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ORIGINAL ARTICLE

Anastomotic biliary stricture following liver transplantation and management analysis: 15 years of experience at a high-volume transplant center

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Abstract

Introduction The occurrence of anastomotic biliary stricture (BS) remains an essential issue following liver transplantation (LT). The present study aimed to compare our findings regarding the incidence of anastomotic BS to what is known.

Methods The present study is a single-center, retrospective cohort study of a total number of 717 consecutive patients (426 men and 291 women) who had undergone LT from January 2001 to March 2016. Multivariable Cox regression analysis was conducted to evaluate the risk factors associated with anastomotic BS development.

Results Post-transplant anastomotic BS developed in 70 patients (9.8%). In the Cox multivariate analysis (a stepwise forward conditional method), factors including biliary leak (hazard ratio [HR]: 6.61, 95% confidence interval [CI]: 3.08–17.58, $p < 0.001$), hepatic artery thrombosis (HR: 2.29, 95% CI: 1.03–5.88; $p = 0.003$), and acute rejection (HR: 2.18, 95% CI: 1.16–3.37; $p = 0.006$) were identified as independent risk factors for the development of anastomotic BS. Surgery in 6 cases (66.7%), followed by endoscopic retrograde cholangiopancreatography (ECRP) with a metal stent in 18 cases (62.1%), percutaneous transhepatic biliary drainage in 9 (20.9%), and ERCP with a single plastic stent in 8 (18.2%), had the highest effectiveness rates in the management of BS, respectively.

Conclusions Risk factors including biliary leak, hepatic artery thrombosis, and acute rejection were independently associated with an anastomotic BS. ERCP with a metal stent may be considered as an effective treatment procedure with a relatively low complication rate in the management of benign post-LT anastomotic BS.

Keywords Bile ducts · Biliary complication · Biliary stent · Biliary strictures · Cholestasis · Endoscopic retrograde cholangiography · ERCP · Jaundice · Liver transplants · Patient survival · Post-liver transplant biliary strictures · Retrograde cholangiopancreatography

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Bullet points of study highlights

What is already known?

- Despite recent advances in surgical techniques, short and long-term postoperative complications remain challenging following liver transplantation (LT).
- Biliary complications after LT are still considered a significant source of morbidity and mortality that can occur in about 10% to 45% of cases.
- The overall incidence rate of bile leak occurs in 2% to 25% of patients after LT.

What is new in this study?

- This study characterizes the clinical characteristics and associated risk factors of patients who developed biliary complications following LT.
- Endoscopic retrograde cholangiopancreatography (ERCP) dilatation is not a reliable procedure for the management of biliary strictures (BS).

What are the future clinical and research implications of the study findings?

- ERCP with a metal stent is an effective treatment procedure with a relatively low complication rate in managing benign BS and should be considered as the first line of treatment.
- Future randomized clinical studies are needed to elucidate the best treatment option for managing BS following LT.

Introduction

Liver transplantation (LT) is considered a widely accepted treatment of choice for treating end-stage liver disease [1, 2]. Despite recent advances in surgical techniques, short- and long-term postoperative complications remain a challenging issue following LT [3]. Biliary complications (BC) after LT are still considered a major source of morbidity and mortality that can occur in about 10% to 45% of cases [4–7]. Postoperative BC may vary greatly in their clinical manifestations due to the impact of immunosuppression therapy and denervation of the biliary tract [8, 9]. These complications manifest with a broad clinical spectrum ranging from fever, abdominal pain, asymptomatic elevation in liver enzymes, and secondary sepsis due to ascending cholangitis [9].

BC can be classified as either early (within 30 days of transplant) or late. The most frequent type of early complication includes bile leaks due to an injury to the liver surface during surgery [10]. Other BC include biliary strictures and the development of bile duct stones. Biliary strictures (BS) are categorized as either anastomotic strictures or non-anastomotic strictures based on their location [11].

