18] in specialized hepatobiliary centers and may be close to 75% in non-referral centers where non-hepatobiliary specialists act as attending surgeons [16]. Postoperative biliary leak incidence have been described at a 5% rate [7]; cholangitis (perioperative and/or recurrent) may present at a 5.7-27% rate [7,16] and the possibility of bilioenteric stricture following BDI repair is between 5% and 10% [7,12]. Some centers have decreased their cholangitis and stricture incidence from 11% to 6% and 13% to 5% respectively, as they have grown in experience over time [8]. Except from unusual high mortality reports (6%) [11], mortality following BDI surgery should be less than 2% [7,8]. We were able to achieve an excellent 82% success rate according to MacDonald classification. We also obtained similar efficacy and safety outcomes (40% morbidity, 8% biliary leak, 13.3% cholangitis and 6.7% stricture with only 1 death) in a myriad series of patients with a majority of complex (grade B and D injuries by Amsterdam classification) and high hilar division/stricture injuries (E3-E5 Bismuth-Strasberg).

Our results could be explained by different facts: i) Patients were referred to our service mostly without prior BDI repair since 28% were primary referred and 40% secondary referred with only bile drainage (previous bilioenteric repair was associated with complications in our univariate analysis); ii) Patients underwent surgery in the absence of biloma, cholangitis and sepsis (only 24% of our patients had WBC within systemic inflammatory response syndrome limits); iii) Standardized surgical technique. In spite of our surgical technique, we found
that stent use (transhepatic and/or transanastomotic) had conflicting results: they were significantly associated with overall biliary complications in univariate analysis but not in multivariate analysis, perhaps by the number of patients included in the analysis. We have always followed stent use recommendations issued by Mercado, et al. unhealthy (i.e. ischemic, scarred) and small (< 4 mm) ducts, and we had similar results as they previously published (16% complications in stent group vs. 7% no stent group, p < 0.05) [15].

Hepatobiliary specialists have been trying to identify any possible risk factors related to successful outcomes after BDI repair or factors related to BDI repair complications by either univariate or multivariate analysis. Some of them have linked older age with overall complications [17] although others have found the opposite [18]. It has been previously mentioned that previous biliaryenteric repairs not performed by hepatobiliary surgeons add a significant increased risk of overall and biliary complications and treatment failure [11,16,17]. High injuries have also been associated in univariate analysis to biliary complications [11,12,17], mostly to cholangitis. We found similar risk factors in our univariate analysis (age > 45 years, previous biliaryenteric repair and Bismuth-Strasberg lesions III-V) related to complications. Nevertheless, we encountered other factors uncommonly associated with biliary complications, such as high ALP levels preoperatively and/or one month after BDI repair. High serum ALP > 400 IU/L in the sixth postoperative month after repair appeared to have a high correlation (p < 0.01) with long-term stenosis as published by Huang, et al. [25]. In our series, abnormal preoperative ALP (> 129 IU/L) and ALP > 400 one month after surgery significantly correlated with biliary complications. This might suggest abnormal healing in the presence of active biliary duct inflammation even though BDI repair surgery underwent in the absence of systemic and peritoneal cavity inflammation.

Our multivariate analysis confirmed age > 45 years as risk factor for biliary complications and neither a previous biliaryenteric repair nor high Bismuth-Strasberg lesions (III-V) were confirmed in our multivariate analysis as others have previously identified [11,13]. This might be related to a limited analysis due to size sample.

Although our study evidences good results and confirms possible risk factors for BDI repair surgery failure, we have to acknowledge that our findings came from a limited retrospective study with small size number of patients. In addition, we did not have a standardized biliary imaging technique as we mentioned in our methods and hepatic vascular inflow was not included in our preoperative management. Such limitations might have a negative effect in our outcomes.

In summary, BDI repair surgery should be carried out with good efficacy and safety outcomes. In our univariate analysis, identified risk factors for biliary complications included age, previous biliaryenteric repair, stent use, high complex Bismuth-Strasberg lesions and high preoperative and postoperative ALP. These factors were not confirmed that multivariate analysis though.

**Conflict of Interest**

None to declare by any of the authors.

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