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ORIGINAL ARTICLE

Differences in Risk Factors for Early-onset and Late-onset Biliary Complications in Liver Transplant Patients

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Context: Despite the use of advanced surgical techniques, the incidence of biliary complications (BCs) after liver transplantation (LT) is high. Hence, there may be additional unidentified causes of BC. **Aims:** To identify the risk factors for BCs occurring within 6 months or beyond 6 months after LT. **Materials and Methods**: We enrolled 237 patients who underwent LT from August 2001 to December 2012. Of the 237 patients, 173 did not have BCs (no BC group), 42 had BCs within 6 months after LT (early-onset BC group), and 22 had BCs beyond 6 months after LT (late-onset BC group). **Statistical Analysis Used:** Patients' demographic, clinical, and biochemical data were analyzed using the Mann–Whitney U-test, Chi-square test, Fisher's exact test, and multiple logistic regression analysis. **Results:** Multivariate analysis indicated that only partial liver graft (odds ratio [OR], 2.741; 95% confidence interval [CI], 1.236-6.077; P=0.013) was an independent risk factor for early-onset BC after LT, whereas acute rejection (OR, 6.556; 95% CI, 2.380-18.056; $P < 0.001$), multiple bile ducts (OR, 4.227; 95% CI, 1.212-14.740; $P = 0.024$), and pre-LT serum albumin level (OR, 2.234; 95% CI, 1.178-4.238; $P = 0.014$) were the independent risk factors for late-onset BC after LT. **Conclusion:** Early-onset and late-onset BCs after LT are associated with different risk factors. Partial liver graft is a risk factor for early-onset BC, whereas pre-LT serum albumin level, multiple bile ducts, and acute rejection are the risk factors for late-onset BC. As it is easily controllable, prevention of acute rejection may help to reduce the incidence of BCs.

Key words: Acute rejection, biliary complication, liver transplantation

INTRODUCTION

Biliary complications (BCs) remain the Achilles' heel of liver transplantation (LT), with an incidence of 5.3-40.6%.[1-12] Despite the efforts made to preserve the blood supply of the bile duct in the recipient and donor,[13] the incidence of BCs remains at 5.3-12.8%,[2-4,6-8] implying the presence of some BC etiologies that are unrelated to the surgical technique.

The duration between the transplantation and the development of BC has not received much attention. Several studies have supported the hypothesis that early-onset and late-onset BCs may have different etiologies.[3,13] In the present study, we aimed to identify the risk factors for BCs occurring within 6 months or beyond 6 months after LT.

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MATERIALS AND METHODS

Two hundred thirty-seven consecutive patients underwent LT at our institution from August 2001 to December 2012. The immunosuppressive protocol consisted of corticosteroid, tacrolimus, and mycophenolate mofetil in all the transplanted patients. The biliary tracts were reconstructed using duct-to-duct anastomosis with either 5-0 or 6-0 prolene sutures or polydioxanone sutures in all the transplanted patients. A stricture was considered to be present when the serum total bilirubin levels were elevated, or dilatation of the intrahepatic bile duct was noted on ultrasonography or computed tomography. The presence of the stricture was subsequently confirmed by endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance imaging (MRI). In the present study, leakage was defined as the presence of biloma formation on ERCP or MRI. In this study, we retrospectively reviewed these ERCP and MRI findings and enrolled the patients with BCs for further analyses.

Moreover, in the present study, early-onset BC (the early-onset BC group) was defined as the diagnosis of BC within 6 months after LT, late-onset BC (the late-onset BC group) was defined as the diagnosis of BC beyond 6 months after LT, and

no BC (no BC group) was defined as the lack of evidence of BCs during the follow-up period after LT.

