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Biliary Complications Following Adult Deceased Donor Liver Transplantation: Risk Factors and Implications at a High-volume US Center

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Background. Biliary leaks and anastomotic strictures comprise the majority of biliary complications (BCs) following liver transplantation (LT). Currently, there are few large contemporary case series of BCs in adult deceased donor liver transplant (DDLT) recipients in the literature. The purpose of this study was to examine the pretransplant and intraoperative risk factors associated with BCs at a high-volume tertiary care center and determine the impact of these BCs on their posttransplant course and long-term transplant outcomes. **Methods.** We retrospectively reviewed all adult patients undergoing a DDLT from a donor after brain death (DBD) at Emory University between January 2015 and December 2019. **Results.** A total of 647 adult patients underwent DDLT from a DBD during the study period and were included in analyses. The median length of follow-up posttransplant was 2.5 y. There were a total of 27 bile leaks (4.2%) and 69 biliary strictures (10.7%). Recipient age and cold ischemic time were identified as risk factors for biliary leak, whereas alcoholic cirrhosis as transplant indication was a risk factor for biliary stricture. Placement of a biliary stent was associated with the development of both biliary leaks and anastomotic strictures. Posttransplant, biliary leaks were a significant risk factor for future episodes of acute rejection but did not impact overall survival. In contrast, biliary strictures were associated with a significantly reduced overall survival at 1- and 4-y post DDLT. **Conclusions.** BCs are a major source of morbidity and mortality following DDLT, with strictures and leaks associated with distinct posttransplant complications.

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Liver transplantation (LT) is the only potentially curative therapy for many patients suffering from chronic end-stage liver failure. Although survival following LT has improved markedly over the past 30 y, transplant remains a highly complex surgical procedure that places patients at risk of significant complications. Biliary complications (BCs) are some of the most common complications encountered by patients following LT, impacting 5%–32% of liver transplant recipients.[1-3] While rare BCs such as hemobilia, bile duct stones, and nonanastomotic biliary strictures have been reported, most of these posttransplant BCs can be categorized as either bile leaks (with an incidence of 2%–25% of deceased donor liver transplant [DDLT] recipients) or anastomotic biliary strictures (with an incidence of 5%–15%).[2]

These two most common types of BCs differ in their timing, clinical presentation and etiologies. Whereas anastomotic biliary strictures usually develop 1–12 mo after transplant, bile leaks are typically early complications, often manifesting within the first month (and often within the first few days) of transplant.[1,3] However, bile leaks associated with T-tube removal can occur with a late presentation.[4] The clinical manifestations of bile leaks and anastomotic biliary strictures also are distinct. Bile leaks are usually detected by the presence of bile staining in the postoperative drains (especially for the typical early-presenting bile leaks) and the onset of fever, peritonitis, leukocytosis, and elevated liver function tests. Definitive diagnosis can be made by magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or insertion of a percutaneous drain with bilious output.

Biliary strictures, in contrast, are usually detected by either asymptomatic elevations in GGT/alkaline phosphatase or by the development of obstructive jaundice. Fever and

peritonitis are not typical features of biliary strictures unless the patient develops ascending cholangitis due to the stricture. Confirmation of biliary strictures can usually be provided by an ultrasound finding of intrahepatic biliary dilation or through direct demonstration of a biliary stricture by MRCP, ERCP, or percutaneous transhepatic cholangiogram (PTC).[1-3]

While there have been several case series of BCs in liver transplant patients published previously,[5-9] the vast majority of these report on only small numbers of BCs or involve historical case series from transplants conducted in the 1990s or even 1980s. Many of these previous case series of posttransplant BCs occurred during the era when T-tubes were routinely inserted through the biliary anastomosis, a practice almost universally abandoned after the publication of randomized controlled trials showing that utilization of T-tubes was associated with a higher incidence of complications such as bile leak, cholangitis, and biliary stricture.[10-13]

There are currently few large contemporary case series of BCs in adult DDLT recipients in the literature. We present here a comprehensive review of BCs after adult deceased donor LT at a high-volume tertiary care center during a 5-y period (from January 1, 2015, through December 31, 2019). We explore the pretransplant and intraoperative risk factors that predispose transplant recipients to develop these BCs, and we detail the treatment course used to manage these complications in these patients at our transplant center. Finally, we examine the impact of these BCs on their posttransplant course and long-term transplant outcomes.

MATERIALS AND METHODS

Study Population and Data Source

Data on adult liver transplant recipients at Emory University were obtained through retrospective review of the electronic medical record. Patients were included if they were adults (age ≥ 18 at the time of transplant) who received a DDLT from a donor after brain death between January 1, 2015, and December 31, 2019. Patients were excluded from analysis if they received an organ from a donation after circulatory death (n = 3), or if they died within 30 d of transplant (n = 15). Donors after circulatory death (DCD) were excluded as an insufficient number of these transplants were performed to allow analysis, and recipients who died within 30 d of transplant were excluded as they did not survive long enough to develop BCs such as biliary strictures (none of these recipients died from sepsis resulting from bile leak). The study was approved by the Emory University Institutional Review Board.

