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Risk Factors and Management for Biliary Complications Following Adult Living-Donor Liver Transplantation

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Background: Biliary complications (BCs) following liver transplantation are very serious. Nevertheless, it is still uncertain which components influence the incidence of BCs the most.

Material/Methods: A consecutive sample of 74 adult recipients who underwent living-donor liver transplantation were enrolled in this study. BCs that were Clavien-Dindo classification grade II or higher were determined as BCs.

Results: There were 11 out of the 74 recipients who experienced BCs. There were no differences in preoperative background factors between the BCs+ and BCs– group. Unexpectedly, the number of bile duct orifices did not contribute to the BCs (p=0.722). In comparison with the BCs– group, the frequency of post-operative bleeding requiring re-operation was relatively higher (27.3% *vs.* 7.9%, p=0.0913) and this complication was the only independent risk factor (p=0.0238) for the onset of BCs. Many of the BCs+ recipients were completely treated by endoscopic or radiological intervention (81.8%). However, surgical revision was required for 2 recipients (18.2%).

Conclusions: Given these results, it is reasonable to believe that definite hemostasis is required to prevent future BCs. In addition, bile duct multiplicity was not associated with BCs.

MeSH Keywords: **Biliary Tract • Liver Transplantation • Living Donors**

Abbreviations: **BCs** – biliary complications; **CIT** – cold ischemia time; **ERBD** – endoscopic retrograde biliary drainage; **LT** – liver transplantation; **HA** – hepatic artery; **LDLT** – live-donor related liver transplantation; **MELD** – model for end-stage liver disease; **PTCD** – percutaneous transhepatic biliary drainage; **PV** – portal vein

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Background

Biliary reconstruction in adult living-donor liver transplantation (LDLT) is considered a delicate procedure because it is usually narrower and more fragile compared to that of a deceased-donor related liver transplantation. Furthermore, there are occasions where multiple bile duct reconstruction is required for donor safety to prevent biliary stricture and leakage. Although it is complex, there appears to be consensus regarding biliary reconstruction techniques in LDLT.

The onset of biliary complications (BCs) usually requires repeated and long-term intervention. Thus, it is of vital importance to understand the risk factors for developing BCs. However, it is still unclear which components influence the future incidence of BCs the most. Moreover, the management of BCs is crucial to maintain long-term graft survival.

In the current study, a consecutive sample of 74 adult LDLT recipients were retrospectively analyzed in terms of the incidence, factors, and management of BCs.

Material and Methods

A total of 74 adult patients who had undergone LDLT at our university hospital, Kyoto Prefectural University of Medicine, from 2003 to 2015, were retrospectively enrolled. Ethics Committee approval was obtained from the Internal Research Ethics Committee of the Kyoto Prefectural University of Medicine. The patients were divided into the following groups according to the onset of BCs (n=11): biliary leakage (n=2); biliary stricture (n=8, onset range: 0.5–24 months following LT); and leakage and stricture (n=1, 3 months following LT).

Definition of biliary complications

The BCs in this research were Clavien-Dindo classification grade II or higher [1] and Grade 2b of the classification of common complications of liver transplantation [2].

We defined a biliary stricture as an anastomotic stricture [3]: segmental narrowing, where biliary anastomosis was performed or a drainage tube was inserted, confirmed by endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography. Diffuse biliary stricture, such as recurrent primary sclerosing cholangitis irrelevant to surgical procedure, was excluded. On the other hand, bile leakage was diagnosed by bile collection in abdominal drainage bags or leakage confirmed directly by endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography.

Operation procedure of biliary reconstruction

In terms of biliary reconstruction, choledochocholedochostomy was performed in all enrolled cases. In brief, a 4-French biliary stent was inserted from the distal front side of the common bile duct as an external drainage beforehand. Then, the posterior wall was sutured continuously or interrupted, and the anterior wall was sutured interrupted using 6-0 PDS (Ethicon, Somerville, NJ). Subsequently, the biliary stent was removed at 3 months, on average, after LDLT.

Immunosuppression

Tacrolimus and low-dose steroids were used as immunosuppression protocol. Intravenous tacrolimus was commenced following LDLT. The whole-blood concentration target level was 12–15 ng/mL during the first weeks. Generally, the intravenous tacrolimus infusion was terminated around the second week, and the initial target trough level was 10 ng/ml. Methylprednisolone at 10 mg/kg body weight was administered intravenously immediately before graft reperfusion. Methylprednisolone 1 mg/kg was given intravenously during post-operative days 1–3, followed by 0.5 mg/kg during post-operative days 4–6, and 0.3 mg/kg on post-operative day 7. Steroid administration was converted from intravenous to oral thereafter; 0.3 mg/kg/day prednisolone was administered and gradually decreased and terminated around post-operative day 60, except in cases of primary biliary cirrhosis or other autoimmune diseases as the original disease.

