Biliary Complications After Liver Transplantation in the United States: Changing Trends and Economic Implications

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Background. Biliary complications (BCs) continue to impact patient and graft survival after liver transplant (LT), despite improvements in organ preservation, surgical technique, and posttransplant care. Real-world evidence provides a national estimate of the incidence of BC after LT, implications for patient and graft outcomes, and attributable cost not available in transplant registry data. **Methods.** An administrative health claims–based BC identification algorithm was validated using electronic health records (N = 128) and then applied to nationally linked Medicare and transplant registry claims. **Results.** The real-world evidence algorithm identified 97% of BCs in the electronic health record review. Nationally, the incidence of BCs within 1 y of LT appears to have improved from 22.2% in 2002 to 20.8% in 2018. Factors associated with BCs include donor type (living versus deceased), recipient age, diagnosis, prior transplant, donor age, and donor cause of death. BCs increased the risk-adjusted hazard ratio (aHR) for posttransplant death (aHR, 1.43; $P < 0.0001$) and graft loss (aHR, 1.48; $P < 0.0001$). Nationally, BCs requiring intervention increased risk-adjusted first-year Medicare spending by $39 710 ($P < 0.0001$). **Conclusions.** BCs remain an important cause of morbidity and expense after LT and would benefit from a systematic quality-improvement program.

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INTRODUCTION

Biliary complications (BCs) remain a significant source of morbidity after deceased donor liver transplant (DDLT) and living donor liver transplant (LDLT).[1] BCs encompass leaks, either at the anastomosis or from the cut surface in LDLT recipients, anastomotic strictures, and peripheral cholangiopathy. The incidence of biliary anastomotic strictures in large case series is estimated at 8% to 31% after LDLT and 5% to 15% after DDLT, of which 70% to 87% are diagnosed in the first year.[2-4] Nonanastomotic strictures (NASs) are reported in 1% to 15% of cases.[5,6] The incidence of biliary leaks varies from 2% to 25%, whereas diffuse cholangiopathy, which is most common after DDLT from a donor after circulatory death, varies from 2% to 20%.[7]

BCs are diagnosed using clinical signs or laboratory evidence. After diagnosis, BCs are confirmed with imaging procedures, including endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography. BCs may be treated using minimally invasive interventions such as stenting, percutaneous transhepatic cholangiography, surgical revision, or retransplantation.[8] Reported risk factors for BCs include impaired arterial inflow, advanced donor age, partial or split liver grafts, prolonged ischemic time, and DCD donation.[9] If not treated, BCs can lead to recurrent cholangitis, secondary biliary cirrhosis, and, eventually, graft failure.[9]

Prior investigations using health insurance claims have identified significant variation in the risk-adjusted frequency of BCs and have correlated the cost of liver transplant (LT) care with the development of BCs.[10,11] However, these real-world evidence methods have not been validated using clinical chart review or recently updated in light of revisions to the organ allocation system. The current investigation assessed sensitivity and specificity of a healthcare claims real-world evidence algorithm to identify BCs through a direct medical record review of a large institutional sample. This validated algorithm was then applied to a national cohort of Medicare-insured patients to assess the impact of recent changes in liver allocation on the prevalence of BC and impact of LT clinical and economic outcomes.

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TABLE 1.

Estimated institutional cost of biliary complications after liver transplantation

	Total charges per patient (mean)	Estimated cost of care per patient (mean)	Estimated Medicare payment per patient (mean)	Estimated hospital margin %
Diagnosis and procedure	$868 726	$234 556	$216 115	–8.5
Diagnosis and surgery	$523 355	$141 306	$145 013	2.6
Diagnosis alone	$488 952	$132 017	$122 073	–8.1
No complications	$405 690	$109 536	$111 556	1.8

MATERIALS AND METHODS

Institutional Patient Clinical Events and Claims Analysis

Detailed electronic health record review of data was performed during a review of 128 DDLT procedures performed at the University of Iowa from 2010 to 2019. Patients' electronic health records were reviewed to identify patients with BCs. Subsequently, hospital billing claims were extracted for all LT recipients regardless of payer. Estimated hospital cost and hospital contribution margin were determined by converting all hospital charges to cost using the hospital cost-to-charge ratio. Next, estimated Medicare reimbursement was available for 112 recipients (regardless of actual payer) and calculated using standard Medicare diagnosis related group (DRG) payment methodology, including outlier payments.

National Data

National clinical, demographic, and claims information for adult (age >18 y) patients who underwent LT from 2002 to 2018 was obtained from a database linking Scientific Registry of Transplant Recipients (SRTR) LT files with Medicare billing claims. SRTR data were analyzed for this study. The SRTR system includes data on all donors, waitlisted candidates, and transplant recipients in the United States submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services (HHS), oversees the activities of OPTN and SRTR contractors. Medicare billing claims data include diagnostic and procedure codes for patients with Medicare fee-for-service primary or secondary insurance. After regulatory approvals, beneficiary identifier numbers from Medicare's databases were linked using Social Security number, sex, and birthdate to unique, anonymous registry identification numbers. Because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, a waiver of informed consent was granted per the HHS Code of Federal Regulations (Title 45, Part 46, Paragraph 46.116). Analyses were performed using Health Information Portability and Accountability Act–compliant, limited datasets, from which all direct identifiers were removed.

