



Endoscopic treatment of biliary complications following liver transplantation

LIVER

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ABSTRACT

Background/Aims: The aims of the present study were to review biliary complications following liver transplantation in a single-center experience, to identify the factors associated with biliary complications, and to evaluate the success of endoscopic and percutaneous treatment in such patients.

Materials and Methods: Between January 1994 and June 2010, a total of 176 patients with liver disease underwent liver transplantation; 119 recipients were included in this retrospective analysis. Median posttransplant follow-up period was 49 months.

Results: Mean age was 43.0±12.7 years. Living donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT) were performed in 71 and 48 patients, respectively. Duct-to-duct anastomosis and Roux-en-Y hepaticojejunostomy were performed in 68 and 51 patients, respectively.

The overall incidence of posttransplant biliary complications was 36%; anastomotic biliary strictures were the most common biliary complications (42%), followed by biliary leakage (28%). On logistic regression analysis, duct-to-duct anastomosis was the only risk factor associated with the development of biliary complications (Odds ratio (OR), 3.346; p=0.005). Endoscopic and percutaneous treatment was successful in the majority of patients (81%), and the remaining 19% recipients underwent surgery for biliary repair. Endoscopic retrograde cholangiopancreatography (ERCP) guided drainage and balloon dilatation with stent placement were the most common treatment modalities.

Conclusion: Biliary complications were most frequent after liver transplantation; biliary strictures were the most commonly seen. The use of duct-to-duct anastomosis for biliary reconstruction is a risk factor for the development of biliary complications. Endoscopic and percutaneous treatment was successful in the majority of these patients.

Keywords: Biliary complications, liver transplantation, biliary stricture, therapeutic endoscopy

INTRODUCTION

Biliary complications following liver transplantation remain a major problem and may become a significant cause of morbidity, ranging from 7% to 27.9%, and mortality, ranging from 6%-12.5%, in different transplantation centers (1-5). The prevalence of biliary complications following liver transplantation varies from 4% to 34% (4,5). The spectrum of biliary complications includes anastomotic and non-anastomotic strictures, anastomotic bile leaks, biliary stones, and cholangitis (1,4,5). Several risk factors include primary underlying

disease, type of donor, ABO incompatibility, ischemic time, surgical technique, hepatic artery problems, and rejection for the development of posttransplant biliary complications (4-10). Several studies previously demonstrated that endoscopic treatment modalities effectively treat the majority of biliary complications following liver transplantation (11-18). The aims of the present study were to review biliary complications following liver transplantation in a single-center experience to identify the factors associated with the frequency of biliary complications, and to evaluate the

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success of endoscopic and percutaneous treatment modalities in such patients.

MATERIALS AND METHODS

Patients

Between January 1994 and June 2010, a total of 176 patients with acute and chronic liver failure underwent liver transplantation in our Transplantation Unit. Among them, 57 recipients were excluded as a result of death within the first 30 days of transplantation and insufficient medical follow-up records, and the remaining 119 recipients were enrolled into this analysis. Data were retrospectively collected from patient hospital charts. Oral and written informed consents were taken from all participants.

Surgical procedures for liver transplantation

Portal and aortic flush with University of Wisconsin (UW) (Chicago, IL, USA) solution was done during procurement from deceased donors. Histidine tryptophan ketoglutarate (HTK) solution (Chemie GmbH, Germany) was perfused through the portal vein and hepatic artery of live-donor segmental grafts on the back table. Duct-to-duct anastomosis with or without an internal stent was preferred when possible. Otherwise, biliary reconstruction was performed using mainly and/or Roux-en-Y hepaticojejunostomy. All anastomoses were performed with interrupted 5/0 polydactyl sutures under 3.5X magnification. Hepatic artery reconstruction was performed under surgical microscope magnification.

The immunosuppression regimen usually consisted of either tacrolimus or cyclosporine with prednisone and mycophenolate mofetil as a triple therapy.