Biliary Anastomoses

Biliary anastomoses were constructed using standard techniques with 6-0 polydiaxanone (PDS) sutures. Surgeon preference dictated whether these sutures were placed running, all interrupted, or running the posterior wall while interrupting the anterior wall. Use of a biliary stent was selective, with stents employed in settings of small donor ducts or large duct-to-duct size discrepancy. Biliary stents were fashioned out of 5 Fr, 8 Fr, or 10 Fr pediatric feeding tubes, with size dictated by the surgeon's preference and by the size of the donor and recipient bile ducts. A barb was cut into the end of the stent to prevent migration of the stent up into the liver itself, and multiple side holes were cut into the stent before placement. The stent was always advanced across the choledochocholedochostomy and down past the ampulla into the duodenum. All patients receiving a biliary stent obtained a KUB radiograph around postoperative week 6, and all patients with retained biliary stents at that point underwent an EGD to retrieve the stent.

Variables

Outcomes

We identified the presence of BCs after liver transplant through chart review. Bile leaks and anastomotic biliary strictures were identified and categorized by history of surgical revision of the biliary anastomosis (either choledochocholedochostomy or conversion to Roux-en-Y choledochojejunostomy) or by ERCP, MRCP, or PTC imaging demonstrating these complications. Our standard algorithm to address rising liver function tests (the most common manifestation of biliary stricture and/or leak) is to obtain a duplex liver ultrasound and often an abdominal MRI, so the hepatic artery is also typically assessed at the time the BC is identified. We identified several outcomes of interest to evaluate the impact of BCs on morbidity and mortality. The first outcome was overall survival time, calculated by subtracting the date of transplant from the date of death. Among patients who did not have a date of death, survival time was censored at the date of last known survival, which is when patients were last seen at the transplant clinic. The second outcome of interest was time to acute rejection, calculated as the time between the date of transplant and the date of first rejection. Patients were censored at the time of death or date of the last follow-up. The third outcome of interest was time to graft failure, calculated as the time between the date of transplant and date of graft failure, and censored at the time of death or date of last follow-up. The final outcome of interest was the number of days alive and out of the hospital (DAOH), which has been previously validated as a measure of morbidity in liver transplant recipients.[14] DAOH was calculated as the number of days alive minus the number of days admitted to the transplant center after the initial transplant.

Covariates

Demographic characteristics of interest included age at transplant, gender, race (classified as Black, White, and other), and primary payor at transplant (classified as public or private). Preoperative characteristics included the underlying cause of liver disease, which was classified as alcohol-related, viral hepatitis, nonalcoholic steatohepatitis (NASH), autoimmune, primary sclerosing cholangitis, acute liver failure, or other. These categories were not mutually exclusive, and patients could be classified as having multiple underlying etiologies. Additional preoperative characteristics included whether the patient had a multiorgan transplant, hepatocellular carcinoma (HCC), model for end-stage liver disease (MELD) exception points, whether the surgery was a retransplant, calculated MELD at the time of transplant, body mass index at transplant, and diabetes at transplant.

Intraoperative factors included donor age, cold ischemic time (measured in hours), warm ischemic time (measured in minutes), whether the recipient or donor had prior history of cholecystectomy, anastomosis type (duct-to-duct versus Roux-en-Y choledochojejunostomy), whether the patient required a ductoplasty during their transplant, and whether

the patient had a biliary stent placed during surgery (as well as biliary stent size).

Statistical Analyses

We described the demographic and clinical characteristics of patients with and without BCs. We used log-binomial regression to estimate the association between each demographic, preoperative and intraoperative factors, and the risk of overall BCs after liver transplant. We performed multivariable Poisson regression with robust standard errors to estimate risk ratios for each factor, adjusted for all other factors. We also estimated the association between risk factors and complications separately for bile leaks and biliary strictures. We performed a secondary analysis among those who received a biliary stent to determine if biliary stent size was associated with the development of BCs.

To estimate the association between BCs and time to acute rejection, graft failure, and death, we used Cox proportional hazards models, treating the development of BCs as a time-dependent covariate to avoid immortal person-time bias. Patients were considered to be unexposed until diagnosed with a BC, at which point they became exposed. Analyses were adjusted for factors associated with either the development of BCs or post liver transplant outcomes, including age, race, gender, MELD at transplant, underlying cause of disease, HCC, retransplant status, body mass index, anastomosis type, and whether the patient received a stent. We also calculated the mean DAOH among those who did and did not go on to develop BCs after transplant.

Missing values were imputed using the missRanger package, which combines chained random forests with predictive mean matching. All analyses were performed in R.

RESULTS

Incidence and Timing of BCs

A total of 647 adult patients underwent LT using donors after brain death (DBD) during the study period and were available for analysis. The median time of follow-up posttransplant was 2.5 y. In addition to 2 cases of biliary lithiasis and 3 cases of nonanastomotic ischemic cholangiopathy, there were a total of 96 patients (14.8%) who developed a BC from bile leak and/or biliary stricture. There were a total of 27 bile leaks (4.2%) and 69 biliary strictures (10.7%). Only 2 of these patients developed both a bile leak and a subsequent biliary stricture. The majority of patients with an identified BC also had imaging that assessed their hepatic artery (a duplex ultrasound and/or an abdominal MRI), and no patient was identified who had both a BC and a hepatic artery thrombosis or stricture. Whereas bile leaks were detected a median of 4 d after transplant (range: 0–65 d), biliary strictures were detected a median of 139 d after transplant (range: 5–1060 d). BCs are often defined as presenting early (occurring <30 d posttransplant) or late (occurring >30 d posttransplant). Of patients who developed a bile leak, only 11.1% presented late, whereas 87% of biliary strictures presented late.