Recipient and Donor Clinical Characteristics

Information on recipient national clinical and demographic characteristics was drawn from OPTN Standard Analysis and Research files and included records of recipient age, sex, race, blood type, primary cause of end-stage liver disease, mean biologic Model for End-Stage Liver Disease (MELD) score, comorbidities, insurance type, and listing region. Donor characteristics included mode of death (donation after brain death [DBD] or donation after circulatory death [DCD]), ischemic time, age, race, and comorbidities.

Definition of BC Scale

BCs were ascertained from Medicare billing claims with corresponding *International Statistical Classification of Diseases and Related Health Problems*–9/10 diagnosis codes and procedures using Common Procedure Terminology codes within 180 d of transplant. BCs were defined using the Medicare claims records (Table 1) and grouped by need for intervention. Group 1 included all patients with biliary diagnoses (eg, cholangitis, biliary stricture) posttransplant. Group 2 is a subgroup of patients in group 1 who underwent an endoscopic or radiologic procedure (eg, ERCP) or a surgical procedure. Group 3 includes the subgroup of patients in group 1 with a posttransplant surgical procedure for a BC (eg, choledochoenterostomy or retransplantation). The same methodology was used to evaluate hospital claims generated for the local cohort. The resulting designations based on health claims were then compared with a detailed medical record review to determine concordance.

Statistical Analyses

Baseline characteristics of the study cohort of Medicare-insured LT candidates were compared with all OPTN candidates without Medicare by the chi-square test or the Student *t* test as appropriate. The incidence of BCs was estimated by Kaplan-Meier analysis based on time from transplant to the first BC. Incidence estimates were computed for the overall population and after stratification for transplants from donors after DBD and DCD. Independent correlates of BCs were estimated from multivariate Cox models, considering time from transplant to the first claim for a complication in each group (diagnosis for group 1, procedure for groups 2 and 3).

Dates of death and graft failure were defined by OPTN reports. Cox regression was used to assess the impact of a diagnosis of BC (group 1) or need for a biliary procedure (group 2) or surgical revision (group 3) on the risk of patient and graft survival after LT. Time of origin was the date of transplant, and patients were censored at the last follow-up or the end of the study. The biliary diagnosis or procedure was included in the model as a time-varying covariate assigned at the date of the first claim.

Economic analysis included paid Medicare claims for all care beginning with the LT (DRG 005 and 006) and concluding at 1 y after transplant. Actual payment was

included rather than calculations based on Common Procedure Terminology or DRG code. Attributable BC costs were defined as the difference in aggregate 1-y paid claims for patients with and without BCs (including multiple interventions when required). Data management and analyses were performed using SAS, version 9.3 (SAS Institute Inc, Cary, NC).

Approval

The study was approved by the University of Iowa and the Saint Louis University institutional review boards, the data oversight committee of the OPTN, and HRSA.

RESULTS

Institutional Cohort

Over an 8.5-y period, 128 patients underwent DDLT at the University of Iowa (characteristics in **Table S1, SDC**, http://links.lww.com/TP/C690). Medical record review of these patients demonstrated that 30 (23.4%) developed a BC, including 22 anastomotic strictures, 7 leaks, and 1 NAS within the first year after transplant. These patients required 18 ERCPs, of which 83% demonstrated a BC, and 6 percutaneous transhepatic cholangiocatheters, all of which confirmed a BC. Five patients required reoperation with conversion to a Roux-en-Y hepaticojejunostomy (RYHJ), and 1 patient required retransplant. Assessment of billing claims identified 97% of patients with a diagnosed BC. Among patients with a biliary procedure, the claims analysis was 79% sensitive and 97% specific. The negative predictive value of the claims analysis was 94% in excluding a BC in this population.

Estimated Financial Implications of BCs

Single institutional accounting data review demonstrated that mean charges and estimated cost of care, exclusive of organ acquisition, were significantly higher for patients with a BC (total charges: $488 952; estimated cost: $132 017) than for patients without a BC ($405 690; $109 536) over the first 12 mo after transplant (Table 1). Patients who required a biliary procedure ($868 726; $234 556) were substantially more resource intensive than patients treated with surgical revision ($523 355; $141 306). Overall, although expected Medicare reimbursement was 94% higher for patients managed with ERCP/percutaneous transhepatic cholangiocatheter than patients without complications, the higher cost of care resulted in an estimated loss (contribution margin of –8.5% versus 1.8% for patients without complications). For patients undergoing surgical revision, the estimated payment was 30.0% higher, and the estimated hospital contribution margin was significantly improved (2.6%).

National Data

The incidence of a diagnosis consistent with a BC (group 1) has remained largely stable. The cumulative incidence rate of any BC at 1 y post-LT was 22.2% in 2002 to 2006, 21.9% in 2007 to 2010, 24% in 2011 to 2014, and 20.8% in 2015 to 2018 ($P = 0.51$; Table 2; Figure 1). However, 1-y incidence of BC requiring intervention (group 2) decreased from 18.7% in 2002 to 2005 to 16.3% in 2015 to 2018 ($P = 0.06$). These patients underwent a mean of 3 procedures (25%: 1–75%: 4). The use of surgery to address BCs has markedly decreased from 4.6% in 2002 to 2005 to 1.6% of LT in 2015 to 2018 ($P < 0.0001$) because endoscopic techniques have improved.