The patients' characteristics were retrospectively recorded, including age, gender, underlying liver disease (hepatitis B virus infection, hepatitis C virus infection, alcohol abuse, or hepatocellular carcinoma), medical history before LT (diabetes mellitus, hypertension, uremia, ascites, hepatic encephalopathy, and bleeding from esophageal varices), blood test results before LT (albumin, creatinine, international normalized ratio [INR], total bilirubin, platelet count, and ammonia levels), and model for end-stage liver disease (MELD) scores. MELD scores were calculated according to the following formula: MELD score = $(3.78 \times \log_e$ [bilirubin level in mg/dL]) + $(11.2 \times \log_e$ [INR]) + $(9.6 \times \log_e$ [creatinine level in mg/dL]) + (6.4 × [etiology: 0 if cholestatic or alcoholic, 1 otherwise]).[14] The surgery-related factors were also recorded, including surgery type (deceased-donor LT or living-donor LT), graft type (whole graft or partial graft), ABO-incompatible LT, number of bile ducts (single or multiple), implementation of splenectomy, implementation of ductoplasty, amount of intraoperative blood loss, operative time, and graft weight. Postoperative complications were recorded and included acute rejection, posttransplant hemodialysis, posttransplant diabetes mellitus, or cytomegalovirus infection.

The risk factors for early-onset BCs were analyzed by comparing the variables in the no BC group and the early-onset BC group. The risk factors for late-onset BCs were analyzed by comparing the variables in the no BC group and late-onset BC group. The study was approved by the institutional review board of our hospital.

Statistical analysis

Unless otherwise stated, continuous variables are presented as the median (interquartile range), and categorical variables are expressed as the number (percentage) of events. To detect the differences between the groups, the Mann–Whitney U-test was used for continuous variables, and the Chi-square test was used for categorical variables. If 20% of the expected numbers were <5, Fisher's exact test was used instead of the Chi-square test. Patients' characteristic variables with a P value of <0.10 were entered into a binary logistic regression model for the univariate analysis. Statistically significant variables with a P value of <0.05 in the univariate analysis were entered into a backward multivariate analysis. All the statistical calculations were performed using SPSS version 15.0 (IBM-SPSS, Inc., Chicago, IL, USA). Significance was defined as $P < 0.05$.

RESULTS

Patients' characteristics

The study included 237 patients (183 men and 54 women), with a mean age of 52.4 years. Of 237 patients, 173 did not have BCs (the no BC group), 42 had BCs within 6 months after LT (the early-onset BC group), and 22 had BCs beyond 6 months after LT (the late-onset BC group). The characteristics of the early-onset BC group and the late-onset BC group are summarized in Table 1. In the early-onset BC group, 9.5% had leakage, 64.3% had stricture, and 26.2% had both leakage and stricture. In the late-onset BC group, 4.5% had leakage, 86.4% had stricture, and 9.1% had both stricture and leakage. The mean diagnostic time was 2.38 ± 0.28 months and 20.7 ± 3.68 months in the early-onset BC group and late-onset BC group, respectively. There were no significant differences in stricture site, stricture number, dilatation of intrahepatic

Table 1: Types of BCs

Parameters	Early-onset BC (n = 42)	Late-onset BC (n = 22)	P
Type of BC*			
Leakage	4 (9.5)	1 (4.5)	0.172
Stricture	27 (64.3)	19 (86.4)	
Leakage and stricture	11 (26.2)	2 (9.1)	
Time to BC (month)	2.38±0.28	20.7±3.68	<0.001‖
Prediagnosis level of			
Total bilirubin (mg/dL)‡	7.2 (12.3)	2.2 (8.5)	0.081
Alkaline phosphatase (U/L)‡	74 (107.5)	73.5 (91.7)	0.429
Alanine phosphatase (U/L)‡	129.5 (177.2)	118 (159)	0.697
Pattern of biliary tract			
Dilatation of IHD*	13 (31)	6 (27.3)	0.760
Tortuosity of IHD†	4 (9.5)	0	0.289
Dilatation of CBD†	1 (2.4)	2 (9.1)	0.270
Tortuosity of CBD†	3 (7.1)	3 (13.6)	0.406
Pattern of stricture			
Stricture type*			0.613
Anastomosis	26 (68.4)	13 (61.9)	
Nonanastomosis	12 (31.6)	8 (38.1)	
CBD	7	5	
IHD	5	3	
Number of stricture sites†			
Single	36 (94.7)	19 (90.5)	0.611
Multiple	2 (5.3)	2 (9.5)	