Biliary complications were defined based on the clinical manifestation of fever, jaundice, and/or right upper quadrant abdominal pain; biochemical results of abnormal serum aminotransferase, bilirubin, alkaline phosphatase (ALP), and gamma glutamyltransferase (GGT) levels; and radiological evaluation results of magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC). Anastomotic biliary stricture was defined as a segmental narrowing around the biliary anastomosis by ERCP. Biliary leakage was basically defined as bile leak through the abdomen and diagnosed by imaging modalities, including ultrasonography, computerized tomography, and ERCP. Graft rejection and ischemic type biliary lesions included ischemia-reperfusion injury and hepatic artery abnormalities (thrombosis, stenosis) and were excluded based on histological and radiological evaluation.

Management

The management of biliary complications following liver transplantation was basically divided into two approaches: ERC-

P-guided drainage and PTC-guided drainage. All interventions were performed with pre-medication, including propofol, by an anesthesiologist. Endoscopic biliary sphincterotomy was performed in the majority of patients, and a variety of guide-wires were used for biliary cannulation. Biliary stricture was dilated by a balloon catheter 6 or 8 mm in diameter, and subsequently, a biliary plastic stent was placed. Biliary leaks were treated with endoscopic biliary plastic stent (8.5-10 Fr) insertion. When bile duct stone or casts were detected during ERCP, they were extracted at the same time. The biliary plastic stent was removed 3 months after the follow-up period. No endoscopic intervention was required for a recipient who had adequate stricture dilatation or improved biliary leak.

Statistical analysis

Categorical variables were expressed as percentage, and continuous variables were expressed as mean±standard deviation. Continuous variables were compared by the student's t-test or the Mann-Whitney test. The chi-square test was used for categorical variables. Univariate logistic regression analysis was performed on the following variables: age, donor gender, indication for transplantation, type of donor, type of bile duct reconstruction, blood type, and Rhesus type incompatibility. All statistical analyses were performed with SPSS 16.0 software (IBM Corp., NY, USA). P values were considered statistically significant at a level of less than 0.05.

RESULTS

Median posttransplant follow-up period was 49 months (range, 3-180 months). Among liver transplant recipients, mean age was 43.0±12.7 years (range, 18-66 years), and male gender was predominant. Etiologic causes for liver transplantation were hepatitis B virus (HBV)-induced cirrhosis in 39 patients (36%, 39/110), hepatitis C virus (HCV)-induced cirrhosis in 12, hepatitis delta virus (HDV)-induced in 15, autoimmune liver disease in 15 patients, cryptogenic cirrhosis in 14 patients, ethanol-induced cirrhosis in 8 patients, Wilson's disease in 4 patients, and other etiologies in 3 patients. Acute liver failure was seen in 9 patients (4 drug-induced, 3 HBV-induced, 1 Wilson's disease, and 1 idiopathic). Hepatocellular carcinoma (HCC) was detected in 11 patients (6 HBV-induced cirrhosis, 2 HCV-induced cirrhosis, and 3 HDV-induced cirrhosis). The characteristics of all patients are shown in Table 1.

Living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) were performed in 71 (60%) and 48 (40%) recipients, respectively. Duct-to-duct and Roux-en-Y anastomosis were performed in 68 and 51 recipients, respectively: 31 and 40 LDLT recipients and 37 and 11 among DDLT recipients, respectively.

The overall incidence of posttransplant biliary complications was 36% among the recipients (n=43). The mean age was 44.2±12.1 years, and male recipients (61%) had more experienced. Anastomotic biliary strictures were the most

Table 1. Characteristics of the 119 liver transplanted patients with biliary complication

	n=119
Age (years), mean (range)	43.0 ±12.7 (18-66)
Gender (male/female)	72/47
Underlying liver disease	
End-stage liver disease	
Hepatitis B	39
Hepatitis C	12
Hepatitis D	15
Autoimmune liver disease	15
Primary sclerosing cholangitis	8
Autoimmune cirrhosis	4
Primary biliary cirrhosis	3
Cryptogenic cirrhosis	14
Alcoholic cirrhosis	8
Wilson's disease	4
Other etiologies	3
Acute fulminant hepatitis	9
Drug	4
Hepatitis B	3
Wilson's disease	1
Idiopathic	1
With hepatocellular carcinoma	11
HBV-induced cirrhosis	6
HDV-induced cirrhosis	3
HCV-induced cirrhosis	2

HBV: hepatitis B virus; HDV: hepatitis delta virus; HCV: hepatitis C virus

common biliary complications following liver transplantation (42%, n=18) (Figure 1), followed by biliary leakage in 12 recipients (28%) (Figure 2); biliary stricture and leakage in 7; biliary stricture, biliary stricture, and cholelithiasis in 4; biliary leakage and cholelithiasis in 1; and isolated cholelithiasis in 1 (Table 2).