Anastomotic biliary stricture is one of the most frequent complications after LT, with an incidence of 4% to 9% [12–14]. Endoscopic retrograde cholangiopancreatography (ERCP) is currently a preferred treatment modality for the management of these strictures. Other treatment modalities include percutaneous transhepatic cholangiodrainage and surgical approach [15]. Although our knowledge regarding anastomotic BC management has increased recently, identifying risk factors associated with BC development is crucial. The majority of the previous studies had reported several risk factors related to anastomotic BC and focused on a particular technique for the management of BS with a relatively short follow-up period [16–19]. Therefore, the present study aimed to assess risk factors for biliary adverse events and analyzed the effectiveness of the different management of post-transplant anastomotic BS among LT recipients.

Methods

Patients

The present study is a single-center, retrospective cohort study with a total of 717 consecutive patients who had undergone a LT program (affiliated to Tehran University of Medical Sciences, a tertiary referral center for end-stage liver disease) [20]. This study was undertaken between January 2001 and March 2016. Data regarding patient demographics, age at LT, time to diagnosis of BS, diagnostic delay, type of intervention, intervention-related complications, time to resolution of BS, and liver function tests including bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma- glutamyl transpeptidase (GGT), before intervention and 1 month after intervention,

were extracted by reviewing the patients' charts. Liver function tests (LFTs) were assessed twice weekly for the first 8 weeks, weekly for the next 12 weeks, and monthly for 6 months.

Livers were harvested from brain-dead donors and preserved in the University of Wisconsin solution before transplantation. The routine procedure at our center is the piggyback technique with cavo-caval anastomosis in side-to-side and end-to-end fashion. In patients with enlarged liver due to Budd-Chiari syndrome and primary sclerosing cholangiopathy (PSC) diagnosis, the standard surgical technique was performed with cavo-caval end-to-end anastomosis. Patients were evaluated for BC if they developed signs and symptoms of BS such as fever, jaundice, and elevated levels of the biliary markers. This study was approved by the ethics committee of Tehran University of Medical Science, and all the patients were asked to fill an informed consent form before the procedures were performed. The study was conducted in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations [21].

Definitions

BCs were defined as postoperative anastomotic leak and/or biliary stricture requiring endoscopic or surgical intervention. Biliary stricture involving the donor common bile duct (or bifurcation) was classified as anastomotic or nonanastomotic (ischemic) stricture. Anastomotic biliary stricture was defined as a dominant narrowing up to 1 cm in length occurring at the site of biliary anastomosis, without drainage of contrast material. Non-anastomotic strictures were defined as strictures being present more than 0.5 cm away from the anastomotic site. The diagnosis of biliary stricture was achieved using clinical symptoms, biochemical findings, and radiologic investigation including magnetic resonance cholangiopancreatography (MRCP) and contrast-enhanced cholangiography. Bile leakages were diagnosed based on clinical symptoms including abdominal pain, fever or jaundice, persistent bile discharge through a drain, and extravasation of contrast from the biliary anastomotic site, the T-tube tract, or the cut surface of the liver during cholangiography. Success in the therapeutic intervention (endoscopic or surgical) was defined as completing all intended therapeutic procedures. Biliary stricture resolution was defined as the absence of signs and symptoms of cholestasis and evidence of dilated common bile duct on ultrasonography or MRCP during follow-up. Recurrence was defined as the occurrence of cholangitis or stricture recurrence documented by ERCP or MRCP after initial clinical resolution. The treatment effectiveness was defined as no evidence of stricture recurrence 1 year after the last treatment procedure without further need to repeat endoscopic or surgical procedures. Therapeutic failure was defined as the presence of altered cholestatic hepatic function or biliary dilatation or biliary symptoms requiring further treatment 1 month after intended therapeutic procedures, or recurrence of biliary stasis markers after stent removal. Donor warm ischemia time was defined as the interval from withdrawal of life support to initiation of cold organ preservation. Cold ischemic time was defined as the time period between organ preservation and putting the graft into the recipient. Overall survival time was calculated from date of first procedure to the date of last follow-up.

Radiological assessment

For radiological evaluation, imaging records of all cases of suspected BS who underwent ultrasonography, cholangiograms, computed tomography, MRCP, and ERCP were retrieved from the hospital archive and reviewed by an experienced radiologist. The definition of BS was anastomotic narrowing at the site of the biliary anastomosis with irregular caliber changes.