Statistical analysis

Data were analyzed by Mann-Whitney test, the *t* test was used for continuous data, and the chi-square test was used for categorical data. Data are presented as mean ± SD. Patient survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Variables theoretically correlated with BCs were considered candidates for multivariate analysis (logistic regression analysis). $p<0.05$ was considered as statistically significant. All analysis was carried out using GraphPad Prism 6 (GraphPad Software, Inc., San Diego, CA) and SPSS (Chicago, IL).

Results

During a minimum follow-up of 4 months, 11 (14.9%) out of 74 recipients experienced BCs (BCs group): biliary leakage (n=2); biliary stricture (n=8, onset range: 0.5–11 months following LDLT); and leakage and stricture (n=1, 3 months following LDLT).

Biliary stricture

In terms of the incidence, 9 out of 74 recipients (12.2%) had complications with biliary stricture. The onset of biliary stricture

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ranged from 0.5 month to 11 months (median: 4 months) following LDLT. Treatment for post-operative biliary stricture was as follows: endoscopic retrograde biliary drainage (ERBD); percutaneous transhepatic biliary drainage (PTCD); and surgical management. Generally, combined treatment of ERBD and PTCD was applied. In these cases, 8 recipients were initially treated by ERBD (5.5±2.8 months following LDLT), but 6 out of 8 patients were subsequently managed by PTCD (10.7±8.9 months following LDLT) primarily due to unsatisfactory outcomes. Only 1 patient underwent PTCD as an initial treatment 1 month after LDLT. Surgical revision is usually applied when ERBD/PTCD fails. Consequently, in our institution, 2 recipients (2.7%) required re-operation with hepaticojejunostomy at 3 and 11 months following LDLT. One patient, whose primary disease was primary biliary cirrhosis (PBC), was difficult to manage only by ERBD/PTCD because of subsequent diffuse intrahepatic biliary stricture. Other BCs+ recipients were successfully managed by ERBD/PTCD and hepaticojejunostomy; no recipients underwent re-transplantation. In a refractory case with a multiple bile duct graft, for example, the recipient had received a right lobe liver graft with anterior and posterior bile ducts: recipient right hepatic duct and the posterior branch were anastomosed, the recipient left hepatic duct and the anterior branch were also anastomosed, respectively. Biliary stricture was confirmed at both anastomotic sites 9 months after LDLT. The anterior segment was treated by ERBD and the posterior segment was managed by both PTCD and ERBD. The patient underwent both repeated endoscopic and radiological intervention over 2 years.

Biliary leakage

Three out of 74 (4.1%) patients demonstrated biliary leakage. One recipient had complications with biliary leakage from the anastomotic site and 2 recipients demonstrated leakage from the cut liver surface. Management for post-operative biliary leakage was as follows: percutaneous biliary drainage; ERBD; endoscopic ultrasound-guided biliary drainage; and surgical management. Percutaneous biliary drainage was effective to improve biliary leakage from the anastomotic site, which took 1 to 2 months. However, it can be difficult to treat non-communicating biliary fistula on the cut surface. As an example of an intractable case, a patient diagnosed with non-communicating biliary fistula was managed with percutaneous drainage and endoscopic ultrasound-guided biliary drainage through the stomach, waiting for atrophy of the responsible liver segment. Finally, the recipient improved at 6 months following LDLT.

Risk factors for biliary complications

There were no differences in recipient and donor age, model for end-stage liver disease (MELD) score, amount of blood loss, operative time, or cold and warm ischemia time between the BCs group and BCs-free group (Table 1). Furthermore, unexpectedly, bile duct multiplicity did not contribute to the BCs (p=0.722). In comparison with the BCs-free group, the frequency of post-operative bleeding (generally occurring within 3 weeks from transplantation) that required re-operation was relatively higher (27.3% *vs.* 7.9%, p=0.0913) and this complication was the only independent risk factor (p=0.0238, adjusted odds ratio 10.5) for the onset of BCs determined by the multivariate logistic regression analysis (Table 2). Although there was no significant difference due to the small number of patients, in terms of bleeding sites, it is notable that 100% (3/3; 2/3: anastomotic bleeding; 1/3: bleeding from a dead end of the middle hepatic artery) in the BCs group, and 20.0% (1/5: bleeding from a stripped hepatic arterial surface) in the BCs-free group were hepatic arteries, respectively.