When compared to two donor types, no significant difference in terms of the frequency of biliary complications was observed (39.4% vs 31.3%, p>0.05). Twenty-eight recipients among the LDLT group experienced biliary complications as follows: biliary stricture in 13; biliary leakage in 8; biliary stricture and leakage in 4; biliary stricture, leakage, and cholelithiasis in 1; biliary stricture and cholelithiasis in 1; and isolated cholelithiasis in 1 recipient-whereas 15 recipients among the DDLT group had experienced biliary complications as follows: biliary stricture in 5, biliary leakage in 4, biliary stricture and leakage in 3, and biliary stricture and cholelithiasis in 3 recipients.

Table 2. Characteristics of the biliary complications following liver transplantation

	LDLT (n=71)	DDLT (n=48)	Overall (n=119)
Biliary stricture	13	5	18
Biliary leak	8	4	12
Biliary stricture + leak	4	3	7
Biliary stricture + stone	1	3	4
Biliary stricture + leak + stone	1	-	1
Biliary stone	1	-	1

LDLT: live donor liver transplantation; DDLT: deceased donor liver transplantation

Table 3. Factors influenced on the development of biliary complications following liver transplantation

Variable	OR (95% CI)	p value
Age	1.013 (0.982-1.044)	0.417
Gender	1.590 (0.727-3.477)	0.244
ABO incompatibility	0.416 (0.079-2.191)	0.462
Type of donor	1.433 (0.661-3.106)	0.362
Type of biliary anastomosis	3.346 (1.409-7.946)	*0.005
Primary underlying disease		
The presence of HCC	1.278 (0.379-4.305)	0.756
Biliary diseases	0.683 (0.127-3.681)	1.000

*p value of <0.05 is statistically significant.
HCC: hepatocellular carcinoma

Endoscopic retrograde cholangiopancreatography guided drainage and balloon dilatation with/without stent placement were the most common treatment modalities in patients with biliary stricture (Figure 1a-e), whereas in patients with biliary leakage, ERC-guided drainage and stent placement were the most commonly used (Figure 2). The overall success rate of endoscopic treatment modalities, both ERC-based and PTC-based, was 81%. No significant difference in terms of the success rate between patients with LDLT and DDLT was observed (75% vs 93.3%, p>0.05). Eight recipients (19%) required surgical revision for repairing the biliary complications: 7 among LDLT recipients (5 biliary leakage, 1 anastomotic stricture, 1 biliary leakage with anastomotic stricture) and 1 DDLT recipient with anastomotic stricture. Roux-en-Y reconstruction was generally the preferred type of surgical biliary reconstruction for salvage therapy.

On logistic regression analysis, several factors, including recipient age, gender, ABO and Rhesus incompatibility, donor type, type of biliary reconstruction, and primary etiology of disease, were evaluated as a risk factor for biliary complications (Table 3). Type of biliary reconstruction was the only variable associated with the development of biliary complications. The frequency of biliary complications was significantly higher among the duct-to-duct anastomosis group than among the