Recipient Demographics and Pretransplant Risk Factors for BCs

Recipient demographics and pretransplant risk factors for recipients who developed BCs (leaks and/or strictures) and for those recipients who did not develop BCs are listed in

Table 1. In our case series, the median age of patients undergoing liver transplant was 56 y old. The majority of recipients were male (60%) and Caucasian (69%). The median MELD score at time of transplant was 28. The most common etiologies for end-stage liver disease in our series were alcoholic cirrhosis (31.4%), chronic hepatitis C infection (24%), and NASH (20%). Of the transplant recipients, 165 (25.5%) had associated HCC, 44 (6.8%) were retransplantations, and 65 (10%) received a multiorgan transplant (64 liver-kidney and 1 liver-pancreas).

For univariate and multivariate analysis of pretransplant recipient risk factors, BCs were separated into a combined end-point of any BCs (ie, leaks and/or strictures), leaks alone, and strictures alone (Table 2). Among the pretransplant recipient risk factors evaluated, univariate analysis revealed no significant risk factors for the combined BC end-point. However, recipient age at transplant (relative risk [RR], 1.06; 95% confidence interval [CI], 1.02–1.11) was a risk factor for bile leaks on univariate analysis, whereas alcoholic cirrhosis as the indication for liver transplant (RR, 1.94; 95% CI, 1.24–3.04) was associated with the development of biliary strictures.

Donor and Intraoperative Risk Factors for BCs

Donor demographics and intraoperative risk factors for these 2 cohorts (BCs and no BCs) are listed in Tables 3 and 4. Compared to the control group lacking BCs, univariate analysis revealed that patients who developed BCs (either leak or stricture) had no statistically significant difference in donor age (38.6 versus 40.2 y), warm ischemic time (35.3 versus 35.7 min), history of prior donor cholecystectomy (25.8%

TABLE 1.

Recipient characteristics undergoing deceased donor liver transplantation

	Without biliary complications	With biliary complications	
	(N = 551)	(N = 96)	*P*
Age at transplant (mean + SD)	53.4 ± 12.0	54.9 ± 10.3	0.22
Sex			
Male	328 (59.5%)	56 (58.3%)	0.91
Female	223 (40.5%)	40 (41.7%)	
Race			
Caucasian or White	378 (68.6%)	66 (68.8%)	0.89
African American or Black	123 (22.3%)	21 (21.9%)	
Other	23 (4.2%)	3 (3.1%)	
Underlying cause of disease			
EtOH	165 (30.1%)	38 (38.8%)	0.08
Viral hepatitis	144 (26.2%)	29 (29.6%)	0.48
NASH	109 (19.9%)	20 (20.4%)	0.92
Autoimmune	41 (7.4%)	7 (7.3%)	0.99
PSC	33 (6.0%)	1 (1.0%)	0.08
ALF	11 (2.0%)	1 (1.0%)	0.82
Other	85 (15.5%)	11 (11.2%)	0.39
Hepatocellular carcinoma?	138 (25.0%)	25 (26.0%)	0.94
Received exception points?	130 (23.6%)	18 (18.8%)	0.36
Retransplanted?	40 (7.3%)	5 (5.2%)	0.61
MELD at transplant (mean + SD)	29.1 ± 7.29	30.7 ± 7.65	0.06
BMI at transplant (mean ± SD)	29.0 ± 8.04	29.8 ± 11.3	0.55
Diabetes at time of transplant?	181 (32.8%)	30 (31.2%)	0.83

ALF, acute liver failure; BMI, body mass index; EtOH, alcoholic; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis.

TABLE 2.