In multivariate regression, factors associated with increased rates of BCs included younger age, male sex, allocation MELD score, previous transplant, donor age, donor stroke or cerebrovascular disease, and partial or split transplant, including living donors (Table 3; **Figure S1, SDC,** http://links.lww.com/TP/C690). After accounting for donor, recipient, and transplant factors, the overall risk of BCs was essentially unchanged from 2002 to 2010 but 22% higher from 2011 to 2014 (adjusted hazard ratio [aHR], 1.22; $P < 0.001$) and 2015 to 2018 (aHR, 1.22; $P < 0.0001$). BCs requiring endoscopic or radiologic intervention (group 2) remained stable or increased across all age groups and eras of transplant, whereas the need for surgical intervention decreased significantly ($P < 0.001$). Male sex, blood group AB, and allocation MELD were associated with higher incidence of BCs, as was cold ischemic time CIT between 7 and 12 h. Warm ischemic time was not associated with a higher incidence of BCs.

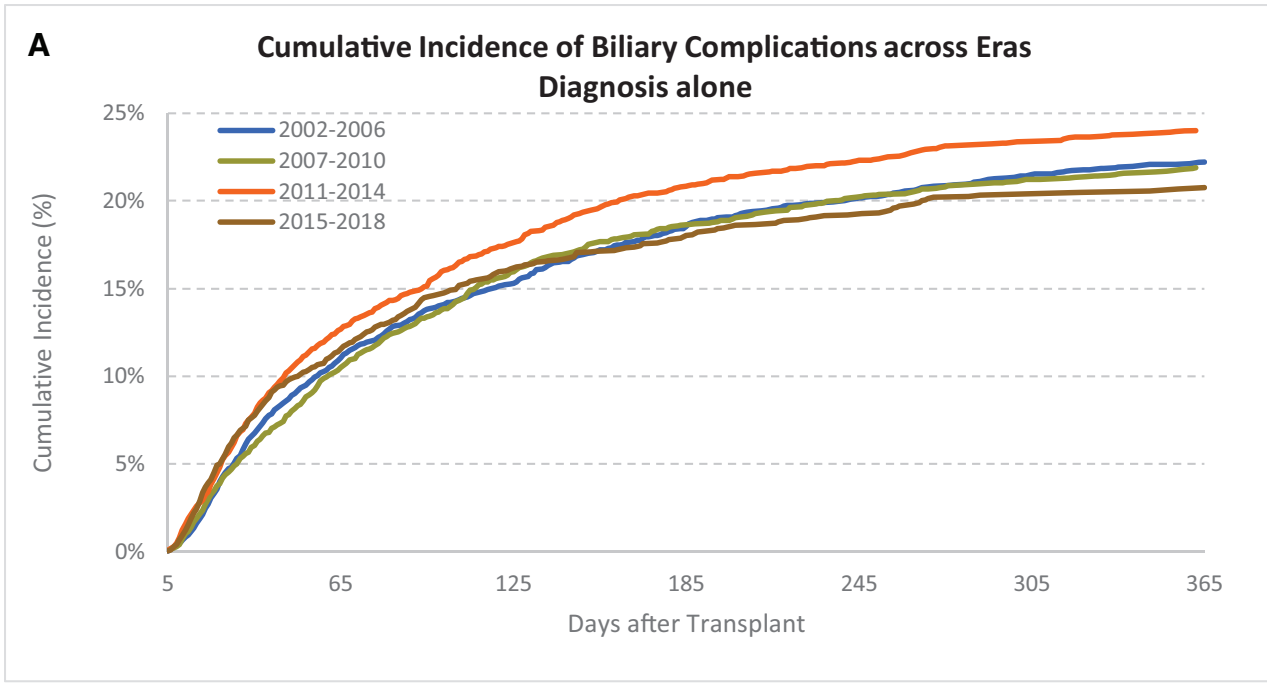
Donor type was strongly associated with the frequency of BCs. In this cohort, the incidence of any BC was significantly higher in DCD recipients (44%) than in recipients of LDLT (36%) and DBD organs (29%; $P < 0.001$). Similarly, the need for interventions was nearly twice as

TABLE 2.

National incidence of biliary complications by era and donor type

	Group 1: Diagnosis (%)	*P*	Group 2: Diagnosis + procedure or surgery (%)	*P*	Group 3: Diagnosis + surgery (%)	*P*
Era of transplant						
2002–2006	22.2	Reference	18.7	Reference	4.6	Reference
2007–2010	21.9	0.75	16.8	0.03	3.0	0.004
2011–2014	24.0	0.04	19.9	0.17	3.2	0.003
2015–2018	20.8	0.51	16.3	0.06	1.6	<0.0001
Donor type						
Living donor	42.8	<0.0001	34.8	<0.0001	7.3	<0.0001
DCD	27.1	<0.0001	22.2	<0.0001	4.0	0.03
DBD	20.8	Reference	16.8	Reference	3.0	Reference

DBD, donation after brain death; DCD, donation after circulatory death.



