


# Incidents and risk factors of biliary complications after orthotopic liver transplantation

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## Abstract

Biliary complications (BC) especially stenosis and strictures are the most common complications after orthotopic liver transplantation (OLT) procedure in adult recipients. The intention of this study was analyzed BC in 273 patients after OLT for the last 4 years in our department.

Retrospective study of 273 patients underwent cadaveric donor liver transplantation between January 2014 and December 2017. Most of them (n=268) have anastomosed bile duct in end to end, rest of them (n=5) underwent hepaticojejunostomy. Statistical analysis was performed using Fischer exact test and Student *t* test. A *P* value <.05 was considered significant.

BC were developed in 48/273 transplants (17.6%). The most frequent was biliary stricture (n=42, 87.5%) followed by bile leak (n=4, 8.3%) and choledocholithiasis (n=2, 4.2%). Treatment was usually using endoscopic retrograde cholangiopancreatography. Recipients with hypotension during and after OLT treated by norepinephrine have a higher index of BC.

Self-expanding metal stents implantation seems to be more effective than repeated balloon dilatation of anastomotic strictures with subsequent plastic biliary stent placement and associated with similar complication rate. Good fluid management against inotropic therapy may reduce risk of BC.

**Abbreviations:** AS = anastomotic strictures, BC = biliary complications, CIT = cold ischemia time, ERCP = endoscopic retrograde cholangiopancreatography, MELD = model of end-stage liver disease, OLT = orthotopic liver transplantation, PBS = plastic biliary stent, SEMS = self-expanding metal stents.

**Keywords:** biliary complications, endoscopic retrograde cholangiopancreatography, orthotopic liver transplantation, plastic biliary stent, self-expanding metal stents

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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## 1. Introduction

Liver transplantation is the only lifesaving therapeutic option for patients with the end-stage liver disease. Complications involving biliary tract have been the common problem after orthotopic liver transplantation (OLT). Classification of biliary complications (BC) is based on their occurrence, location and etiology. The most frequent are: biliary stenosis, strictures and leakage; less frequent are: Oddi sphincter dysfunction, hemobilia, and obstructions caused by stones, sludge or casts.<sup>[1]</sup> Despite the progress in the donor selection, methods of preservation and transportation of harvested organs, immunosuppression or surgical techniques, the rate of BC remains high. These complications occur in 10 to 30% of all OLT, usually early after surgery within the first 3 months, and are responsible for 10% of deaths.<sup>[2–7]</sup> Most of them are treated using endoscopic retrograde cholangiopancreatography (ERCP), but selected cases require reoperation or retransplantation. The standard method for ERCP management of anastomotic strictures (AS) is repeated balloon dilation of the stricture with subsequent insertion of a plastic biliary stent (PBS) 3 months apart.<sup>[8,9]</sup> Recent studies show that in post-OLT patients not responding to standard endoscopic treatment, the placement of self-expanding metal stents (SEMS) is a valid alternative to surgical treatment.<sup>[10,11]</sup> Different risk factors have been related to BC, such as recipient age, indications for OLT, Child–Pugh and model of end-stage liver disease

(MELD) score, cold ischemia time (CIT), hepatic artery complications.<sup>17]</sup>

The aim of this retrospective study was to analyze BC in patients after OLT performed in our department with a special attention on risk factors that might play role in BC development.