Continuous variables are presented as mean ± SD, whereas categorical variables are presented as number (percentage). P values were derived from *The Chi-square test; †Fisher's exact test; ‡The Mann–Whitney U-test; ‖$P < 0.05$. BC = Biliary complication; IHD = Intrahepatic duct; CBD = Common bile duct; SD=Standard deviation

Table 2: Characteristics of patients without BCs and with early-onset BCs

Parameters	No BC group (n = 173)	Early-onset BC (n = 42)	P
Age‡	54 (12)	53 (8)	0.762
Gender*			
Male	130 (75.1)	36 (85.7)	0.143
Female	43 (24.9)	6 (14.3)	
Underlying liver disease			
HBV*	112 (64.7)	23 (54.8)	0.230
HCV*	41 (23.7)	12 (28.6)	0.511
Alcoholism*	39 (22.5)	13 (31.0)	0.254
HCC*	80 (46.2)	19 (45.2)	0.907
Past history			
Diabetes mellitus*	62 (35.8)	13 (31.0)	0.551
Hypertension*	30 (17.4)	7 (16.7)	0.905
Uremia†	7 (4.0)	2 (4.8)	0.689
Ascites*	112 (64.7)	30 (71.4)	0.412
Hepatic encephalopathy*	82 (47.4)	18 (42.9)	0.597
EV bleeding*	70 (40.5)	18 (42.9)	0.777
Laboratory investigation			
Albumin (g/dL)‡	2.9 (0.8)	2.9 (0.9)	0.883
Creatinine (mg/dL)‡	0.8 (0.5)	0.9 (0.5)	0.133
INR‡	1.4 (0.6)	1.3 (0.3)	0.121
Total bilirubin (mg/dL)‡	2.9 (7.1)	2.6 (4.2)	0.553
Platelet ($\times 10^3/\mu L$)‡	70 (59)	68 (46)	0.785
Ammonia (μg/dL)‡	110 (105)	105 (56.5)	0.356
MELD score‡	15 (13)	14 (8)	0.357
Surgery factor			
Surgery type*			
DDLT	77 (44.5)	11 (26.2)	0.030‖
LDLT	96 (55.5)	31 (73.8)	
Graft type*			
Whole liver	74 (42.8)	9 (21.4)	0.011‖
Partial liver	99 (57.2)	33 (78.6)	
ABO incompatible†	5 (2.9)	2 (4.8)	0.625
Number of bile ducts†			
Single	15 (91.3)	35 (83.3)	0.154
Multiple	15 (8.7)	7 (16.7)	
Splenectomy*	41 (23.7)	13 (31.0)	0.331
Ductoplasty†	26 (15.0)	9 (21.4)	0.314
Graft weight, g‡	870 (800)	645 (380)	0.014‖
Blood loss, mL‡	1900 (2675)	2305 (3232)	0.277
Operative time, min‡	540 (145)	580 (153)	0.042‖
Postoperative factor			
Post-LT hemodialysis†	19 (11.0)	3 (7.1)	0.580
Post-LT diabetes mellitus*	68 (39.3)	16 (38.1)	0.885
Post-LT CMV infection†	3 (1.7)	2 (4.8)	0.252
Post-LT rejection*	25 (14.5)	10 (23.8)	0.141
Donor factor			
Donor age‡	30 (17)	29 (21)	0.603
Female donor/male recipient*	48 (27.7)	14 (33.3)	0.473

Continuous variables are presented as median (interquartile range), whereas categorical variables are presented as number (percentage). P values were derived from *The Chi-square test; †Fisher's exact test; ‡The Mann–Whitney U-test; ‖$P < 0.05$. BC = Biliary complication; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HCC = Hepatocellular carcinoma; EV=Esophageal varices; INR = International normalized ratio; MELD = Model for end-stage liver disease; DDLT = Deceased-donor liver transplantation; LDLT = Living-donor liver transplantation; LT = Liver transplantation; CMV = Cytomegalovirus

duct (IHD), tortuous IHD, dilatation of the common bile duct (CBD), and tortuous CBD between the early-onset BC group and late-onset BC group.

