Incidence of and risk factors for bile duct stones after living donor liver transplantation: an analysis of 100 patients

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Running title: Risk for bile duct stone following transplantation

Abstract

Aim: Although bile duct stone (BDS) is one of the biliary complications of liver transplantation, analytical studies, particularly on living donor liver transplantation (LDLT) cases, are rare. This study aimed to clarify the incidence of and risk factors for BDS following LDLT.

Methods: We retrospectively reviewed the medical records of 100 patients who underwent LDLT at our institute from August 2000 to May 2012, and analyzed their clinical characteristics and risk factors for BDS.

Results: Of these, 10 patients (10.0%) developed BDS during the observation period. The median follow-up period to BDS diagnosis was 45.5 (5–84) months after LDLT. Univariate analysis revealed male sex, right lobe graft, and bile duct strictures as factors that significantly correlated with BDS formation. Multivariate analysis revealed bile duct strictures (odds ratio, 7.17; P = 0.011) and right lobe graft (odds ratio, 10.20; P = 0.040) to be independent risk factors for BDS formation. One patient with BDS and biliary strictures succumbed to sepsis from cholangitis.

Conclusion: In the present study, right lobe graft and bile duct strictures are independent risk factors for BDS formation after LDLT. More careful observation and monitoring are required in the patients with high risk factors.

Key words: bile duct stone, complication, living donor liver transplantation, male gender, right lobe graft

Introduction

Liver transplantation (LT) is a powerful therapy for patients with severe liver diseases, and its importance has been clearly recognized worldwide with the progression of surgical and perioperative care techniques. However, various complications still occur after LT, with biliary complications being relatively common. The reported incidence of biliary complications is approximately 5%–25%.[1–3] Bile duct stone (BDS) is one of these biliary complications, often leading to severe cholangitis.[2, 4, 5] The reported incidence of BDS following LT is approximately 5%.[6, 7] Moreover, several authors have reported the following risk factors for BDS after deceased donor LT: bile duct strictures, prolonged warm ischemia periods of grafts and increased total cholesterol levels.[8–11] However, few studies have analyzed BDS incidence after living donor liver transplantation (LDLT). In Japan, LDLT is predominantly performed because of the lack of deceased donor organs. This study aimed to review the clinical characteristics and outcomes of patients who developed BDS after LDLT and clarify the incidence of and risk factors for BDS after LDLT.

Patients and methods

We enrolled 100 patients from a total of 157 patients who underwent LDLT at Nagasaki University Hospital from August 2000 to May 2012, excluding pediatric patients (<18 years) and patients who died in the early post-operative period (until 30 days). All of them were followed up for at least 5

months. We retrospectively reviewed their clinical course records, operative logs, blood examination, and radiology and endoscopic findings to analyze their clinical characteristics and risk factors for BDS.

In our institute, biliary reconstruction was performed by duct-to-duct anastomosis with an interrupting suture over a retrograde transhepatic biliary drainage tube (tube diameter, 2 mm) whenever possible. However, for patients with biliary atresia, primary sclerosing cholangitis and intraoperative bile duct injuries we selected hepatico-jejunostomy over internal stenting. To evaluate the association between biliary ischemic change and BDS formation, the total ischemia time (TIT), defined as the duration from clamping of donor vessels to reperfusion of the recipients' portal vein, was also recorded. In our institute, periodic examinations are regularly conducted after transplantation.

We usually check the liver function of patients by blood examination once a month and perform abdominal enhanced computed tomography (CT) every 6 months, even if recipients have no symptoms. When we detected clinical suspicious symptoms of cholangitis such as abdominal pain with fever or abnormal increase in liver enzymes, we performed either magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiography (ERC). When the cholangitis required drainage, our first choice was endoscopic treatment; therefore, percutaneous

transhepatic cholangiography (PTC) was performed if ERC, including deep endoscopic procedures, failed because of bile duct deformity or hepatico-jejunostomy. Bile duct stricture was defined as any narrowing of bile ducts identified by CT, MRCP, or ERC that is associated with graft dysfunction and required any kind of interventional procedures. Hepatic artery complications and portal vein complications were diagnosed by enhanced CT and Doppler sonography.

Primary immunosuppression was induced after LDLT using standard dual therapy with tacrolimus (Tac) or cyclosporine (CyA) and steroids, although some patients with impaired renal function received basiliximab (BX) or mycophenolatemofetil (MMF).