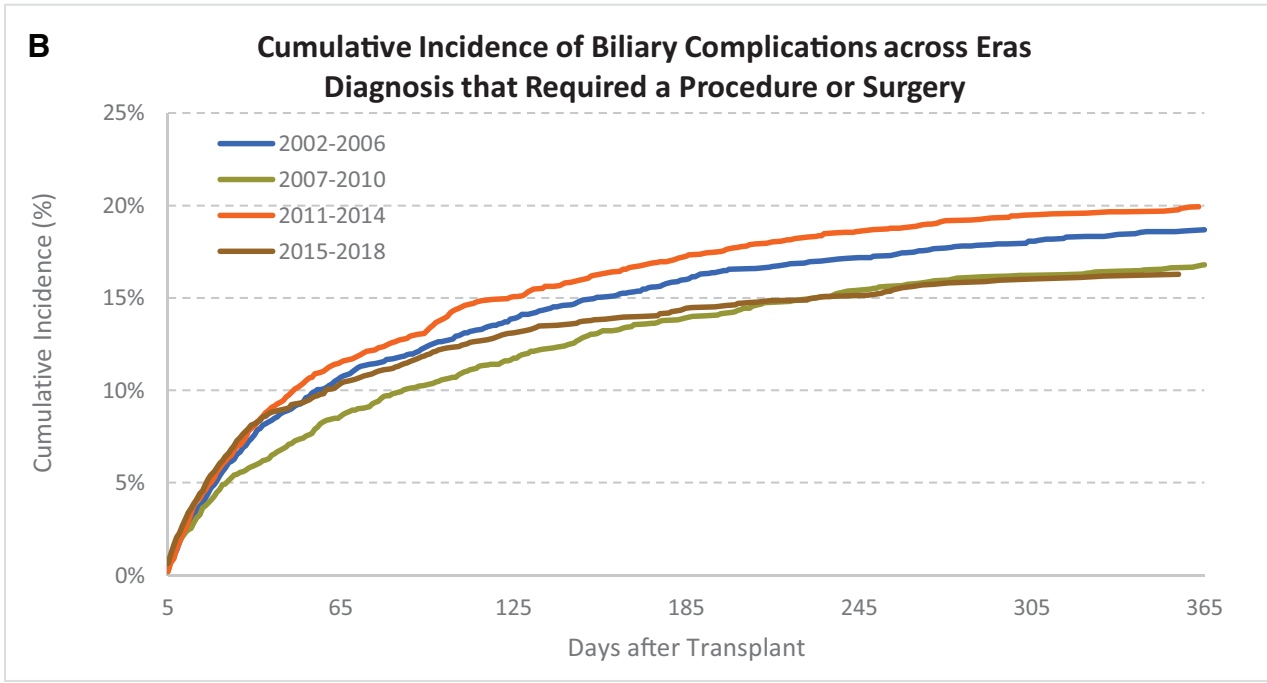


FIGURE 1. Incidence of early biliary complications after liver transplant by era in the United States.

high for LDLT recipients (37%) than for those with DBD (16.6%) and DCD (20.8%; $P<0.0001$). Over time, the incidence of BCs among DCD recipients has improved but is not yet at the level of DBD recipients (Figure 2). In the multivariate analysis, the incidence of BCs in patients with partial liver allografts (including LDLT) remains significantly higher. Other donor characteristics that increased the incidence of BCs were donor age and cerebrovascular accident (CVA)/stroke as cause of death.

Impact of BCs on Long-term Outcomes

BCs continue to significantly increase the risk of death and graft failure. After risk adjustment, group 1 BCs increased the risk of all-cause mortality by 43% (aHR, 1.43; $P<0.001$; Table 4). Group 2 BCs, those requiring procedural interventions (aHR, 1.46; $P<0.0001$), and group 3 BCs, requiring surgery (aHR, 1.43; $P=0.008$), were also associated with an increased risk of death. Although Black race was not associated with the incidence of BC, Black individuals continue to have an overall increased risk of death after LT ($P<0.05$). Although metabolic liver disease was associated with the lowest risk of death in recipients, the presence of diabetes significantly increased the risk of death after BCs in LT patients ($P<0.0001$). Nonviral indication for transplant was associated with a lower risk of death after BCs developed ($P<0.0001$). Older donors and split/partial liver graft recipients were at higher risk of death, as were those with

TABLE 3.

Multivariate Cox regression analysis characteristics associated with biliary complications after liver transplant