Endoscopic approach

All ERCPs were performed independently by an experienced gastroenterologist (Fig. 1). All procedures were performed with sedation, with levels from moderate sedation to general anesthesia. Patients received prophylactic intravenous antibiotics before the procedure. ERCP was performed using standard techniques. After cannulation, cholangiography was performed to confirm the stenosis. In the case of BS, an occlusion cholangiogram with a balloon catheter was performed to determine the stricture site. Endoscopic intervention (balloon dilatation with or without stent placement) was applied after confirmation of the BS. Biliary stent placement was performed across the stricture site.

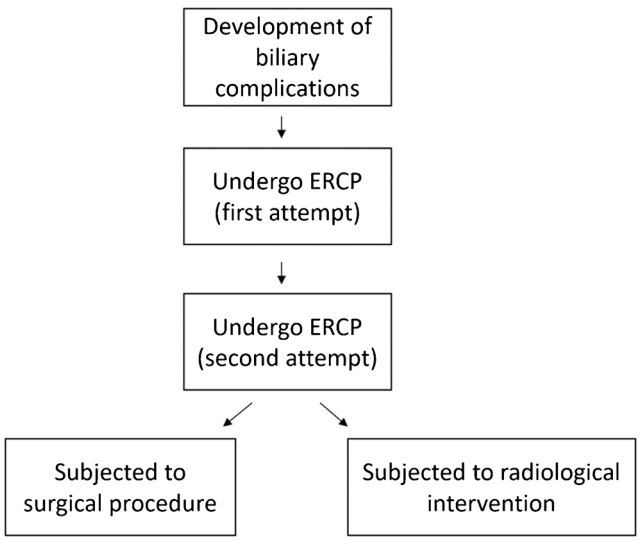

Fig. 1 The flow diagram showing management protocol for patients who were managed for biliary complications. *ERCP* endoscopic retrograde cholangiopancreatography

Statistical analysis

Categorical variables are reported as percentages and analyzed using the Chi-square test. Continuous numeric variables were reported as mean ± standard deviation (SD) or the median and 25th and 75th percentiles if non-normally distributed. Statistical comparisons were performed using independent *t* test (for quantitative variables) and the Chi-square test (for qualitative variables). A Student's *t* test was used to compare continuous variables, and Chi-square and Fisher's exact tests were used to compare categorical data. Multivariable Cox regression analysis adjusted for both donor's and recipient's demographics was conducted to evaluate the risk factors associated with BS development. Two-tailed *p*-values < 0.05 were used for significance testing. All data were analyzed using Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA).

Result

Patient characteristics

The characteristics of patients are depicted in Table 1. In total, 717 patients (426 males and 291 females) with a mean age of 43.41 were considered for the final analysis. The median time for the development of anastomosis strictures after performing LT was 11.9 months, ranging from 8 days through 72 months. The mean follow-up duration after biliary intervention was 18.61 ± 4.05 months. Liver cirrhosis due to viral hepatitis (24.4%) was the main indication for LT. Other common causes of cirrhosis of patients who underwent LT were as follows: 143 (19.9%) with cryptogenic, 110 (15.3%) with autoimmune hepatitis, 65 (9.1%) with PSC, 39 (5.4%) with re-transplant, and 37 (5.2%) with acute liver failure. There was no statistically significant difference between various causes of cirrhosis and occurrence of BC (p = 0.436). End-to-end ductal anastomosis and Roux-en-Y anastomosis were performed in 632 (90%) and 70 patients (9.7%), respectively. The incidence rate of known risk factors for BS is as follows: hepatic artery thrombosis (HAT) occurred in 40 patients (5.6%), prolonged donor warm ischemic time (defined by more than 30 min), and cold ischemic times (defined by more than 720 min) in 162 (22.5%) and 8 (1.1%), respectively. The presence of HAT was significantly different between patients with and without the diagnosis of BS (11 cases [15.7%] vs. 29 cases [4.5%], respectively; p < 0.001) (Table 1). The most common comorbid conditions were diabetes seen in 92 (13.5%), hypertension in 25 (3.7%), and inflammatory bowel disease in 22 (3.3%) recipients.