The characteristics of the no BC group and the early-onset BC group are summarized in Table 2, whereas the characteristics of the no BC group and the late-onset BC group are summarized in Table 3. The average follow-up duration was 38.3 months (range: 0-136 months).

Univariate and multivariate analyses of the early-onset biliary complication group with the no biliary complication group

Univariate analysis showed that the surgery type ($P = 0.033$) and graft type ($P = 0.013$) were significantly differed between the groups [Table 4]. These factors were included into the multivariate analysis, which indicated that only graft type (odds ratio [OR], 2.741; 95% confidence interval [CI], 1.236-6.077; $P = 0.013$) was an independent risk factor for early-onset BCs after LT [Table 4].

Univariate and multivariate analyses of the late-onset biliary complication group with the no biliary complication group

Univariate analysis showed that postoperative rejection ($P < 0.001$), graft type (whole vs. partial; $P = 0.034$), serum albumin level ($P = 0.016$), and graft weight ($P = 0.038$) were significantly differed between the groups [Table 5]. However, the surgery type ($P = 0.051$), number of bile ducts (single vs. multiple; $P = 0.050$), preoperative ascites ($P = 0.084$), and preoperative uremia ($P = 0.071$) were not the significant risk

Table 3: Characteristics of patients without BCs and with late-onset BCs

Parameters	No BC group (n = 173)	Late-onset BC (n = 22)	P
Age‡	54 (12)	53 (14)	0.835
Gender*			
Male	130 (75.1)	17 (77.3)	0.827
Female	43 (24.9)	5 (22.7)	
Underlying liver disease			
HBV*	112 (64.7)	14 (63.6)	0.919
HCV*	41 (23.7)	5 (22.7)	0.919
Alcoholism*	39 (22.5)	7 (31.8)	0.334
HCC*	80 (46.2)	10 (45.5)	0.944
Past history			
Diabetes mellitus*	62 (35.8)	9 (40.9)	0.642
Hypertension†	30 (17.4)	4 (18.2)	1.000
Uremia†	7 (4)	3 (13.6)	0.089
Ascites*	112 (64.7)	10 (45.5)	0.078
Hepatic encephalopathy*	82 (47.4)	9 (40.9)	0.565
EV bleeding*	70 (40.5)	6 (27.3)	0.232
Laboratory investigation			
Albumin (g/dL)‡	2.9 (0.8)	3.2 (1.4)	0.046‖
Creatinine (mg/dL)‡	0.8 (0.5)	0.8 (0.4)	0.355
INR‡	1.4 (0.6)	1.5 (0.5)	0.893
Total bilirubin (mg/dL)‡	2.9 (7.1)	2.9 (13.7)	0.846
Platelet ($\times 10^3/\mu L$)‡	327 (59.5)	63.5 (69.2)	0.705
Ammonia (μg/dL)‡	110 (105)	102 (99.2)	0.612
MELD score‡	15 (13)	17 (15)	0.490
Surgery factor			
Surgery type*			
DDLT	77 (44.5)	5 (22.7)	0.051
LDLT	96 (55.5)	17 (77.3)	
Graft type*			
Whole liver	74 (42.8)	4 (18.2)	0.027‖
Partial liver	99 (57.2)	18 (81.8)	
ABO incompatible†	5 (2.9)	0 (0)	1.000
Number of bile ducts†			
Single	158 (91.3)	17 (77.3)	0.056
Multiple	15 (8.7)	5 (22.7)	
Splenectomy*	41 (23.7)	8 (36.4)	0.197
Ductoplasty†	26 (15)	6 (27.3)	0.216
Graft weight, g‡	870 (800)	625 (383.7)	0.041‖
Blood loss, mL‡	1900 (2675)	1485 (4750)	0.241
Operative time, min‡	540 (145)	549 (112.5)	0.501
Postoperative factor			
Post-LT hemodialysis†	19 (11.0)	3 (13.6)	0.720
Post-LT diabetes mellitus*	68 (39.3)	10 (45.5)	0.579
Post-LT CMV infection†	3 (1.7)	1 (4.5)	0.383
Post-LT rejection*	25 (14.5)	11 (50)	<0.001‖
Donor factor			
Donor age‡	30 (17)	32 (13)	0.890
Female donor/male recipient*	48 (27.7)	6 (27.3)	0.963