Analysis of recipient risk factors for biliary complications

	Any biliary complications				Leak				Stricture			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Age at transplant	1.01	0.99, 1.03	1.00	0.98, 1.03	1.06	1.02, 1.11	1.05	1.00, 1.12	1.00	0.98, 1.02	0.99	0.96, 1.02
Sex												
Male	Ref											
Female	1.04	0.71, 1.51	1.23	0.78, 1.94	1.35	0.62, 2.93	1.38	0.53, 3.56	0.97	0.60, 1.51	1.24	0.71, 2.12
Race												
Black/African American	0.97	0.60, 1.48	1.11	0.63, 1.89	0.50	0.12, 1.42	0.55	0.12, 1.79	1.04	0.59, 1.71	1.28	0.66, 2.39
Other	0.76	0.20, 1.87	0.88	0.21, 2.53	1.83	0.30, 5.84	1.91	0.25, 9.07	0.36	0.02, 1.53	0.47	0.03, 2.30
Caucasian	Ref											
Multiorgan transplant												
No	Ref											
Yes	1.16	0.61, 1.95	1.08	0.52, 2.06					1.73	0.89, 2.98	1.84	0.85, 3.69
Underlying cause of disease												
EtOH	1.43	0.98, 2.07	1.86	0.90, 3.67	0.55	0.18, 1.33	1.79	0.41, 6.58	1.94	1.24, 3.04	2.40	1.00, 5.40
Viral hepatitis	1.19	0.78, 1.75	1.83	0.87, 3.68	2.15	0.97, 4.64	5.54	1.25, 27.1	0.99	0.58, 1.61	1.62	0.67, 3.64
NASH	1.06	0.65, 1.62	1.48	0.64, 3.25	1.00	0.34, 2.42	2.39	0.44, 12.9	1.14	0.64, 1.89	2.00	0.75, 4.99
Autoimmune	0.98	0.43, 1.83	1.52	0.48, 0.32	1.70	0.41, 4.69	2.83	0.30, 22.5	0.58	0.14, 1.47	1.28	0.25, 4.92
PSC	0.19	0.01, 0.81	0.22	0.01, 1.39					0.27	0.02, 1.15	0.73	0.04, 4.82
ALF	0.56	0.03, 2.17	0.89	0.03, 5.92					0.79	0.05, 3.10	1.54	0.07, 12.5
Other	0.74	0.39, 1.27	1.23	0.47, 2.94	0.78	0.19, 2.20	3.00	0.44, 16.5	0.66	0.28, 1.29	1.33	0.42, 3.74
Hepatocellular carcinoma												
No	Ref											
Yes	1.06	0.67, 1.56	1.23	0.58, 2.47	1.98	0.88, 4.27	1.80	0.46, 6.61	0.84	0.47, 1.41	1.48	0.57, 3.48
Received exception points												
No	Ref											
Yes	0.78	0.47, 1.22	0.76	0.34, 1.71	1.59	0.66, 3.49	1.08	0.29, 4.26	0.58	0.29, 1.05	0.54	0.19, 1.53
Retransplanted												
No	Ref											
Yes	0.76	0.27, 1.53	0.54	0.34, 1.71	2.54	0.77, 6.35	1.51	0.22, 8.62				
MELD at transplant	1.02	1.00, 1.05	1.03	0.99, 1.06	1.02	0.96, 1.07	1.03	0.95, 1.10	1.03	1.00, 1.06	1.03	0.99, 1.06
BMI at transplant	1.01	0.99, 1.03	1.00	0.98, 1.03	1.03	0.99, 1.08	1.04	0.99, 1.09	1.00	0.98, 1.03	0.99	0.96, 1.02
Diabetes at time of transplant												
No	Ref											
Yes	0.98	0.66, 1.44	1.00	0.61, 1.59	1.31	0.58, 2.84	1.04	0.40, 2.58	0.88	0.53, 1.41	0.96	0.52, 1.70

Unadjusted, univariate analysis; Adjusted, multivariate analysis.
ALF, acute liver failure; BMI, body mass index; CI, confidence interval; EtOH, alcoholic; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis; RR, relative risk.

versus 27.1%), or Roux-en-Y biliary reconstruction (10.7% versus 8.3%). However, univariate analysis demonstrated cold ischemia time (RR, 1.12; 95% CI, 1.01–1.24) and biliary stent placement (RR, 2.16; 95% CI, 1.45–3.12) as risk factors for the combined end-point of any BC. When bile leaks and strictures were considered separately, cold ischemic time (RR, 1.33; 95% CI, 1.07–1.63), and stent placement (RR, 4.18; 95% CI, 1.92–8.99) were significant risk factors for leaks, whereas only stent placement (RR, 1.76; 95% CI, 1.05–2.81) was a risk factor for strictures.

Multivariate analysis adjusting for all pretransplant, donor, and intraoperative risk factors was also performed. In this analysis, biliary stent placement (RR, 2.25; 95% CI, 1.39–3.57) was the only identified risk factor for the combined complication end-point of leaks and/or strictures. Risk factors for biliary leaks on multivariate analysis included viral hepatitis as an etiology of liver failure (RR, 5.54; 95% CI, 1.250–27.1) and biliary stent placement (RR, 4.32; 95% CI, 1.69–11.3). An analysis of other intraoperative factors (estimated blood loss and total surgical time) was also conducted using a limited dataset of the 261 liver transplants performed in 2018 and 2019, and this failed to show any significant impact of these intraoperative factors on the development of biliary leak or stricture (data not shown).

Management of BCs

Management of BCs is described in Table 5. In our series, 77% of biliary leaks were managed surgically through either a revision of the biliary anastamosis (42.3%), revision of the Roux-en-y choledochojejunostomy (15.4%), or conversion from a duct-to-duct anastamosis to a Roux-en-y choledochojejunostomy (19.2%). In this series, no patient required >1 surgical revision to address a BC. One biliary leak (3.8%) was discovered incidentally on a return to the operating room for a separate indication and was irrigated, but no revision was necessary. The remaining biliary leaks (19.2%) were managed endoscopically with ERCP and stent placement. "Early" biliary leaks diagnosed prior to postoperative day (POD)

TABLE 3.

Donor/intraoperative characteristics

	Without biliary complications	With biliary complications	
	(N = 551)	(N = 96)	P
Donor age (mean ± SD)	38.6 ± 15.4	40.2 ± 14.5	0.33
Cold ischemic time, h			
Mean (SD)	7.06 (1.75)	7.49 (1.61)	0.02
Warm ischemic time, min			
Mean (SD)	35.3 (7.30)	35.7 (7.58)	0.60
Recipient cholecystectomy?	252 (45.7%)	45 (46.9%)	0.92
Donor cholecystectomy?	142 (25.8%)	26 (27.1%)	0.89
Anastomosis type			
Duct to duct	492 (89.3%)	88 (91.7%)	0.61
Roux-en-Y	59 (10.7%)	8 (8.3%)	
Ductoplasty?			
No	186 (33.8%)	28 (29.2%)	0.67
Yes	35 (6.4%)	7 (7.3%)	
Not recorded	330 (59.9%)	61 (63.5%)	
Biliary stent placement?	86 (15.6%)	31 (32.3%)	<0.001
Stent size (Fr)			
No stent	465 (84.4%)	65 (67.7%)	<0.001
5	30 (5.4%)	5 (5.2%)	
8	7 (1.3%)	8 (8.3%)	
10	49 (8.9%)	18 (18.8%)	