Biliary complications

As shown in Table 1, patients' data regarding preoperative, intraoperative, and postoperative variables were compared between two groups of with and without development of BS. Overall, 70 patients (9.7%) developed BS following LT. All of the 70 BS cases were anastomotic type. The most common presenting symptoms in patients with BS was fever (45 patients) followed by abdominal pain (14 patients), and jaundice (9 patients). There was no statistical difference between BS and type of anastomosis (p = 0.66). The presence of HAT was significantly higher in patients with BS compared to those without BS (15.7% vs. 4.5%; p < 0.001). Among patients who developed BS, Cytomegalovirus (CMV) infection was confirmed in 23 cases (32.9%). Thirteen patients (18.6%) with BS did not survive during the study period. There was a significant difference in terms of mortality rate among patients with and without BS (p < 0.001) (Fig. 2).

Analysis of risk factors associated with BC

Univariate analysis identified the following parameters to be significantly associated with BC development including biliary leakage, HAT, acute rejection, CMV infection, portal vein stenosis, donor warm ischemic time, and operation duration (Table 2). In the Cox multivariate analysis (a stepwise forward conditional method), factors including biliary leak (hazard ratio [HR]: 6.61, p < 0.001), HAT (HR: 2.29, p = 0.003), and acute rejection (HR: 2.18, p = 0.006) were identified as independent risk factors associated with BC development (Table 2).

Management of BC

Overall, 207 diagnostic and 189 therapeutic procedures were performed for patients with signs and symptoms of post-LT BC (Table 3). The types of treatment procedures performed for these patients were as follows: ERCP in 137 cases (72.5%), percutaneous transhepatic biliary drainage (PTBD) in 43 cases (22.8%), and surgery in 9 cases (4.8%). All of our patients who underwent surgery had prior ERCP. Different types of ERCP procedures used for management of BS include ERCP-dilatation in 18 cases (9.5%), ERCP-single plastic stent in 44 cases (23.3%), ERCP-metal stent in 29 cases (15.3%), ERCP for stone extraction in 11 cases (5.8%), and ERCP performed with two or more than two plastic stents in 5 cases (2.6%). Moreover, failure in ERCP was observed in 32 cases (15.9%).

The ERCP was successfully completed in 105 (76.6%) patients. All the 9 patients who underwent surgical management had a successful outcome as well. No significant difference was observed between types of intervention and success rate (p = 0.22).

Table 1 Comparison of different variables between patients with and without biliary stricture

Parameters	Total (n = 717)	With BS (n = 70)	Without BS (n = 647)	p value
Gender (%)				0.71
Male	426 (59.4)	43 (61.4)	383 (59.2)	
Female	291 (40.6)	27 (38.6)	264 (40.8)	
Donor's age (years)	43.41 ± 13.42	42.04 ± 12.05	43.56 ± 13.53	0.368*
Etiology of cirrhosis, %				0.436
HBV	97 (13.5)	9 (12.9)	88 (13.6)	
HCV	78 (10.9)	9 (12.9)	69 (10.7)	
Autoimmune	110 (15.3)	15 (21.4)	96 (14.7)	
Cryptogenic	143 (20)	17 (24.3)	126 (19.5)	
PSC	67 (9.3)	7 (10)	60 (9.3)	
PBC	16 (2.2)	1 (1.4)	15 (2.3)	
Wilson's	28 (3.9)	2 (2.9)	26 (4)	
NASH	33 (4.6)	1 (1.4)	32 (4.9)	
Budd-Chiari syndrome	16 (2.2)	2 (2.9)	14 (2.2)	
Re-transplant	39 (5.4)	4 (5.7)	35 (5.4)	
Acute liver failure	37 (5.2)	3 (4.3)	34 (5.3)	
Other	53 (7.4)	0 (0)	53 (8.2)	
Biliary anastomosis fashion				0.668
End to end	632 (90)	62 (88.6)	570 (90.2)	
Roux-en-Y	70 (10)	8 (11.4)	62 (9.8)	
Mortality	163 (22.7)	13 (18.6)	150 (23.2)	0.382
CMV infection	161 (22.4)	23 (32.9)	138 (21.3)	0.034
MELD score	21.02 ± 6.31	20.71 ± 6.21	21.06 ± 6.32	0.66*
Child-Pugh score	10.01 ± 2.03	10.31 ± 1.87	9.98 ± 2.05	0.22*
Cold ischemic time, min	301.42 ± 94.51	308.39 ± 73.14	300.66 ± 96.57	0.51*
Warm ischemic time, min	20 (16–30)	22.5 (17.2–42.0)	20.0 (16.0–29.2)	0.96**
Operation duration, min	305.86 ± 89.72	326.96 ± 93.72	303.58 ± 89.05	0.04*
Laboratory findings				
Bilirubin total (mg/dL)	3.7 (2.4–7.1)	4.1 (2.5–8.0)	3.6 (2.4–6.9)	0.206**
Bilirubin direct (mg/dL)	1.5 (0.8–3.5)	1.6 (0.8–3.5)	1.4 (0.8–3.4)	0.52**
AST (IU/L)	67 (43–112)	81 (45–133)	65 (43–110)	0.103**
ALT (IU/L)	44 (28–78)	61 (34–89)	42 (28–76)	0.04**
ALP (IU/L)	323 (221–489)	344 (241–516)	322 (219–489)	0.56**
Albumin (g/L)	3.1 (2.8–3.5)	3.0 (2.7–3.6)	3.1 (2.8–3.5)	0.56**
PT	17.2 (15.5–19.9)	17.4 (16.0–19.8)	17.2 (15.5–20.0)	0.89**
INR	1.8 (1.5–2.2)	1.8 (1.5–2.2)	1.8 (1.3–2.4)	0.76**
Emergency transplantation	40 (5.6)	3 (4.3)	37 (5.7)	0.788
Acute rejection, %	214 (29.8)	35 (50.7)	179 (29)	0.001
HAT, %	40 (5.5)	11 (15.7)	29 (4.5)	0.001
PVT, %	21 (2.9)	2 (2.9)	19 (3)	0.343