Continuous variables are presented as median (interquartile range), whereas categorical variables are presented as number (percentage). P values were derived from *The Chi-square test; †Fisher's exact test; ‡The Mann–Whitney U-test; ‖$P < 0.05$. BC = Biliary complication; HBV = Hepatitis B virus; HCV=Hepatitis C virus; HCC = Hepatocellular carcinoma; EV = Esophageal varices; INR=International normalized ratio; MELD = Model for end-stage liver disease; DDLT = Deceased-donor liver transplantation; LDLT = Living-donor liver transplantation; LT = Liver transplantation; CMV = Cytomegalovirus

factors for late-onset BCs, based on the results of univariate analysis. The significant factors in the univariate analysis ($P > 0.05$ and <1.00) were included in the multivariate analysis. Multivariate analysis showed that acute rejection (OR, 6.556; 95% CI, 2.380-18.056; $P < 0.001$), number of bile ducts (OR, 4.227; 95% CI, 1.212–14.740; $P = 0.024$), and serum albumin level (OR, 2.234; 95% CI, 1.178-4.238; $P = 0.014$) were the independent risk factors for late-onset BCs after LT [Table 5].

DISCUSSION

In the present study, we analyzed the risk factors for early-onset and late-onset BCs in the patients who underwent LT. In our cohort, the risk factors for BCs were dependent on the time interval after LT. A partial liver graft was the only identified independent risk factor for BC occurring within the first 6 months after LT. In contrast, acute rejection, multiple bile ducts, and pretransplant serum albumin level were identified as the independent risk factors for BCs occurring beyond 6 months after LT.

The risk factors for BCs have been investigated in several studies. These risk factors include hepatic artery complications,[15] cytomegalovirus infections,[15] female donor/male recipient,[16] different era of LT,[16] intensive care unit stay,[16] donor age of >50 years,[5] number of bile ducts,[5] cold ischemia time,[17] placement of the T-tube,[18] and bile duct diameter.[18] In contrast, other studies determined that MELD score,[15] donor age,[15] blood type incompatibility,[15] graft/recipient weight ratio,[15] cold ischemia time,[15] and warm ischemia time[15] were not associated with BCs. Thus, the actual risk factors for BC

Table 4: Univariate and multivariate analysis of early-onset BCs after liver transplantation

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Surgery type: LDLT	2.26 (1.067-4.787)	0.033*	0.458 (0.072-2.903)	0.407
Graft type: Partial graft	2.741 (1.236-6.077)	0.013*	2.741 (1.236-6.077)	0.013*
Operative time, min	1.002 (0.999-1.004)	0.130	1.001 (0.999-1.004)	0.412

*$P < 0.05$. OR = Odds ratio; CI = Confidence interval; LDLT = Living-donor liver transplantation; BC = Biliary complication

Table 5: Univariate and multivariate analysis of late-onset BCs after liver transplantation

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Uremia	3.744 (0.893-15.700)	0.071	4.43 3(0.786-24.992)	0.091
Ascites	0.454 (0.185-1.111)	0.084	0.623 (0.198-1.959)	0.418
Albumin, g/dL	2.056 (1.146-3.689)	0.016*	2.234 (1.178-4.238)	0.014*
Surgery type: LDLT	2.727 (0.963-7.725)	0.059	0.656 (0.017-26.066)	0.828
Graft type: Partial liver	3.364 (1.093-10.356)	0.034*	1.898 (0.553-6.512)	0.308
Number of bile ducts	3.098 (1.002-9.581)	0.050	4.227 (1.212-14.740)	0.024*
Graft weight, g	0.999 (0.997-1.000)	0.038*	1.000 (0.997-1.003)	0.826
Acute rejection	5.929 (2.319-15.110)	<0.001*	6.556 (2.380-18.056)	<0.001*

*$P < 0.05$. OR = Odds ratio; CI = Confidence interval; LDLT = Living-donor liver transplantation; BC = Biliary complication

after LT are unclear. Hence, it will be necessary to analyze additional large series studies to better identify the actual risk factors.