Patient survival

Unexpectedly, the overall survival rate following LDLT in the BCs+ group was not significantly lower compared with that in the BCs– group. (100% *vs.* 88.7% at 1 year, 100% *vs.* 85% at 3 years, 85.7% *vs.* 82.5% at 5 years, 35.7% *vs.* 64.2% at 10 years, respectively (BCs+ *vs.* BCs–); p=0.5416) (Figure 1). The difference in 10-year survival was 28.5±21.6% (P_{d10}=0.285 (survival rate difference), SE_{di}=0.216 (standard error of the mean)) (P_{d10}/SEdi=1.30< t0.05 (1.99)). Thus, there was a tendency for patient survival to be lower in the BCs+ group at 10 years after LDLT, but the difference was not statistically significant.

Four out of 11 cases in the BCs+ group died during the follow-up period. Regarding the cause of death, 1 recipient died of graft failure primarily due to diffuse biliary stricture (recurrence of primary biliary sclerosis). The other 3 cases died due to reasons unrelated to BCs: brain hemorrhage, hepatitis C virus-related cirrhosis, and unknown cause.

Discussion

Biliary system complications following LDLT remain a significant cause of morbidity and mortality, and affect up to 30% of recipients [4]. To prevent the onset of BCs, various risk factors were identified in previous studies, such as a high MELD score [5], advanced donor age [6], longer cold ischemia time [7–9], and hepatic artery thrombosis [10,11].

It can be argued that blood supply, especially arterial blood, to the biliary system is closely related to BCs, because it is believed that both the intra- and extra-hepatic bile ducts are largely dependent on the arterial system for oxygenation [12]. Actually, hepatic arterial insufficiency, such as hepatic artery stenosis or thrombosis, has a significant effect on biliary stricture after liver transplantation [10,13]. In our institution,

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Table 1. Background factors of the two groups.

	BCs– (n = 63)	BCs+ (n = 11)	p-Value
Follow-up Period(month) Mean ±SD	63.7±47.0	64.1±44.4	0.981
Follow-up Period (month) Median (Range)	63.4 (4–146)	66.4 (5–147)	0.952
Background			
Gender	M30.F33	M3.F8	0.326
Recipient Median Age (Range)	53 (18–72)	56 (41–69)	0.624
Donor Median Age (Range)	44 (18–65)	38 (20–47)	0.044
MELD	16.4±7.6	18.6±4.7	0.364
Child-Pugh score	9.7±2.0	10.5±1.2	0.16
ABO-incompatible(%)	15.4	9.1	1.00
Operation			
Op time (min)	766.9±113.6	809.7±149.0	0.282
Blood Loss(ml)	5502.2±5662.6	7690±6230.6	0.254
CIT (min)	76.6±51.6	94.7±102.6	0.382
Put in to HA reflow (min)	130.7±35.6	146.2±33.5	0.199
WIT (min)	46.2±10.0	40.0±8.5	0.062
Graft type	Rt37.Lt26	Rt6.Lt5	1.00
Bile duct multiplicity (%)	28.6	36.4	0.722
Post operation			
Post operative bleeding (%) (at POD)	7.9 (9.0±3.2)	27.3 (11.3±11.0)	0.091
Rejection (%) (at POD)	23.8 (16.5±14.5)	18.2 (14.6±2.1)	1.00
Infection (%) (at POD)	44.4 (17.2±12.0)	54.5 (33.5±57.7)	0.745
HA thrombosis (%) (at POD)	1.6 (28)	0	1.00
PV thrombosis/stenosis (%) (at POD)	4.8 (43±49)	0	1.00

HA – hepatic artery; PV – portal vein; MELD – model for end-stage liver disease.

Table 2. Risk factors for biliary complications in living donor liver transplantation.

Variable	P value	Odds ratio	95% confidence interval
CIT	0.27	1.01	0.99–1.02
Bile duct multiplicity	0.93	1.07	0.20–5.10
Put in to HA reflow	0.23	1.01	0.99–1.03
Post-operative bleeding	0.0238	10.5	1.40–99.9

CIT – cold ischemia time; HA – hepatic artery.