Data are presented as mean ± SD. $p < 0.05$ was considered to be significant

HBV hepatitis B virus, *HCV* hepatitis C virus, *PSC* primary sclerosing cholangitis, *PBC* primary biliary cholangitis, *NASH* nonalcoholic steatohepatitis, *MELD* model for end-stage liver disease, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *PT* prothrombin time, *INR* international normalized ratio, *HAT* hepatic artery thrombosis, *PVT* portal vein thrombosis, *IQR* inter quartile range with 75th and 25th percentiles, *BS* biliary stricture, *CMV* Cytomegalovirus

* The between-group comparison was made using independent t test

** The between-group comparison was made using Mann–Whitney's U test

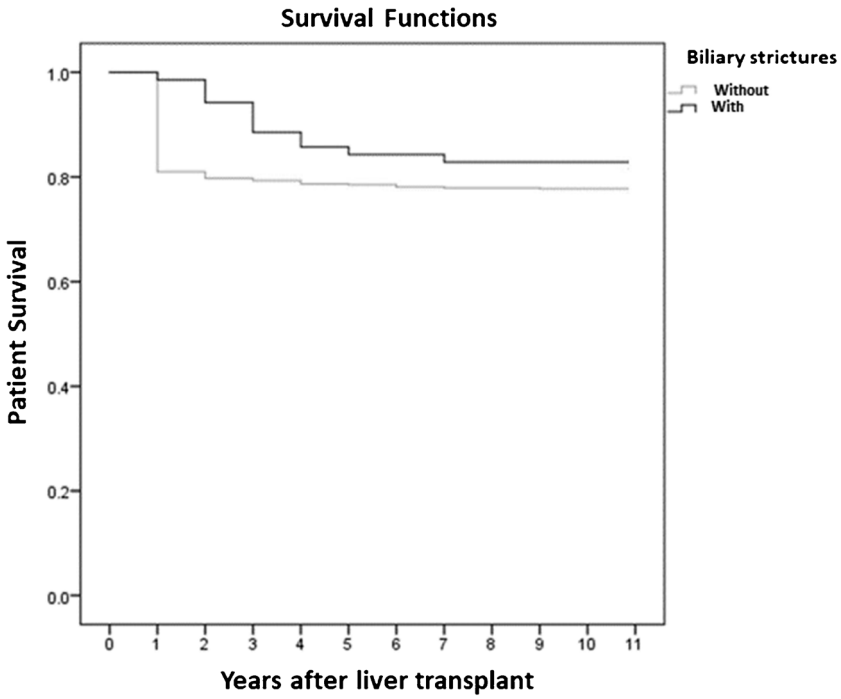

Fig. 2 Kaplan-Meier survival analysis for patients with and without biliary strictures