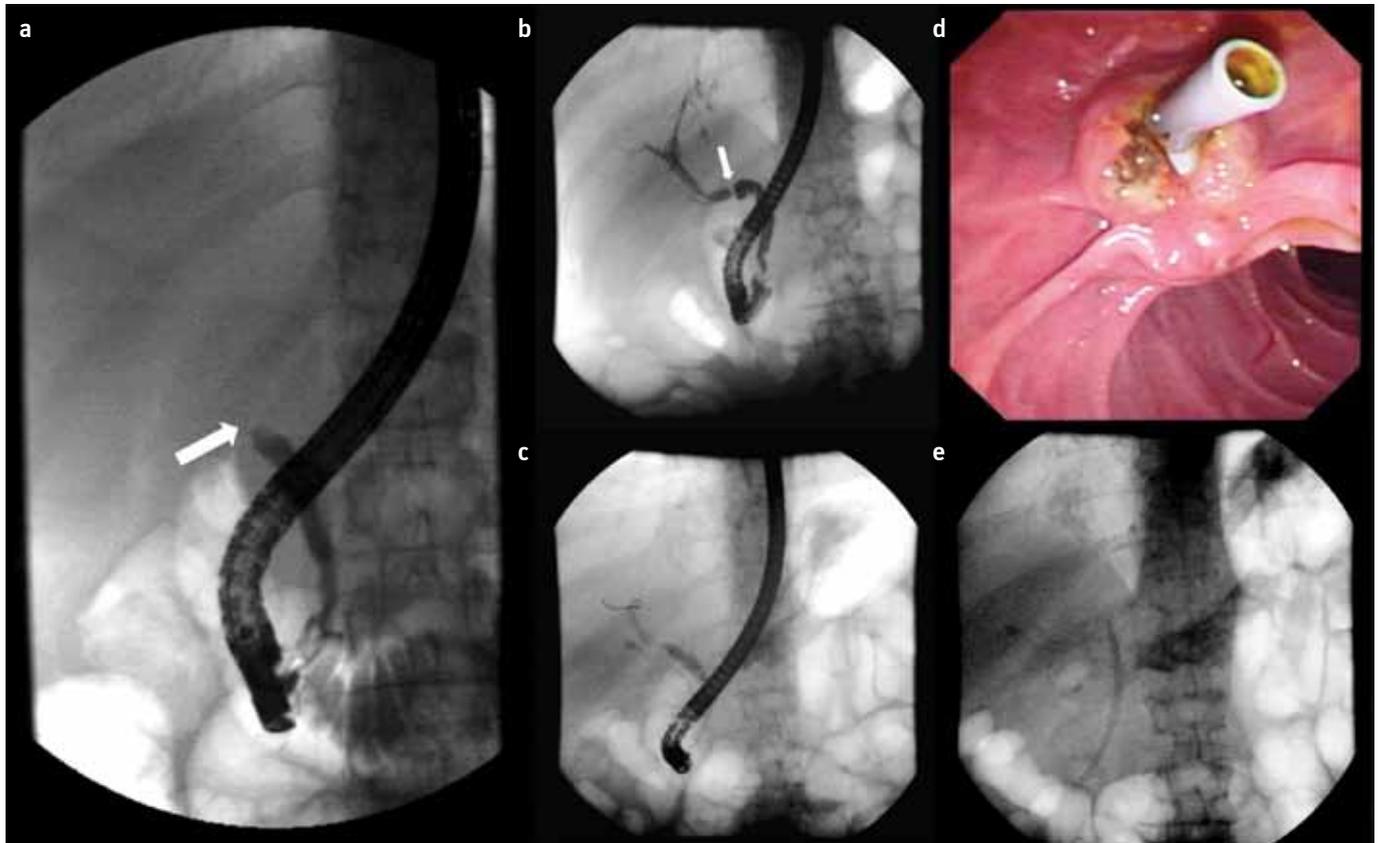


Figure 1. a-e. Biliary stricture (white arrow) following liver transplantation (a, b). ERCP guided drainage and balloon dilatation with stent placement (c, d). Fluoroscopic image after stent placement (e).