	Group 1: Diagnosis aHR (95% CI)	Group 2: Diagnosis + procedure or surgery aHR (95% CI)	Group 3: Diagnosis + surgery aHR (95% CI)
Era of transplant			
2002–2006	Reference	Reference	Reference
2007–2010	1.02 (0.93-1.13)	0.91 (0.81-1.02)	0.67 (0.52-0.86)[1]
2011–2014	1.22 (1.10-1.35)[2]	1.16 (1.04-1.30)[1]	0.76 (0.59-0.99)[1]
2015–2018	1.22 (1.06-1.40)[1]	1.11 (0.95-1.29)	0.42 (0.28-0.62)[3]
Recipient characteristics			
Age, y			
19–30	Reference	Reference	Reference
31–45	0.68 (0.51-0.89)[1]	0.86 (0.60-1.23)	0.74 (0.40-1.37)
46–60	0.59 (0.45-0.76)[3]	0.84 (0.60-1.17)	0.56 (0.32-0.99)[1]
>60	0.51 (0.39-0.66)[3]	0.70 (0.50-0.97)[1]	0.43 (0.24-0.76)[1]
Male	1.12 (1.03-1.21)[1]	1.08 (0.99-1.18)	1.43 (1.15-1.78)[1]
Race			
White	Reference	Reference	Reference
Black	1.11 (0.97-1.27)	0.98 (0.84-1.15)	1.22 (0.86-1.72)
Hispanic	0.90 (0.81-1.02)	0.92 (0.81-1.04)	1.21 (0.92-1.60)
Other race	0.93 (0.78-1.12)	0.95 (0.78-1.16)	0.85 (0.50-1.45)
ABO type			
A	Reference	Reference	Reference
AB	0.82 (0.68-0.98)[1]	0.74 (0.59-0.92)[1]	0.70 (0.40-1.21)
B	0.94 (0.83-1.06)	0.98 (0.86-1.12)	0.81 (0.58-1.13)
O	0.95 (0.87-1.03)	1.00 (0.92-1.10)	1.02 (0.83-1.26)
Laboratory MELD at transplant	1.01 (1.00-1.02)[2]	1.01 (1.00-1.01)[1]	1.01 (1.00-1.03)
Cause of ESLD			
HCC	Reference	Reference	Reference
HCV	1.10 (0.99-1.23)	1.13 (1.01-1.28)[1]	1.04 (0.77-1.39)
HBV	1.29 (0.94-1.76)	1.30 (0.93-1.83)	2.00 (1.03-3.88)[1]
Metabolic	0.89 (0.69-1.15)	0.89 (0.68-1.18)	1.51 (0.85-2.67)
Alcoholic	0.92 (0.80-1.06)	0.92 (0.79-1.08)	0.96 (0.65-1.41)
Other	1.12 (1.01-1.24)[1]	0.96 (0.85-1.08)	1.46 (1.10-1.93)[1]
Cold ischemic time, h			
0–6	Reference	Reference	Reference
7–12	1.12 (1.03-1.22)[1]	1.12 (1.02-1.24)[1]	1.03 (0.82-1.30)
>12	1.22 (0.98-1.52)	1.20 (0.94-1.53)	1.36 (0.83-2.23)
Not reported	1.05 (0.94-1.17)	1.06 (0.94-1.19)	1.04 (0.79-1.38)
Warm ischemic time, min			
0–30	Reference	Reference	Reference
>30	0.92 (0.83-1.02)	0.91 (0.82-1.02)	1.28 (0.98-1.67)
Not reported	0.82 (0.73-0.93)[1]	0.83 (0.73-0.95)[1]	1.07 (0.77-1.48)
Previous transplant	1.20 (1.02-1.41)[1]	1.02 (0.84-1.24)	1.23 (0.83-1.83)
Peritonitis	0.96 (0.84-1.10)	1.02 (0.88-1.18)	0.95 (0.67-1.35)
Previous abdominal surgery	1.16 (1.08-1.26)[2]	1.13 (1.04-1.23)[1]	1.10 (0.89-1.34)
Portal vein thrombosis	1.04 (0.93-1.16)	1.07 (0.95-1.20)	1.16 (0.87-1.55)
Diabetes	0.88 (0.81-0.95)[1]	0.90 (0.82-0.99)[1]	0.95 (0.76-1.17)
On life support	0.77 (0.57-1.05)	0.84 (0.60-1.18)	0.34 (0.11-1.07)
Donor characteristics			
Donor age, y	1.00 (1.00-1.01)[1]	1.00 (1.00-1.01)[1]	1.01 (1.00-1.01)[1]
Donor cause of death			
Cerebrovascular/stroke	1.14 (1.03-1.26)[1]	1.13 (1.01-1.27)[1]	1.20 (0.92-1.58)
Anoxia	0.92 (0.83-1.03)	0.92 (0.81-1.04)	1.03 (0.76-1.39)
Head trauma	Reference	Reference	Reference
CNS tumor	0.77 (0.32-1.86)	0.73 (0.27-1.94)	1.21 (0.17-8.70)
Other	1.05 (0.76-1.43)	1.13 (0.80-1.59)	1.76 (0.86-3.62)
Partial/split liver	1.88 (1.48-2.41)[3]	1.75 (1.33-2.30)[3]	2.32 (1.27-4.24)[1]

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TABLE 3. (CONTINUED)

	Group 1: Diagnosis aHR (95% CI)	Group 2: Diagnosis + procedure or surgery aHR (95% CI)	Group 3: Diagnosis + surgery aHR (95% CI)
Donor type			
Living	1.36 (0.91-2.04)	1.37 (0.88-2.14)	0.86 (0.34-2.23)
DCD	1.44 (1.30-1.61)[3]	1.47 (1.31-1.65)[3]	1.55 (1.17-2.05)[1]
DBD	Reference	Reference	Reference

Group 1: any diagnosis of biliary complication; group 2: patients with a diagnosis of biliary complication who require either an endoscopic/radiographic or a surgical procedure; group 3: patients with a biliary complication diagnosis who required a surgical revision

Data presented as aHR (95% CI).

[1]$P < 0.05$–0.002.

[2]$P = 0.001$–0.0002.

[3]$P < 0.0001$.

"Other race" includes Asian, Native American, Pacific Islander, and multiracial.

[a]HR, adjusted hazard ratio; CI, confidence interval; CNS, central nervous system; DBD, donation after brain Death; DCD, nonheart beating donor; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease.