## 2. Material and methods

We retrospectively analyzed 273 consecutive patients who were transplanted between January 2014 and December 2017 in our department. Informed consent was given in all cases. Ethical approval was not necessary, because of standard treatment. All patients underwent cadaveric donor liver transplantation. The main solution used for preservation was University of Wisconsin. The organ was perfused through aorta after clamping it and through the portal vein. All transplantations were performed with a piggyback technique. The majority of patients ( $n=268$ ) have had bile duct anastomosed in end to end fashion using a continuous 6-0 Monoplus suture without T-tube drainage; only 5 patients underwent hepaticojejunostomy. Standard immunosuppression based on tacrolimus, mycophenolate mofetil and steroids. BC diagnosis based on biochemical test results and clinical symptoms of cholestasis. To confirm the diagnosis, cholangio-magnetic resonance imaging and/or ERCP were done. All ERCP procedures were performed by 2 experienced endoscopists using Olympus duodenoscope model EVIS EXERA II TJF-Q180V (Olympus Co., Tokyo, Japan). Procedures were performed under propofol sedation in the semiprone position. Three of the recipients underwent balloon dilatation of the stricture followed by PBS placement. After 3 months ERCP was repeated, stent was removed and the stricture was assessed again. If the stricture persisted, the whole procedure was repeated. If otherwise, the patient was placed on a clinical follow-up. The rest of the recipients ( $n=16$ ) underwent ERCP with SEMS implantation using KAFFES Biliary Stent (Taewoong Medical, Seoul, Korea), which was designed to treat AS after liver transplantation. At approximately 6 months after the first ERCP, the stent was removed to assess the stricture. If the stricture resolved, the patient was placed on a clinical follow-up. If the stricture did not resolve, further stenting was performed, in some cases with additional balloon dilatation.

Factors related to the recipient (sex, age, etiology of liver disease, MELD score, Pugh–Child classification) and to the procedure (donor age, CIT, operation time, and inotropic therapy for hypotension) were analyzed and compared between recipients with and without BC. Results of endoscopic treatment with SEMS and PBS were also compared. Statistical analysis was performed using Fischer exact test and Student *t* test. A *P* value of less than .05 was considered significant.

## 3. Results

Between 2014 and 2017, 273 adult patients (161 males, 58.9%) in a median age of 53 years (range 18–72) underwent cadaveric donor liver transplantation. Their characteristics is shown in Table 1. The main indication for OLT was cirrhosis due to viral hepatitis C or B, followed by alcoholic disease. The average severity score of liver dysfunction was 14.3 according to the model for end-stage liver disease (MELD) and 7.8 points according to the Child–Pugh classification. Due to a significant hypotension 82 patients received inotropic therapy with norepinephrine (Levonor) during and soon after OLT. BC were

**Table 1**

**Patient's characteristics (n=273).**

	Mean or numbers	SD or (%)	Range
Etiology			
Hepatitis C	108	(40.0)	
Hepatitis B	18	(6.6)	
Alcoholic	66	(24.2)	
PBC	13	(4.8)	
PSC	8	(2.9)	
NASH	3	(1.1)	
Wilson disease	7	(2.6)	
AIH	16	(5.9)	
Others	34	(11.9)	
Inotropic therapy (Levonor)	82	(30.0)	
Gender (male)	161	(58.9)	
Recipient age (yr)	53.3	11.8	18 to 72
Child–Pugh score	7.8	2.4	4 to 15
MELD score	14.3	8.6	5* to 40
Donor age (yr)	46.2	13.5	12 to 73
CIT (min)	330.6	105.4	125 to 700
Operation time (min)	332.8	56.0	190 to 520

AIH=autoimmune hepatitis, CIT=cold ischemia time, MELD=model of end-stage liver disease, NASH=nonalcoholic steatohepatitis, OLT=orthotopic liver transplantation, PBC=primary biliary cirrhosis, PSC=primary sclerosing cholangitis, SD = standard deviation.

\* Patients with hepatocellular carcinoma had MELD score between 5 and 15.

diagnosed in 48/273 recipients (17.6%). The most frequent was biliary stricture ( $n=42$ , 87.5%) followed by bile leak ( $n=4$ , 8.3%) and choledocholithiasis ( $n=2$ , 4.2%). Endoscopic treatment, based on sphincterotomy, balloon dilatation, and stenting of the bile duct, was performed in 19 cases. Comparison of the results of SEMS implantation and standard ERCP stricture management protocol is shown in Table 3. Surgical treatment such as hepaticojejunostomy, reoperation, or retransplantation was necessary in 7 patients. Remaining 22 patients did not require any treatment of BC. BC were more frequent in those recipients who were treated with norepinephrine (Levonor) during perioperative period (48% vs 21%,  $P<.05$ ). Recipients with BC were significantly younger in comparison with recipients without any biliary problems ( $50.9\pm 12.1$  vs  $54.3\pm 11.4$ ,  $P<.05$ ). The other risk factors such as donor age, Child–Pugh and MELD score, CIT were not statistically significantly different between groups with and without BC (Table 2).