14 (n = 19) were exclusively managed surgically (100%), while "late" biliary leaks diagnosed after POD 14 (n = 7) were managed primarily endoscopically (71%). Attempted endoscopic management of one "late" biliary leak was unsuccessful, and the patient eventually required surgical revision. In contrast to the management to biliary leaks, the vast majority of anastomotic strictures following LT were definitively managed endoscopically (95.7%), while only 4.3% required surgical management. Of those managed endoscopically, 88% were managed with ERCP and stent placement, 4.4% were managed with ERCP but did not require stent placement, 4.4% required both ERCP and PTC, and 2.9% were managed with PTC and stent placement alone. The mean number of procedures required for endoscopic management of anastomotic strictures was 3.2 procedures. Of those managed surgically (n = 3), 1 patient underwent revision of a duct-to-duct anastamosis, while 2 patients required conversion to a Roux-en-y choledochojejunostomy.

BCs Associated With Reduced Patient Survival and Increased Acute Rejection

Overall patient survival at 1 and 4 y among all patients undergoing LT were 96.3% and 94.6%, respectively. Patient survival was stratified by the presence or absence of BCs is illustrated in Table 6 and Figure 1A. Patients with BCs had a significantly increased risk of mortality compared to those without complications on both univariate (hazard ratio [HR], 4.49; 95% CI, 2.23–9.06) and multivariate (HR, 5.02; 95% CI, 2.36–10.7) analysis. Specifically, biliary strictures were significantly associated with decreased patient survival on both univariate (HR, 4.09; 95% CI, 1.84–9.07) and multivariate (HR, 5.70; 95% CI, 2.40–13.5) analysis. In contrast, bile leaks were not associated with a statistically significant decrease in patient survival in either univariate (HR, 2.63; 95% CI, 0.81–8.60) or multivariate analysis (HR, 2.17; 95% CI, 0.46–10.30). Overall, patients with any BCs did not have a significantly higher incidence of acute rejection than those without BCs (Figure 1B). However, multivariate analysis identified biliary leaks as a significant risk factor for future episodes of acute rejection (HR, 2.47; 95% CI, 1.04–5.93). Finally, neither biliary leaks nor anastomotic strictures appeared to be a significant risk factor for graft loss (Figure 1C).

TABLE 4.

Analysis of donor/intraoperative risk factors for biliary complications

	Combined				Leak				Stricture			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Donor age	1.01	0.99, 1.02	1.01	1.00, 1.03	0.99	0.96, 1.02	1.01	0.98, 1.03	1.01	1.00, 1.03	1.02	1.00, 1.04
Cold ischemic time, per h	1.12	1.01, 1.24	1.13	0.99, 1.28	1.33	1.07, 1.63	1.23	0.95, 1.59	1.04	0.92, 1.18	1.04	0.89, 1.20
Warm ischemic time, per 5 min	1.04	0.92, 1.17	1.05	0.91, 1.20	1.13	0.88, 1.42	1.17	0.88, 1.55	1.03	0.88, 1.19	1.05	0.90, 1.23
Recipient cholecystectomy												
No	Ref											
Yes	1.04	0.72, 1.50	1.36	0.49, 3.64	1.09	0.50, 2.36	1.17	0.43, 3.14	1.05	0.66, 1.64	1.16	0.32, 4.02
Donor cholecystectomy												
No	Ref											
Yes	1.06	0.69, 1.58	0.96	0.35, 2.52	0.25	0.04, 0.83	0.36	0.05, 1.48	1.46	0.89, 2.31	1.36	0.38, 4.72
Anastomosis type												
Duct to duct	Ref											
Roux-en-Y	0.79	0.36, 1.44	2.26	0.80, 5.65	2.16	0.74, 5.14	5.18	0.99, 2.57	0.13	0.01, 0.58	0.24	0.01, 1.37
Ductoplasty												
No	Ref											
Yes	1.27	0.54, 2.55	0.92	0.35, 2.13	2.18	0.49, 7.52	2.00	0.37, 8.84	1.02	0.31, 2.53	0.80	0.22, 2.26
Biliary stent												
No	Ref											
Yes	2.16	1.45, 3.12	2.25	1.39, 3.57	4.18	1.92, 8.99	4.32	1.69, 11.3	1.76	1.05, 2.81	1.73	0.95, 3.02

Unadjusted, univariate analysis; Adjusted, multivariate analysis.
CI, confidence interval; RR, relative risk.

TABLE 5.

Management of biliary complications

	No. patients
Complication	
Leak	26
Stricture	70
Ischemic cholangiopathy	3
Leak management	
Return to OR—revision of duct-to-duct anastomosis	11 (42.3%)
Return to OR—revision of Roux-en-Y	4 (15.4%)
Return to OR—conversion to Roux-en-Y	5 (19.2%)
Return to OR—washout	1 (3.8%)
ERCP with stent	5 (19.2%)
Stricture management	
ERCP with stent	59 (84.3%)
ERCP no stent	3 (4.3%)
ERCP + PTC	3 (4.3%)
PTC with stent	2 (2.9%)
Return to OR—revision of duct-to-duct anastomosis	1 (1.4%)
Return to OR—conversion to Roux-en-Y	2 (2.9%)
Ischemic cholangiopathy management	
Retransplant	2 (66.7%)
PTC with stent	1 (33.3%)

ERCP, endoscopic retrograde cholangiopancreatography; OR, operating room; PTC, percutaneous transhepatic cholangiogram.