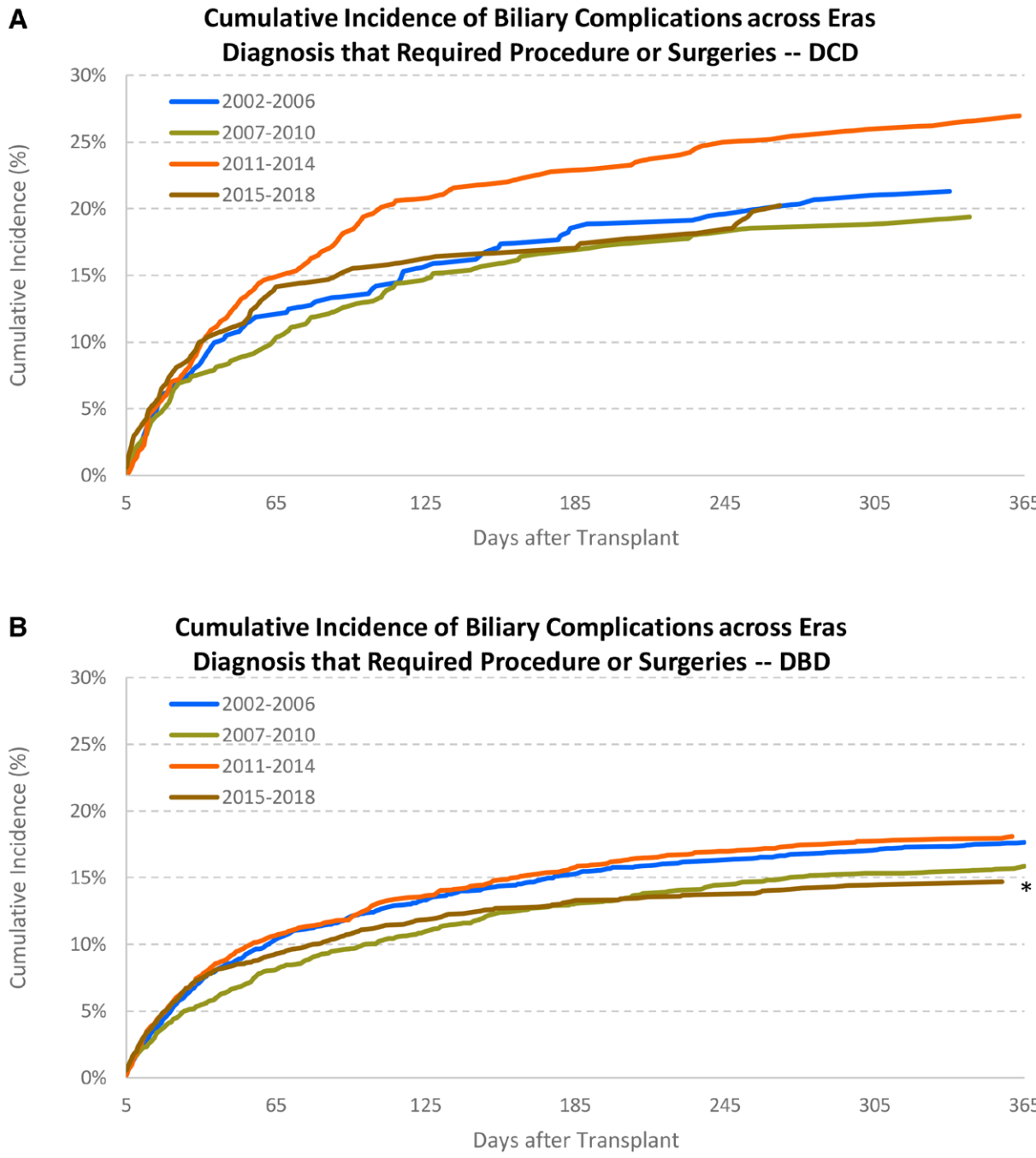

FIGURE 2. Incidence of biliary complications after liver transplant requiring intervention. (A) DCD. (B) DBD. DBD, donation after brain death; DCD, donation after circulatory death donor.

TABLE 4.