## 4. Discussion

BC still belong to the commonest problems after liver transplantation. Our analysis revealed that the incidence of BC

**Table 2**

**Recipients with and without biliary complications after OLT with regard to potential risk factors for these complications.**

Risk Factor	Biliary complications (n=48)	Without biliary complications (n=225)	<i>P</i> value
Recipient age (yr)	50±12.1	54.3±11.4	.026
Child–Pugh score	8±2.4	7.8±2.4	NS
MELD score	14.5±8.8	14.4±8.8	NS
CIT (min)	331.1±105.2	353.9±124.9	NS
Inotropic therapy	21 (44%)	61 (27%)	.0017
Donor age (yr)	46.3±13.4	46.2±11.8	NS

CIT=cold ischemia time, MELD=model of end-stage liver disease, NS = nonsignificant.

**Table 3****Results of endoscopic treatment.**

	SEMS	PBS	P value
Number of procedures n (%)	16/19 (84.2)	3/19 (15.8)	.0001
Recurrence n (%)	2/16 (12.5)	3/3 (100)	.0103
Successful treatment n (%)	14/16 (87.5)	0/3 (0)	.0103
Complication: cholangitis n (%)	2/19 (10.5)	1/3 (33)	NS

PBC=primary biliary cirrhosis, NS = nonsignificant, SEMS = self-expanding metal stents.

was comparable to that reported in large OLT series. Previously reported risk factors of BC such as donor age, prolonged CIT, and severity of liver insufficiency expressed as MELD and Child–Pugh scores were not statistically significant in our series. We noticed that recipients with hypotension treated with norepinephrine during and after OLT procedure are at greater risk of BC than those managed without vasoconstrictors. Norepinephrine, also called noradrenalin, is a human hormone and neurotransmitter. It is routinely used to increase heart rate and blood pressure in patients with a critical hypotension. During graft reperfusion, systemic pressure decreases because blood fills in liver vessels. Therefore inotropic therapy is needed to help achieve mean arterial pressure >50 during and after reperfusion. However, it causes vasoconstriction of peripheral arteries that results in a reduced blood flow to the gastrointestinal tract and increases blood flow to the skeletal muscles. Particularly sensitive to this redistribution of blood are the bile ducts, where ischaemia quickly leads to stenosis or strictures.

Many studies have shown that prolonged ischemia time can be the main risk factor for the development of biliary stricture.<sup>[1,5,6]</sup> In our series CIT rarely exceeded 10 hours. Probably this is the reason why we did not observe any relationship between duration of CIT and the rate of BC. As many as 60% of the patients with BC, who required treatment, were managed endoscopically. ERCP is the treatment of choice in the management of postoperative AS after OLT. Despite the necessity of repeating the procedure in many instances, AS dilatation followed by PBS placement is considered a gold standard treatment modality in post-OLT patients.<sup>[8]</sup> However, the continuous rise in the number of reports on the application of SEMS is observed, and the relevance of SEMS insertion in AS management increases.<sup>[8,10,11]</sup> Compared with balloon dilatation with subsequent PBS placement, SEMS implantation is associated with similar or higher resolution rates, often over 80%.<sup>[8,9]</sup> It is a safe and successful procedure which can reduce the need for further surgical interventions.<sup>[7]</sup>

The limitation of our study is the small number of patients who were treated with plastic stents. More comprehensive studies are needed.

In conclusion, the incidence of BC in our institution is comparable with the incidence reported in the other liver transplant centers worldwide. In comparison to the standard endoscopic management of post-OLT AS, SEMS implantation seems to be more effective than repeated balloon dilatation of AS

with subsequent PBS placement and is associated with a similar complication rate. An appropriate fluid management using crystalloids or colloids in recipients with hypotension instead of using inotropic therapy can preserve the best blood supply to the bile duct.

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