Statistical analysis

Categorical variables were analyzed using the χ-square test or Fisher's exact test, while continuous variables were analyzed using Student's *t*-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. Logistic regression analysis was used to identify variables that independently predicted BDS incidence. A P-value of <0.05 was considered statistically significant in all analyses. All statistical analyses were performed using STATFLEX Version 6 (Artech Co., Ltd. Osaka, Japan).

Results

Clinical characteristics of patients

Totally, 100 patients [42 males, 58 females; mean age, 52.9 ± 12.2 (22–72) years] with LDLT were analyzed. The median observation period was 49.5 (5–143) months. The indications for liver transplantation are summarized in **Table 1**. The ABO blood type was incompatible in 15 (15%) patients. Of the 100 patients, 52 (52%) underwent right lobe transplantation and 48 (48%) underwent left lobe transplantation. For 92 (92%) patients, duct-to-duct anastomosis was selected to reconstruct the biliary system, while hepatico-jejunostomy was selected for eight (8%). Multiple biliary reconstruction was performed in 13 patients, 12 of whom underwent right lobe grafting. Of the 13 patients, 12, including one who underwent left lobe grafting, required double anastomosis; the remaining one required triple anastomosis. The median TIT was 170 (106–555) minutes. Primary immunosuppression was induced after transplantation using Tac in 55 patients, Tac with MMF in 28 patients, CyA in 9, CyA with MMF in 3, BX in 1, BX with MMF in 3, and BX with Tac in 1. With regard to other medications, ursodeoxicholic acid (UDCA) was used in 37 (37%) patients.

Incidence of BDS and other complications

Ten patients (10%) developed BDS during the observation period. Of the 10 patients, 4 developed BDS in the proximal bile duct above the anastomotic site, including intrahepatic duct. Composition of the stones was identified in 6 of 10 patients: one patients had a cholesterol stone and the rest had

bilirubinate calcium stones. There was no bile duct filing defects diagnosed as biliary cast. The median duration from transplantation to BDS diagnosis was 45.5 (5–84) months. Twenty-two patients (14% of 157 patients) had bile duct strictures, six of whom also developed BDS. Bile duct stenting was performed for all patients with strictures, with 16 undergoing endoscopic stenting and 6 undergoing percutaneous stenting. Hepatic artery complications occurred in 7 patients (7%): thrombosis (n = 2), endothelial dissection (n = 1), hemorrhage (n = 2), blood flow decrease (n = 2). Patients with thrombosis, endothelial dissection and hemorrhage required surgical therapy, while blood flow decrease was treated with warfarin sodium.

Risk factors for BDS formation

To clarify the risk factors for BDS formation, we analyzed the relationships among some clinical variables and BDS formation. (**Table 2**) BDS was significantly common in male patients ($P < 0.05$), right lobe graft cases ($P < 0.05$), and those with bile duct strictures ($P < 0.01$). There was no significant difference in age, body mass index (BMI), model for end stage liver disease (MELD) score, rate of ABO blood type incompatibility, biliary reconstruction method (duct-to-duct anastomosis versus hepatico-jejunostomy, single anastomosis versus multiple anastomosis), hepatic artery complications and TIT between patients with BDS and those without. We also analyzed whether serum total cholesterol (TC) and serum triglyceride (TG) levels were elevated above 200

mg/dL and 150 mg/dL, respectively, during the observation period; however, there were no significant differences between groups. With regarding to medication use, we found that the use of CyA and UDCA did not influence BDS formation.

Univariate analysis revealed that male sex, right lobe graft, and bile duct strictures significantly correlated with BDS formation. Multivariate analysis revealed that bile duct strictures (Odds ratio 7.17; P = 0.011) and right lobe graft (odds ratio 10.20; P = 0.040) were independent risk factors for BDS formation. (**Table 3**)