Among 105 successful ERCP procedures, resolution rates were obtained in 80 procedures (76%) and treatment effectiveness was achieved in 35 cases (33.3%). In the PTBD method, the resolution rate was obtained in 23 procedures (71%). A significant difference was identified between resolution rate of various treatment procedures ($p < 0.001$). The highest resolution rate was obtained in ERCP with metal stent (96.6%). Moreover, the most effective treatment procedure was

Table 2 Cox regression analysis of risk factors associated with biliary complication

Predictors	Crude (univariable)			Adjusted (multivariable)		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Donor's age (years)	01.03	0.91–1.03	0.65	–	–	–
Gender	1.09	0.34–1.89	0.76	–	–	–
Biliary leak	2.01	1.18–3.17	0.006	6.61	3.08–17.58	< 0.001
HAT	3.43	1.16–8.02	< 0.001	2.29	1.03–5.88	0.03
Acute rejection	1.89	1.47–3.64	< 0.001	2.18	1.16–3.37	0.006
CMV infection	1.38	1.05–2.48	0.07	–	–	–
PVS	2.73	1.03–24.81	0.09	–	–	–
PVT	0.49	0.11–1.43	0.2	–	–	–
DM	1.06	0.65–1.73	0.127	–	–	–
HTN	0.93	0.36–1.19	0.57	–	–	–
Biliary anastomosis fashion	1.13	0.36–1.85	0.65	–	–	–
Biliary anastomosis type	0.49	0.21–2.11	0.58	–	–	–
Cold ischemic time	1.014	0.77–1.15	0.483	–	–	–
Warm ischemic time	1.05	1.006–1.11	0.005	–	–	–
Operation duration	1.002	1.001–1.03	0.03	–	–	–
MELD score	0.93	0.89–1.02	0.361	–	–	–
Child score	1.04	0.92–1.28	0.118	–	–	–

CI confidence interval, *HR* hazard ratio, *HAT* hepatic artery thrombosis, *CMV* cytomegalovirus, *PVS* portal vein stenosis, *PVS* portal vein thrombosis, *DM* diabetes mellitus, *HTN* hypertension, *MELD* model of end-stage liver disease

Table 3 Description of outcomes of different treatment modalities for management of biliary complications following liver transplantation

Treatment type, *n (%)*	Total	Success	Resolution	Effectiveness	Complications
PTBD	43 (100)	32 (74.4)	23 (53.4)	9 (20.9)	1 (2.3)
Surgery	9 (100)	9 (100)	8 (88.9)	6 (66.7)	1 (11.1)
ECRP	137 (100)	105 (76.6)	80 (76.2)	35 (43.8)	14 (10.2)
ERCP dilation	18 (100)	18 (100)	11 (64.7)	3 (17.6)	1 (5.6)
ERCP with plastic stent	44 (100)	44 (100)	29 (65.9)	8 (18.2)	4 (9.1)
ERCP with metal stent	29 (100)	29 (100)	28 (96.6)	18 (62.1)	6 (20.7)
ERCP with stone extraction	11 (100)	11 (100)	11 (100)	6 (66.7)	1 (9.1)
ERCP with multiple plastic stent (> 2)	5 (100)	5 (100)	3 (60)	0 (0)	0 (0)

PTBD percutaneous transhepatic biliary drainage, *ERCP* endoscopic retrograde cholangiopancreatography

obtained with the surgical Roux-en-Y method with 66.7%, while ERCP with plastic stent placement had the lowest effectiveness.

Among the 189 procedures performed, 170 (89.9%) procedures were without complications, while complications developed in 19 (10.1%) procedures. No significant difference was observed between the occurrence of complications and different treatment procedures ($p = 0.5$). The frequency of complications based on different treatment modalities is summarized in Table 4.

Discussion

In the present study, the risk factors associated with BS development following LT in an Iranian cohort were analyzed. Risk factors including biliary leak, HAT, and acute rejection were found to be independently associated with formation of BC. Other risk factors reported by previous studies such as donor's age and prolonged cold ischemia were not significantly associated with BC development.