We also analyzed the impact of BCs on total days alive and out of hospital. Overall, the presence of BCs did decrease both the mean and median patient total days alive and out of hospital; however, these did not reach statistical significance (Table 7).

DISCUSSION

BCs represent one of the most common complications encountered by adult liver transplant recipients. Risk factors for these BCs identified by older case series include advanced donor and/or recipient age, prolonged cold and warm ischemia time, cholestatic liver disease, use of Roux-en-Y hepaticojejunostomies, and recipient MELD at transplant.[5,15] However, many of these series either contain small numbers of patients or report on transplants performed >15 y ago and may not represent current practices given the evolving landscape of LT, including the widespread cessation of t-tubes, increased use of livers from marginal donors, and increased incidence of alcoholic hepatitis and NASH as indications for liver transplant. Furthermore, many analyses combine biliary leaks and anastomotic biliary strictures into a single analysis of BCs despite differences in the presentation, management and presumably etiologies of these 2 entities. In addition to the potential morbidity and mortality associated with BCs, they have important economic implications and represent a significant cost to the healthcare system. Critical analyses of BCs are an opportunity to identify areas of improvement and facilitate improved patient outcomes. Single-center series from high-volume centers are valuable in analyzing risk factors and transplant outcomes, as they offer a more granular level of data that permit analyses that may not be possible using large national data sets.

Biliary leaks and anastomotic biliary strictures comprise the majority of BCs in adult recipients of liver allografts from DBD. While nonanastomotic biliary strictures and ischemic cholangiopathy are widely described for recipients of allografts from DCD,[16] we constrained our analysis only to recipients of DBD grafts, as the number of DCD transplants at our center during the time period examined was too small to draw meaningful conclusions.

Bile leaks are often the result of technical issues with the anastomosis formation such as creation of an anastomosis under tension, duct-to-duct size mismatch, active bleeding at the cut bile duct end, electrocautery injury of the bile duct wall, improperly placed sutures, failed ligation of the cystic duct stump, or ischemia from disruption of the blood supply to the bile duct (potentially from excessive dissection at the time of procurement).[1] Premature removal of T-tubes is also commonly associated with bile leaks, which often manifest relatively late; in one study, 31% of patients with a T-tube reported a bile leak and 7% presented late.[4] In our analysis, older recipient age, prolonged cold ischemia times and placement of a biliary stent at time of transplant were all independent risk factors for the development of a posttransplant biliary leak, at least on univariate analysis. Older recipient age is an especially relevant risk factor as the recipient criteria for LT expand to include older patients.

Technical issues such as tension, duct-to-duct size mismatch, and bile duct ischemia also contribute to many anastomotic biliary strictures, but these have also been attributed to recurrence of primary disease (eg, primary sclerosing cholangitis), cytomegalovirus infection, cold and warm ischemia times, donation after cardiac death, and advanced donor or recipient age.[1] In our analysis, an additional pretransplant risk factor associated with the development of anastomotic strictures was alcoholic cirrhosis as the etiology of liver failure. It is unclear why the etiology of liver disease impacts the risk of BC, but it may reflect subtle differences in the populations of liver transplant recipients (eg, more profound nutritional

TABLE 6.

Implications of biliary complication—statistical analysis

	Patient survival				Allograft loss				Acute rejection			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Combined biliary complications	4.49	2.23, 9.06	5.02	2.36, 10.7	0.67	0.16, 2.83	0.71	0.16, 3.18	1.22	0.67, 2.21	1.34	0.70, 2.56
Leak	2.63	0.81, 8.60	2.17	0.46, 10.3	1.31	0.18, 9.71	1.36	0.17, 10.7	1.57	0.69, 3.58	2.47	1.04, 5.93
Stricture	4.09	1.84, 9.07	5.70	2.40, 13.5	0.46	0.06, 3.41	0.49	0.06, 3.81	0.81	0.33, 2.01	0.69	0.25, 1.91