Treatment of BDS and clinical outcome

Four (40%) patients with BDS who were asymptomatic and showed no abnormalities in liver function test were carefully followed. On the other hand, six (60%) patients required admission and interventional procedures such as ERC and/or PTC because of cholangitis. The median number of admissions and length of hospitalization (days) were 2.67 (1–4) and 37.8 (8–125) respectively, for these patients. The treatments administered to these patients and their clinical outcomes are shown in **Table 4**. In five of six treated patients, primary stone extraction was successful, and stone clearance had been confirmed using balloon cholangiography and intraductal ultrasonography. However, two patients developed recurrence of BDS and one had a residual intrahepatic stone. The patient who had residual intrahepatic stone received stenting across stricture and stone, which stabilized their

condition (**Figure 1**). To prevent ascending cholangitis, we inserted stents into the bile duct in all the patients that required drainage. The stents were placed across the stricture, and the distal edge was located above the sphincter of Oddi. In all patients, we used the stent delivering system (Flexima^{TM} Biliary Stent System, Boston Scientific) and modified plastic tube stent (sizes 7.0 Fr, a 2-0 nylon thread attached to the distal side-hole for easy removal). No procedure-related complications occurred in these patients.

One patient succumbed to sepsis following severe cholangitis. This patient was 56-years-old male who underwent LDLT with duct-to-duct anastomosis using right lobe graft. Four month after LDLT, he developed biliary duct strictures with cholangitis; therefore, PTC and balloon dilation were performed because endoscopic therapy was impossible due to bile duct deformity. However, the patients developed repeated cholangitis, and all our attempt to clearing BDS and bile duct strictures using non-surgical techniques, including cholangioscopy or extracorporeal shock wave lithotripsy, failed. Although the necessity of re-transplantation was recognized and the procedure was scheduled, it was not undertaken because the patients developed sepsis with acute respiratory distress syndrome.

Discussion

In our study, BDS were developed in 10% of adult recipients who underwent LDLT. The reported incidence of post-transplant BDS varies widely among different study groups depending on the nature of the study population and manner of subject setting. In the study of Spier et al., 49 of 1289 recipients (3.8%) developed BDS.[8] In the majority of the other studies, the incidence was reported to be approximately 5%[6, 7], whereas it was as high as 37% in other report.[12] In almost all previous studies, BDS was identified and diagnosed in patients who underwent examinations for clinically suspected cholangitis. However, some patients with BDS in our study had no symptoms and were incidentally diagnosed by protocol CT. Therefore, the incidence of BDS in the present study may be relatively higher than that in other reports, and our data may represent the actual state of BDS after LDLT.

According to multivariate analysis, bile duct strictures and right lobe graft were independent risk factors for BDS. The association between bile duct strictures and BDS has also been reported previous studies.[8, 10, 11] We also speculate that bile duct strictures are likely to cause bile stasis and secondary infection, which results in the formation of bile duct sludge and stones. Nevertheless, eight patients developed common bile duct (CBD) stones, and of these, 6 had only CBD stones. (Table 4) In addition, bile duct strictures were not observed in 4 of 6 patients with CBD stones. For this reason, it is suggested that some factors related to operation other than bile duct strictures, such

as ischemic change or nerve disorder of the tissue surrounding CBD followed by biliary epithelial damage, influence BDS formation.

As shown above, right lobe graft was an independent risk factor of BDS. Some authors also indicated that the incidence of biliary complications was higher in patients who underwent LDLT with right lobe grafting than in those who underwent LDLT with left lobe grafting. In recent studies, the incidence of bile duct strictures in patients who underwent right lobe grafting was 8.3-32.8% [13–15], while that in patients who underwent left lobe grafting was <15%.[16–18] We performed subgroup analysis to elucidate difference between patients who underwent right lobe grafting and those who underwent left lobe grafting and found no statistically significant difference in the incidence of bile duct strictures. (**Table 5**) However, the number of male was significantly higher among the patients who underwent right lobe grafting. It is reasonable that the right lobe is selected to ensure appropriate size of grafts in male patients. With regard to the epidemiological survey of 1997 conducted by the Japanese Ministry of Health, Labor and Welfare, BDS was more common among males than among females. Although its cause is not clear, gender may have some relation to the development of BDS in patients who undergo right lobe grafting.

Several studies have reported that biliary ischemic change was a risk factor for the development of BDS after LDLT.[6, 10] In patients with biliary cast syndrome in particular, identified as the hard dark

material taking the physical shape of the bile duct, biliary ischemia is believed to damage the bile duct mucosa and lead to cast formation.[10] However, ischemic factors such as TIT or hepatic artery complications were not detected as significant risk factors for BDS in the present study. We suggest that the characteristics of patients without cast formation contribute to this result.