Multivariate Cox regression analysis of the risk of all-cause mortality

	Group 1: Diagnosis aHR (95% CI)	Group 2: Diagnosis + procedure or surgery aHR (95% CI)	Group 3: Diagnosis + surgery aHR (95% CI)
Biliary complication			
Time-varying group 1	1.43 (1.29-1.58)[3]		
Time-varying group 2		1.46 (1.32-1.62)[3]	
Time-varying group 3			1.43 (1.14-1.78)[1]
Era of transplant			
2002–2006	Reference	Reference	Reference
2007–2010	0.82 (0.74-0.92)[2]	0.83 (0.74-0.93)[2]	0.83 (0.74-0.93)[2]
2011–2014	0.66 (0.58-0.74)[3]	0.66 (0.58-0.74)[3]	0.67 (0.59-0.75)[3]
2015–2018	1.62 (1.37-1.91)[3]	1.62 (1.37-1.92)[3]	1.65 (1.40-1.96)[3]
Recipient characteristics			
Age, y			
19–30	Reference	Reference	Reference
31–45	1.40 (0.88-2.23)	1.36 (0.86-2.16)	1.37 (0.86-2.17)
46–60	1.21 (0.78-1.88)	1.17 (0.75-1.81)	1.18 (0.76-1.83)
>60	1.31 (0.84-2.03)	1.27 (0.81-1.97)	1.26 (0.81-1.96)
Male	1.01 (0.92-1.11)	1.02 (0.92-1.12)	1.02 (0.93-1.12)
Race			
White	Reference	Reference	Reference
Black	1.35 (1.17-1.56)[3]	1.37 (1.18-1.58)[3]	1.36 (1.18-1.57)[3]
Hispanic	0.82 (0.71-0.94)[1]	0.82 (0.71-0.94)[1]	0.81 (0.71-0.93)[1]
Other race	0.87 (0.71-1.06)	0.87 (0.71-1.06)	0.87 (0.71-1.06)
ABO type			
A	Reference	Reference	Reference
AB	0.91 (0.74-1.12)	0.91 (0.74-1.12)	0.90 (0.73-1.11)
B	0.89 (0.77-1.02)	0.89 (0.77-1.02)	0.89 (0.77-1.02)
O	0.99 (0.90-1.09)	0.99 (0.90-1.08)	0.99 (0.90-1.09)
Laboratory MELD at transplant	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Cause of ESLD			
HCC	Reference	Reference	Reference
HCV	0.85 (0.75-0.96)[1]	0.85 (0.75-0.95)[1]	0.85 (0.75-0.96)[1]
HBV	0.61 (0.41-0.91)[1]	0.61 (0.41-0.91)[1]	0.61 (0.41-0.91)[1]
Metabolic	0.52 (0.37-0.73)[2]	0.52 (0.38-0.73 [2]	0.52 (0.37-0.72)[2]
Alcoholic	0.65 (0.55-0.77)[3]	0.65 (0.55-0.77)[3]	0.64 (0.54-0.76)[3]
Other	0.61 (0.54-0.69)[3]	0.61 (0.54-0.69)[3]	0.61 (0.54-0.69)[3]
Cold ischemic time, h			
0–6	Reference	Reference	Reference
7–12	1.04 (0.95-1.15)	1.04 (0.95-1.15)	1.05 (0.96-1.16)
>12	1.00 (0.77-1.30)	1.00 (0.77-1.30)	1.00 (0.77-1.30)
Not reported	1.02 (0.91-1.16)	1.02 (0.91-1.16)	1.03 (0.91-1.16)
Warm ischemic time, min			
0–30	Reference	Reference	Reference
>30	1.05 (0.94-1.18)	1.05 (0.94-1.18)	1.05 (0.93-1.18)
Not reported	1.11 (0.97-1.27)	1.11 (0.97-1.27)	1.09 (0.95-1.26)
Previous transplant	1.27 (1.03-1.56)[1]	1.28 (1.05-1.58)[1]	1.28 (1.04-1.57)[1]
Peritonitis	1.04 (0.88-1.21)	1.03 (0.88-1.21)	1.03 (0.88-1.21)
Previous abdominal surgery	1.00 (0.91-1.09)	1.00 (0.91-1.09)	1.01 (0.92-1.10)
Portal vein thrombosis	0.95 (0.83-1.09)	0.95 (0.83-1.09)	0.95 (0.83-1.09)
Diabetes	1.20 (1.10-1.31)[3]	1.20 (1.09-1.31)[2]	1.19 (1.09-1.30)[2]
On life support	1.07 (0.76-1.52)	1.06 (0.75-1.50)	1.07 (0.76-1.53)
Donor characteristics			
Donor age, y	1.01 (1.01-1.01)[3]	1.01 (1.01-1.01)[3]	1.01 (1.01-1.01)[3]
Donor cause of death			
Cerebrovascular/stroke	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0.94 (0.84-1.05)
Anoxia	0.97 (0.85-1.09)	0.97 (0.85-1.09)	0.96 (0.85-1.09)

Continued next page

TABLE 4. (CONTINUED)

	Group 1: Diagnosis aHR (95% CI)	Group 2: Diagnosis + procedure or surgery aHR (95% CI)	Group 3: Diagnosis + surgery aHR (95% CI)
Head trauma	Reference	Reference	Reference
CNS tumor	0.74 (0.28-1.99)	0.75 (0.28-2.01)	0.73 (0.27-1.94)
Other	0.73 (0.47-1.11)	0.72 (0.47-1.11)	0.73 (0.48-1.12)
Partial/split liver	0.63 (0.43-0.94)[1]	0.64 (0.43-0.95)[1]	0.66 (0.44-0.98)[1]
Donor type			
Living	1.51 (0.83-2.73)	1.51 (0.83-2.74)	1.53 (0.85-2.76)
DCD	1.00 (0.88-1.15)	1.01 (0.88-1.15)	1.02 (0.89-1.17)
DBD	Reference	Reference	Reference

Group 1: any diagnosis of biliary complication; group 2: patients with a diagnosis of biliary complication who require either an endoscopic/radiographic or a surgical procedure; group 3: patients with a biliary complication diagnosis who required a surgical revision.
Data presented as aHR (95% CI).
[1]$P<0.05$–0.002.
[2]$P=0.001$–0.0002.
[3]$P<0.0001$.
"Other race" includes Asian, Native American, Pacific Islander, and multiracial.
[a]HR, adjusted hazard ratio; CI, confidence interval; CNS, central nervous system; DBD, donation after brain death; DCD, nonheart beating donor; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease.