Unadjusted, univariate analysis; Adjusted, multivariate analysis.
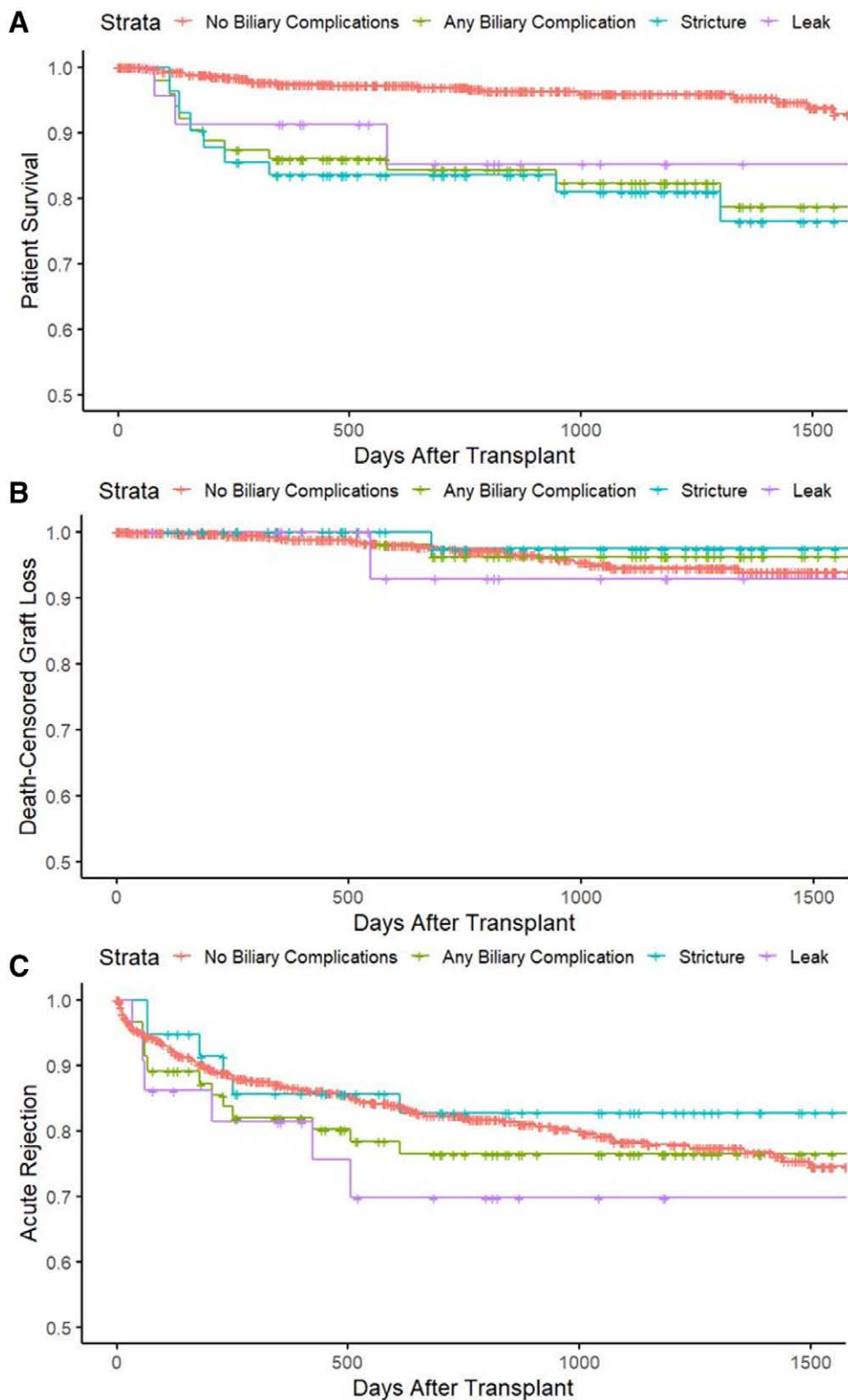CI, confidence interval; HR, hazard ratio.

FIGURE 1. Implications of biliary complications. A, Overall patient survival among patients undergoing DDLT stratified by the presence or absence of biliary complications. Any biliary complication and biliary strictures were associated with an increased risk of mortality compared to those without complications on both univariate and multivariate analysis. B, Graft failure among patients undergoing DDLT stratified by the presence or absence of biliary complications. Biliary complications were not a significant risk factor for graft failure. C, Incidence of acute rejection among patients undergoing DDLT stratified by the presence or absence of biliary complications. Biliary leaks were a significant risk factor for future episodes of acute rejection. DDLT, deceased donor liver transplant.

TABLE 7.

Impact of biliary complications on total days alive and out of hospital

	No biliary complication	Any biliary complication	P	No leak	Leak	P	No stricture	Stricture	P
	(N = 551)	(N = 96)		(N = 622)	(N = 25)		(N = 579)	(N = 68)	
Total days alive and out of the hospital			0.34			0.46			0.50
Mean (SD)	967 (535)	912 (503)		962 (531)	883 (505)		963 (534)	919 (498)	
Median [Min, Max]	918 [54.0, 2100]	868 [47.0, 1920]		917 [47.0, 2100]	820 [48.0, 1800]		901 [48.0, 2100]	1000 [47.0, 1920]	
Days alive and out of the hospital, 1 y post-Tx			0.20			0.46			0.35
Mean (SD)	338 (57.0)	328 (67.2)		337 (57.9)	325 (76.0)		337 (57.9)	329 (65.3)	
Median [Min, Max]	365 [54.0, 365]	351 [47.0, 365]		365 [47.0, 365]	346 [48.0, 365]		365 [48.0, 365]	356 [47.0, 365]	
Days alive and out of the hospital, 3 y post-Tx			0.64			0.56			0.92
Mean (SD)	788 (331)	770 (340)		787 (332)	748 (327)		786 (331)	781 (346)	
Median [Min, Max]	918 [54.0, 1100]	868 [47.0, 1100]		917 [47.0, 1100]	820 [48.0, 1100]		908 [48.0, 1100]	906 [47.0, 1100]	

Tx, transplantation.

deficiencies in alcoholic recipients of liver transplants) that impact wound healing.

Intraoperatively, use of a biliary stent was found to be an independent risk factor for both biliary leaks and biliary strictures, although this finding is likely the result of selection bias as the use of a stent is not routine and may be used in selective patients whose biliary anastamosis is deemed "riskier" given intraoperative findings such as relative increase of anastomotic tension, small donor or recipient duct, or an increase in recipient/donor bile duct size mismatch.