Recently, endoscopic treatment is usually chosen as the primary approach for the management of biliary complications following LT.[19–21] Endoscopic procedure also makes it possible to shorten hospitalization of most post-transplant BDS patients with less invasiveness.[8,11,22] However, in some difficult situation, such as displacement of duodenal papilla or deformity of biliary tract, endoscopic intervention is somewhat complicated and challenging. In addition, duodenobiliary reflux and bacterial contamination of bile duct related to recurrence of BDS may occur after endoscopic intervention. Many authors reported that the incidence of biliary complications, such as cholangitis and recurrence of BDS, was higher in patients after EST than in those after EPBD.[23-25] Moreover, Natsui et al. reported that EPBD has a possibility of suppressing bacterial contamination of the biliary tract compared with EST in patients with small stones.[26] Therefore, it is desirable to choose EPBD for treatment of BDS whenever possible, especially in patients treated with immunosuppressant after transplantation. Although we mainly treated patients who underwent right lobe grafting in the present study, it appears that there is no great difference between right lobe graft cases and left lobe graft cases regarding treatment of CBD stones. Nevertheless, in the case of BDS

locating in proximal bile duct above anastomotic site, endoscopic intervention may be more difficult in patients with right lobe grafting than in those with left lobe grafting because of multiple biliary reconstruction or acute angulation of bile duct. As described in Table 4, we performed endoscopic therapy in six of 10 patients who developed BDS, with successful stone removal in five patients (83%). The success rate of stone extraction in previous studies ranged from 71% to 100%.[8, 11, 22] We believe that endoscopic therapy for BDS can be successfully performed in most cases, even after transplantation. However, two patients (40%) developed recurrence of BDS in our study, and both also had biliary strictures. The recurrence rate of treated BDS developed after LT has rarely been reported. In the study of Rerknimitr et al., 8 of 46 patients (17%) developed recurrence of BDS after treatment.[2] In previous reports on not post-transplant populations, the BDS recurrence rate was 3.2%-8.8%.[27–29] As mentioned above biliary stricture is an independent risk factor, besides it can also be considered as a cause of high recurrence rate in the absence of drastic treatment, namely surgery, including re-transplantation. One patients with biliary strictures and BDS in our study succumbed to biliary sepsis during the observation period. The optimal timing of re-transplantation is difficult to determine because of the limited supply of organs available for LT. In Japan, the shortage of donors is a particularly serious problem because deceased organ donation is not well established owing to religious beliefs. Therefore, we have to rely on graft donation from family members in most patients. However, this is sometimes a restricting factor for re-transplantation.

Several studies about post-transplantation BDS, including biliary cast syndrome, have been reported till date; however, none have centrally focused on BDS after LDLT. In the present study, we determined the risk factors for and clinical features and clinical outcomes of BDS following LDLT. We identified two independent risk factors, namely bile duct strictures and right lobe graft which were significantly related to BDS formation after LDLT. Furthermore, bile duct stricture may be a predictor of poor outcome in patients with BDS after LDLT. Therefore, we should pay special attention to LDLT patients who develop BDS accompanied by bile duct strictures and schedule timely re-transplantation. We believe that it is important to shorten follow-up period of patients with bile duct stricture, especially in right lobe graft cases.

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Figure legend

Figure 1.

(A) A patient with multiple bile duct stones (BDS; arrow head), including intra-hepatic (IH) stones, with anastomotic biliary strictures after living donor liver transplantation. (B) A stone located in common bile duct was extracted successfully by using basket catheter, and it was calcium bilirubinate stone. (C) To prevent cholangitis caused by the residual IH stone, an internal stent (7Fr, 5 cm, plastic stent) was inserted over the anastomotic stricture (arrow head). (D) A 2-0 nylon thread was attached to the distal side hole of stent for easy removal.

Table 1 The indications for liver transplantation.