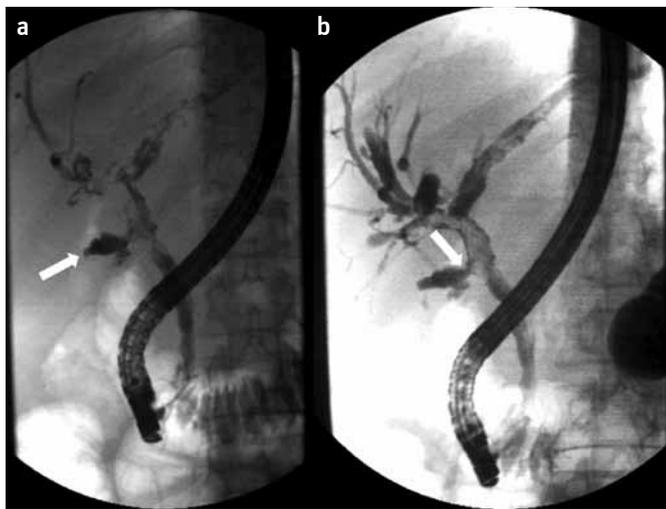


Figure 2. a, b. Biliary leakage (white arrow) following liver transplantation. Roux-en-Y anastomosis group (OR 3.346; 95% CI: 1.409-7.946; $p=0.005$) (Table 3).

No major ERC- or PTC-related complications, including uncontrolled bleeding and perforation, were observed. Mild abdominal discomfort, transient asymptomatic hyperamylasemia, and mild/moderate pancreatitis were observed in a minority of the cases. Hospitalized patients were treated with conservative strategy, including fluid replacement and/or antibiotic treatment, and discharged after 2-3 days.

DISCUSSION

In the present study, the incidence of overall biliary complications following liver transplantation was 36%; anastomotic biliary structure (15%) was the most common biliary complication, followed by biliary leakage (10%). These results are consistent with previous reports (1,4,5,19). A systematic review comprised 61 published papers, demonstrating that the overall incidence of biliary stricture and leakage was 13% and 8% (5). These results indicate that biliary complications following liver transplantation remain the most common problem in transplantation units.

Several studies have investigated the factors, including recipient factors, graft factors, operative factors, and postoperative factors, that predict the development of biliary complications following liver transplantation (4-10). Some, such as hepatic artery thrombosis, have been identified as a risk factor; some, such as prolonged cold and warm ischemia, have been demonstrated to be associated with biliary complications, and some, such as donor type, are still conflicting. Several studies reported that the use of living donor graft was strongly correlated with biliary complications after transplantation as a result of a small duct size, the presence of multiple duct orifices, and devascularization of the bile duct (5,9,16,20). In the present study, no significant difference in overall biliary complications or the type of biliary complications between LDLT and DDLT recipients was observed.

Two biliary reconstruction methods, duct-to-duct and Roux-en-Y anastomosis, are widely used in most transplantation institutes. However, duct-to-duct anastomosis is frequently preferred because of the physiological continuity of the biliary system and technical advantages, such as easier access to the biliary system after transplantation, prevention of bowel content reflux to the biliary duct, and shorter duration of operation. Roux-en-Y anastomosis causes an open path to the bowel; thus, it may lead to the risk of clinical or subclinical ascending cholangitis and subsequently the development of biliary complications. It was emphasized that the type of biliary reconstruction is a major risk factor for biliary complications following transplantation (5). Several investigators documented that the incidence of biliary complication in recipients with duct-to-duct anastomosis is higher than in recipients with Roux-en-Y anastomosis (5,17,21,22). The present study pointed out that duct-to-duct anastomosis was significantly associated with a higher frequency of biliary complications (OR, 3.346), as compared Roux-en-Y anastomosis.

Endoscopic retrograde cholangiopancreatography is the primary approach to diagnosis and treat biliary complications after liver transplantation in our center. Balloon dilatation (range, 6 or 8 mm), combined with stent placement (mostly using one stent, 10Fr), is the most common treatment modality for biliary stricture. The overall success rate of endoscopic and percutaneous treatment modalities was 81% in the present study. The success rate was slightly higher in patients with DDLT than in patients with LDLT (93.3% vs. 75%, $p>0.05$). It has been shown that balloon dilatation, combined with stent placement, is a highly effective treatment approach for biliary stricture, as compared to balloon dilatation alone (5). In the present study, only 2 patients with biliary stricture following transplantation underwent surgical revision for biliary reconstruction, whereas the rest of the patients were successfully treated with endoscopic and percutaneous treatment modalities.

In conclusion, this study indicates that biliary complications remain the most common complication of liver transplantation; biliary stricture was the most commonly seen. The use of duct-to-duct anastomosis for biliary reconstruction is a risk factor for the development of biliary complications. Endoscopic and percutaneous treatment of biliary complications was successful in the majority of these patients.

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