While there is broad consensus regarding the importance of some surgical tenets (such as cutting back the ducts until well-vascularized mucosa is visible and avoiding excessive tension), there is debate in the literature regarding the ideal surgical technique to employ to minimize the risk of BCs. Jafari et al[17] from the University of Bonn found no difference in the rate of BCs between biliary anastomoses that were performed in an entirely running fashion with continuous suture versus those in which only the posterior wall was formed with running suture and the anterior wall with interrupted sutures, although they did argue that this latter technique was superior for its improved visualization and reducing the risk of an anterior wall suture ensnaring the posterior wall. Other groups have also found no difference in the rate of biliary strictures or leak between end-to-end biliary anastomoses performed using continuous suture versus interrupted sutures.[18] In contrast, at least one report found lower BCs associated with continuous rather than interrupted sutures, although these results are confounded by the use of external biliary drainage in the interrupted suture group and no t-tubes in the continuous suture group.[19] Finally, Buczkowski et al[20] in Vancouver have reported superior outcomes by spatulating the ends of the donor and recipient bile duct and then completing the anastomosis with continuous suture and an intraductal stent, compared to their earlier outcomes with a conventional end-to-end biliary anastomosis with interrupted suture. The biliary anastomoses in this series were constructed using 6-0 PDS sutures and a variety of techniques (all continuous, all interrupted, or continuous posterior and interrupted anterior walls) dictated by surgeon preference, with no technique conferring obvious lower rates of BC (data not shown).

A variety of management strategies have been described to treat BCs in liver transplant recipients. While bile leaks and biliary strictures can be treated with surgical revision of the biliary anastomosis (often involving conversion to a Roux-en-Y choledochojejunostomy), the contemporary trend in management of these complications has relied more on endoscopic and percutaneous approaches, which are less invasive than surgery,[2,4,9] and highly successful.[21] Treatment of bile leaks with an ERCP and plastic stent placement resolves early bile leaks in 82%–95% of cases.[22,23] Similarly, ERCP with serial balloon dilation and exchange of biliary stents every 3 mo for 1–2 y is the first-line therapy for most anastomotic biliary strictures. One systematic review of 440 liver transplant patients with anastomotic biliary strictures found that those treated for >12 mo with serial dilation and stent exchange resolved their strictures 97% of the time,[24] and another large series of 69 patients found that 94% of these biliary strictures could be successfully resolved with endoscopic management.[25] When ERCP is not an option (as is the case often with patients receiving a Roux-en-Y biliary reconstruction), strictures can often be managed with placement of a biliary drain via PTC.[1,3] Surgery is typically reserved for patients who fail endoscopic or percutaneous manage of their strictures. In our series, the majority of biliary leaks were discovered early and managed surgically. A recent report suggests that endoscopic management of biliary leaks is a feasible option in the absence of uncontrolled leak or biliary peritonitis[21] and may allow patients to avoid unnecessary surgery.

Despite early reports that BCs may not affect patient survival,[26] our data suggest that overall BCs are associated with worse patient survival at 1 and 4 y posttransplant. In a subgroup analysis, anastomotic strictures but not biliary leaks were associated with worse overall patient survival. This contrasts with recent data that suggest biliary leaks do confer worse survival at 1, 3, and 5 y posttransplant, while anastomotic strictures do not.[5] One hypothesis for this discrepancy may be due to the difference in management of biliary leaks. In contrast to our series, more than half of biliary leaks alone were managed endoscopically (55%) in the report by Senter-Zapata et al.[5] Although biliary leaks were not associated with worse patient survival, they were associated with significantly higher rates of acute rejection. Although the pathophysiology of this remains unclear, we hypothesize that the local inflammatory reaction caused by bile leakage may attract additional immune cells to the liver, subsequently increasing the risk of

rejection. An alternative explanation may be that recipients may be more vulnerable to acute cellular rejection due to purposeful reductions in immunosuppression meant to address the infections that bile leaks can cause. However, it was not the standard protocol at our center to reduce transplant immunosuppression in the setting of a bile leak, and many of these bile leaks were detected very early (POD#1 or 2) before tacrolimus had even been initiated.

Limitations of this study include its single-center, retrospective design and potential documentation discrepancies within our electronic medical records. Additionally, the intraoperative decision to utilize a biliary stent or perform a Roux-en-y choledochojejunostomy was at the discretion of the operating surgeon and the indication was not always immediately clear from the medical record.

In summary, biliary leaks and anastomotic biliary strictures are among the most common BCs following adult deceased LT. This report represents one of the few comprehensive, contemporary series evaluating the risk factors, management and outcomes of these 2 types of BC after adult deceased donor LT from a high-volume US center. In contrast to older case series from an era where biliary T-tubes were used commonly, many of the previously identified risk factors for BCs in adult liver transplant recipients (such as advanced donor age, recipient MELD at transplant, warm ischemic time, hepatic artery thrombosis, and use of Roux-en-Y hepaticojejunostomy) were no longer significant risks for BCs in our case series. These analyses highlight that although few pretransplant recipient or intraoperative risk factors may help to predict the development of these complications, meticulous surgical technique that minimizes tension, duct ischemia, and duct-to-duct size mismatch are critical to prevent the worsened long-term transplant outcomes associated with these complications.

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