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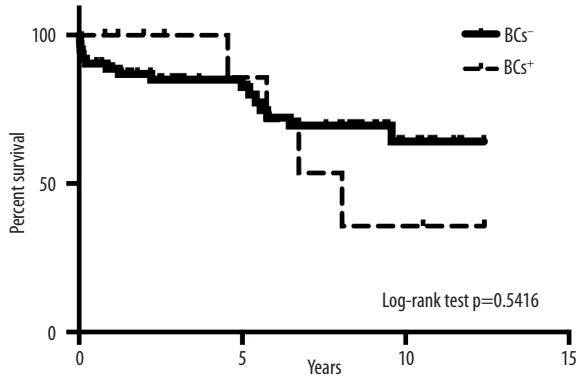

Figure 1. Survival rate following LDLT in the BCs+ group and the BCs– group.

because the incidence of arterial thrombosis/stenosis was relatively low (1.4%), the contribution of arterial thrombosis/stenosis to BCs was unclear.

In terms of cold ischemia time in LDLT, cooperation between the recipient and the donor team could keep it shorter to a certain degree, although it depends on the back-table procedure. In the current study, the cold ischemia time was 76.6 min in the BCs– and 94.7 min in the BCs+ group (NS). To reduce the slight prolongation of the cold ischemia time observed in the BCs+ group, simple graft selection is essential: no venous, artery, or biliary reconstruction are required in the back table, provided that simultaneous donor safety is secured.

Notably, our multivariate analysis indicated that post-operative bleeding is an independent risk factor for the onset of BCs. Generally, other important complications (rejection, infection, hepatic artery thrombosis, and portal vein thrombosis) occurred later than post-operative bleeding (Table 1). There was no apparent relation between these complications and post-operative bleeding.

Generally, in hemorrhagic shock there is a significant decrease in microvascular oxygenation, which is highly correlated with macrocirculatory indexes such as cardiac index and mean arterial pressure [14]. Post-operative bleeding leads to hemodynamic instability, which might result in ischemic injury to the bile duct. Simultaneously, bile duct cells are vulnerable to ischemia reperfusion injury [15]. Thus, it is reasonable to believe that post-operative bleeding leads to development of BCs. To prevent BCs, it is vitally important to keep vital signs stable following liver transplantation.

On the other hand, although there was a slight increase in the onset of BCs, bile duct multiplicity is irrespective of BCs provided that precise reconstruction of the bile ducts is performed. Therefore, it can be argued that graftectomy with multiple bile ducts are justified for live-donor safety.

Regarding the treatment of biliary stricture, ERBD is usually tried as an initial treatment, with attention to the onset of pancreatitis [16]. Unfortunately, PTCD is inevitably applied for the difficult cases in biliary cannulation, even though duct-to-duct reconstruction is performed. Then, an endoscopic biliary stent is placed at the stricture location. For invalid cases of biliary stent placement or difficult cases in both ERBD and PTCD approaches, surgical revision is chosen (retry of biliary reconstruction). In graft loss due to biliary stricture, re-transplantation is the only life-saving procedure available.

In terms of patient survival, there was no remarkable difference between the 2 groups, especially in the early stages following LDLT. This seems to be largely due to extensive care for BCs, as mentioned above. However, long-term outcomes were not satisfactory in the BCs+ group. Although the cause of death in the BCs+ group did not seem to correlate with BCs, intensive repeated treatment might impair the recipients' health, resulting in the onset of life-threating secondary morbidities. In general, unsatisfactory BC management might lead to biliary cirrhosis [17]. In our series of cases, there were no apparent correlations between them: no biliary cirrhosis was observed in the BCs group. Therefore, it can be argued that our intervention for BCs was performed at the appropriate time. To further improve patient survival in the BCs group, it might be better that BCs are addressed by surgery, including re-transplantation at an earlier stage. It is true that ideal timing of surgical revision, switching from ERBD/PTBD managements, still remains controversial. When all interventional methods have failed, re-operation is usually considered [18]. Nevertheless, because hepaticojejunostomy has lower morbidity compared to endoscopic management [19,20], early surgical revision might be justified to avoid long-term treatment, resulting in better long-term survival.

The retrospective nature of our study might have weakened our ability to find a causal relationship. However, this study attempted to demonstrate how the extent of acute-phase hemodynamic instability affected BCs in a single center, and there was no major change in the surgical procedures. In addition, there was an only few cases of hepatic artery thrombosis: a possibly important factor for BCs. This enabled us to detect an important hidden factor, even though the number of cases was limited.

Conclusions

Biliary complications following LDLT are critical in terms of attaining long morbidity-free survival. To avoid BCs, it is of vital

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importance to bear in mind that we need to perform procedures preserving biliary circulation and to establish more effective procedures. It is also crucial to prevent post-operative bleeding and keep vital signs steady after LDLT. Although bile duct multiplicity was not considered as a risk factor, management of BCs in a multiple bile duct graft appears to be burdensome. With this problem in mind, there is no necessity to be particular about avoiding multiplicity of graft bile ducts.

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Conflict of interest

None.

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