In the present study, a partial liver graft was the only identified independent risk factor for BCs occurring within the first 6 months after LT. This result can be logically explained by the proven risk factors themselves, including the number of bile ducts[5] and bile duct diameter.[18] The diameter of the bile ducts in partial liver grafts is smaller than that in whole grafts; moreover, there may be several bile ducts in partial liver grafts, which makes bile duct anastomoses more difficult. In addition, acute rejection, multiple bile ducts, and pretransplant serum albumin level were the independent risk factors for BCs occurring beyond 6 months after LT. However, the number of bile ducts cannot be accurately predicted in some cases because of the anatomic variation. The pretransplant serum albumin level may also vary, as this level is occasionally dependent on commercial albumin supplementation before transplantation.

Acute rejection has received an increasing amount of attention as a risk factor for BCs. The first study to consider this parameter as a risk factor for BCs — By the Hong Kong research group of Chok — Determined that acute cellular rejection was a significant risk factor for anastomotic stricture.[19] Gámán *et al*. also determined that BCs are associated with acute rejection.[20] This association may be explained by the fact that biliary epithelial cells are one of the targets of certain liver diseases such as acute allograft rejection.[21] The relationship between rejection and BCs was also explained by the findings of pathological examination, which indicated that the bile duct damage was greater in the patients with acute rejection than in those with the recurrent liver disease.[22] However, some studies have stated contrasting findings. Verdonk *et al*. showed that anastomotic biliary stricture was not related to acute rejection,[16] whereas Park *et al*. also presented the same opinion.[17] In this study, acute rejection was significantly associated with late-onset BCs but was not related to early-onset BCs. These findings suggest that understanding the difference in early- or late-onset BCs may help to explain the discrepant results obtained in the previous studies.

The preservation of the blood supply of the bile duct is known to play an important role in preventing BCs. Hashimoto *et al*. determined that the hepatic artery buffer response, which is calculated based on the hepatic artery flow and portal vein flow, was associated with early-onset BCs.[23] However, in the present study, factors such as blood loss or ductoplasty were not related to early-onset BCs. This discrepancy may be explained by the inconsistent definition of early-onset or late-onset BCs. Moreover, it is possible that factors such as blood loss or ductoplasty may not reflect the actual blood supply of the bile duct.

The time interval to the development of BCs after LT has been considered in a small number of studies. Greif *et al*. determined that two-third of BCs developed within the first 3 months after LT.[13] Mosca *et al*. defined late BCs as those occurring after the removal of the T-tube drain, that is, after a period of 3 months.[24] Hwang *et al*. used BC-free survival

rates at 1, 3, and 5 years to determine the incidence of BCs over time.[25] In brief, these findings indicated that the time interval may play a role in the development of BCs.[25] Hence, it is necessary to adopt different strategies to prevent BCs during different time periods.

The current study has certain limitations. One limitation is the retrospective nature of the study. Moreover, the cut-off time interval of early or late-onset BCs has not been clearly defined in the literature. Lin *et al*. defined perioperative BCs as those occurring within 90 days after LT and early operative BCs as those occurring within 12 months after LT.[3] Chang *et al*. showed that 78.5% of liver transplant patients developed BCs within 1-year of transplantation and 94.2% of patients had BCs within 2 years of transplantation. Chang also defined the early period as within 1-year after transplantation.[26] Hashimoto *et al*. chose 60 days as the cut-off to define early or late BCs.[23] In the present study, we chose 6 months as the cut-off time interval. Future studies should identify the risk factors for early- or late-onset BCs by using various time intervals in order to determine the optimal cut-off times.

CONCLUSION

There were different risk factors associated with early-onset or late-onset BCs after LT. Moreover, we noted that acute rejection was a risk factor of late-onset BCs. As this condition is potentially controllable, we believe that the optimal prevention of acute rejection may help to lower the incidence of BCs.

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