Primary disease	Number of patients
Hepatitis B virus related cirrhosis (LCB)	28
HCC in LCB	13
Hepatitis C virus related cirrhosis (LCC)	40
HCC in LCC	13
LCC with hepatitis B virus	2
Alcohol induced cirrhosis (LCAL)	11
HCC in LCAL	3
Non-alcoholic steatohepatitis (NASH)	8
HCC in NASH	1
Primary biliary cirrhosis	4
Primary sclerosing cholangitis	1
Fulminant hepatitis	6
Biliary atresia	1
Caroli disease	1

Abbreviation: HCC, hepatocellular carcinoma

Table 2 Multiple variables in living donor liver transplant patients with or without bile duct stone (BDS). (n=100)

Variables	BDS (+)	BDS (−)	P-value
Age (mean ± SD)	58.3 ± 6.8	52.5 ± 12.6	0.146
Sex (number)			0.025
Male	9	49	
Female	1	41	
BMI (mean ± SD)	25.1 ± 3.3	23.9 ± 3.8	0.381
MELD score (mean ± SD)	17.4 ± 10.4	14.5 ± 8.1	0.344
Graft lobe (number)			0.011
Right	9	42	
Left	1	48	
Blood type compatibility (number)			0.720
match and compatible	9	76	
incompatible	1	14	
Reconstruction manner (number)			0.599
Duct-to-duct anastomosis	10	82	
Hepatico-jejunostomy	0	8	
Multiple anastomosis (number)	1	11	0.657
Bile duct stricture (number)	6	16	0.002
Hepatic artery complications (number)	1	6	0.533
TIT (median, minute)	178 (104 - 345)	169 (108 - 555)	0.381
Primary IS (number)			0.687
Cyclosporine	3	9	
Tacrolimus / others	7	81	
Use of UDCA (number)	4	33	0.920
TC elevation >200mg/dl (number)	6	54	0.734
TG elevation >150mg/dl (number)	5	42	0.539

Abbreviation: SD, standard deviation; TIT, total ischemic time; IS, immunosuppressant; UDCA, ulsodeoxycholic acid; TC, total cholesterol; TG, total triglyceride

P-value for age and MELD score based on Student's t-test, and for TIT based on Mann-Whitney *U*-test; all others based on Fisher's exact test.

Table 3 Risk factors for bile duct stone formation after living donor liver transplantation: Multivariate analysis (n = 100)

Variables	OR	CI	P value
Male sex	6.00	0.65 - 55.79	0.115
Right lobe graft	10.20	1.12 - 93.21	0.040
Bile duct stricture	7.17	1.58 - 32.60	0.011

Abbreviation: OR, odds ratio; CI, confidence interval

P-value for all variables based on multiple logistic regression analysis.

Table 4 The summary of treatment and clinical outcome in bile duct stone (BDS) cases.

Case	Location and size of BDS	Treatment	Clinical outcome
63y.o F	CBD (10mm)		
59y.o M	IH (13mm)	These cases have been followed up with no symptoms	
57y.o M	CBD (10mm)		
65y.o M	CBD (5mm)		
56y.o M	CBD, IH (multiple)	ESWL + PTC	death of sepsis
51y.o M	CBD (8.3mm), IH (15.3mm)	EST + stenting*	IH stone remained
63y.o M	CBD (20mm)	EPBD + stenting*	no recurrence
54y.o M	CBD (5mm)	EPBD + stenting*	no recurrence
44y.o M	CBD (10mm)	EST + stenting*	recurrence in CBD
66y.o M	IH (5mm)	stenting*	recurrence in CBD

Abbreviation: CBD, common bile duct; IH, intra-hepatic duct; ESWL, extracorporeal shock wave lithotripsy; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation

*"Stenting" means internal tube-stent insertion over biliary stricture.

Table 5 Comparison and univariate statistical analysis between right lobe graft and left lobe graft. (n = 100)

Variables	Right lobe graft	Left lobe graft	P value
Bile duct stone (number)	9/52	1/48	0.011
Age (mean, y.o)	51.8	53.9	n.s.
Gender (number, male/female)	36/16	22/26	0.018
MELD score (mean, point)	15.1	14.7	n.s.
ABO incompatibility (number)	7/52	8/48	n.s.
TIT (median, minute)	177 (104–555)	165 (109–250)	n.s.
Hepatic artery complication (number)	3/51	4/48	n.s.
Bile duct stricture (number)	13/51	9/48	n.s.
Cholangitis (number)	18/51	10/48	n.s.

Abbreviations: n.s., not significant; MELD, model for end stage liver disease; TIT, total ischemic time

P value for age and MELD score based on Student's t-test, and for TIT based on Mann-Whitney *U*-test; all others based on Fisher's exact test.

Figure 1