The occurrence of biliary adverse events is still considered the Achilles' heel of LT and contributes significantly to morbidity and mortality among liver transplant recipients. This study showed an overall rate of BS incidence at 9.8%, comparable to other centers globally reporting an incidence rate of 5% to 15% in deceased donors [22–26].

The overall incidence rate of bile leak occurs in 2% to 25% of patients after LT [27]. In our hospital, bile leakage occurred in about 3.6% of patients, one of the lowest reported rates in the literature. Biliary leaks may present with exacerbation of abdominal pain, fever, and peritonitis, resulting in severe comorbidities and impairs graft survival. Our findings indicate that bile leak is an independent risk factor for the development of BC. These results are in accordance with previous studies conducted by Verdonk et al. [13] and Welling et al. [28]. These reports suggested that BS resulting from bile leak may be due to free peritoneal bile provoking intra-abdominal inflammation and promoting peribiliary fibrosis.

In this study, 90% of our patients underwent end-to-end biliary anastomosis. Our findings suggest that there was no significant difference between the type of anastomosis and BS occurrence. Similarly, in a study done by Verdonk et al. [13],

Table 4 The complication rates according to different treatment modalities

Treatment approach, n (%)	Complications					
	Pancreatitis	Perforation	Infection	Migration	Bleeding	Death
ERCP-dilation	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)	1 (5.6)
ERCP with plastic stent	1 (2.3)	1 (2.3)	2 (4.5)	0 (0)	0 (0)	0 (0)
ERCP with metal stent	1 (3.4)	2 (6.9)	1 (3.4)	2 (6.9)	0 (0)	0 (0)
PTBD	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	1 (2.3)
Surgery	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)
ERCP with stone extraction	0 (0)	1 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)
ERCP with multiple plastic stent (> 2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	2 (1.6)	4 (2.5)	5 (2.5)	2 (1.1)	1 (0.5)	2 (1.6)

PTBD percutaneous transhepatic biliary drainage, *ERCP* endoscopic retrograde cholangiopancreatography

11% of their study population underwent Roux-en-Y anastomosis, while 89% had a duct-to-duct biliary anastomosis. They also did not find any difference between type of anastomosis and BS. Another study by Greif et al. [29] suggests that duct-to-duct surgical anastomosis was the most important risk factor for developing BS. However, we did not find any association between type of anastomosis and the risk of BS development.

In the present study, there was a significant relationship between acute organ rejection and BS. Several studies suggested no association between transplant rejection and the occurrence of BS [30, 31]. On the other hand, Demetris [32] suggested that rejection is a significant risk factor for BS.

The endoscopic procedure is generally safe and effective in managing post-transplant biliary adverse events, with a success rate ranging from 70% to 80% [22, 33–35]. More than 80% of the patients were managed endoscopically in this study, with a success rate higher than 80%, reducing the need for surgical interventions. ERCP was performed with an acceptable success rate among our patients, although complications such as pancreatitis, intestinal perforation, and bleeding were also observed. The use of a metal stent had the highest success rate compared to other interventions. On the other hand, patients undergoing multiple plastic stents experienced the lowest success outcome. These findings are consistent with previous studies, which reported that metal stents were not inferior to multiple plastic stents in achieving stricture resolution [36, 37]. These results should be further investigated in more extensive multi-center randomized clinical trials to identify the best treatment modality for managing post-liver transplant BS.

In conclusion, risk factors including biliary leak, HAT, and acute rejection were independently associated with BC formation. ERCP with a metal stent is an effective treatment procedure with a relatively low complication rate in managing benign BS and should be considered the first treatment line. Moreover, ERCP dilatation may not be a reliable procedure for the management of these strictures. Further prospective randomized controlled trials are warranted for indicating the best treatment procedure.

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Author contribution OE, critical revision of the manuscript and study concept and design; BM, critical revision of the manuscript; ZEZ, BM, and HS, acquisition, analysis, and interpretation of data and drafting of the manuscript; NR, HD, and NF, participated in the data acquisition, interpretation of data, and statistical analysis; and AJ and MNT, study concept and design, and critical revision of the manuscript.

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Declarations

Conflict of interest OE, BM, ZEZ, NR, HD, NF, HS, AJ, and MNT declare that they have no conflict of interest.

Ethics statement Written informed consent was obtained from all the study subjects. The study protocol conforms to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004.

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