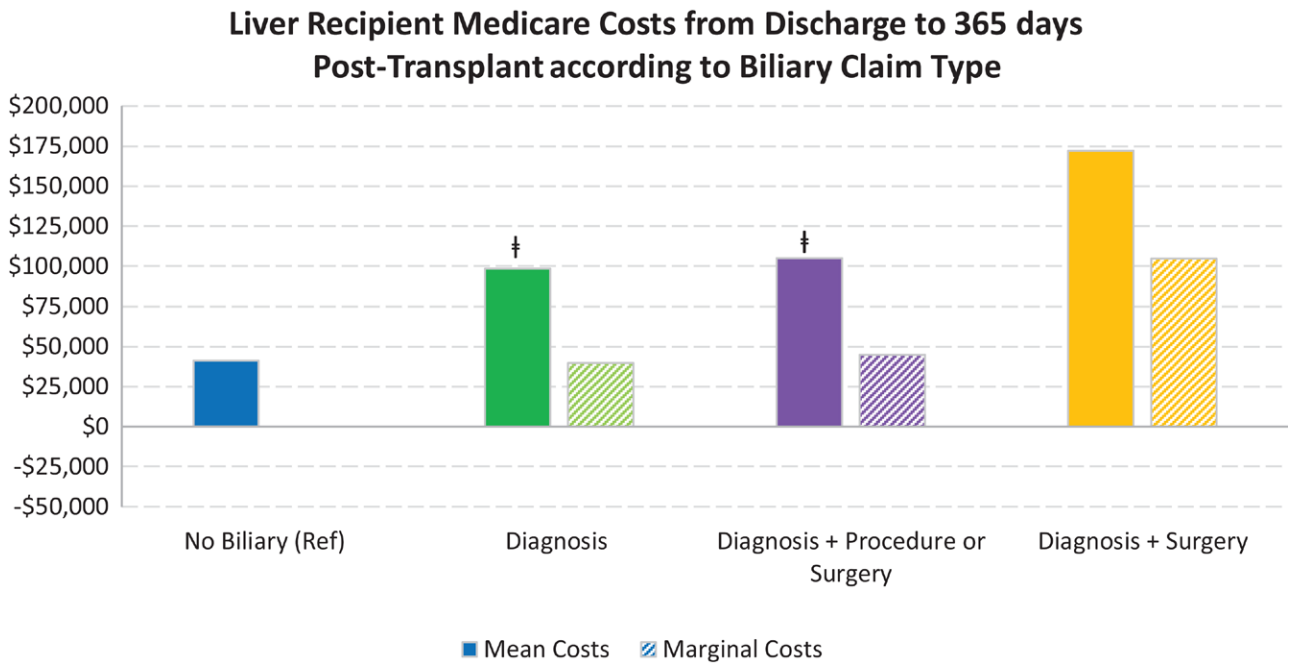

FIGURE 3. Medicare changes from discharge to 1 y after liver transplant categorized by biliary complication. ‡$P<0.0001$.

previous transplants. Patients requiring procedures after being transplanted for metabolic and alcoholic liver disease were also less likely to die, whereas diabetes, donor age, and previous transplants increased risk.

BCs were also associated with higher rates of all-cause graft failure. Liver allografts with BCs were associated with a 48% increased risk of graft loss (aHR, 1.48; $P<0.0001$), with similar significant risks of graft loss as those that occurred in patients requiring procedures (aHR, 1.52; $P<0.0001$) or surgical correction (aHR, 1.56; $P<0.0008$; Table 5). The risk of all-cause graft failure also increased significantly with each subsequent era to peak between 2015 and 2018. Again, being Black increased the risk of graft failure after LTs complicated by BC, and this risk was constant regardless of the need for intervention. Nonviral cause for transplant was associated with a significantly decreased risk of graft failure after BCs. Previous transplant, diabetes, and donor age increased the risk of graft failure after BCs in transplanted liver.

In addition to clinical implications, BCs increased the first-year Medicare payments for LTs. Mean cost for patients with BC diagnosis was $57 561 higher than for patients without BC (Figure 3). Payments were further increased with more complicated BCs (group 2: $64 017; group 3: $130 970). After adjustment for other donor and recipient characteristics, incremental spending for LT patients who develop BCs remained significantly higher.

DISCUSSION

BCs remain a persistent and significant source of morbidity and mortality after DDLT and LDLT. Nationally, the overall incidence of BC diagnoses (group 1) after LT has generally remained consistent during the past 15 y. About

TABLE 5.

Multivariate Cox regression analysis of the risk of all-cause graft failure in years 2 to 5 liver transplant among patients diagnosed with a biliary complication within the first 365 d after liver transplant

	Group 1: Diagnosis aHR (95% CI)	Group 2: Diagnosis + procedure or surgery aHR (95% CI)	Group 3: Diagnosis + surgery aHR (95% CI)
Biliary complication			
Time-varying group 1	1.48 (1.34-1.64)[3]		
Time-varying group 2		1.52 (1.37-1.69)[3]	
Time-varying group 3			1.56 (1.20-2.01)[2]
Era of transplant			
2002–2006	Reference	Reference	Reference
2007–2010	0.82 (0.73-0.92)[2]	0.83 (0.74-0.92)[2]	0.83 (0.74-0.92)[2]
2011–2014	0.66 (0.59-0.75)[3]	0.66 (0.59-0.75)[3]	0.68 (0.60-0.76)[3]
2015–2018	1.57 (1.33-1.86)[3]	1.58 (1.34-1.87)[3]	1.62 (1.37-1.91)[3]
Recipient characteristics			
Age, y			
19–30	Reference	Reference	Reference
31–45	1.16 (0.75-1.78)	1.12 (0.73-1.72)	1.12 (0.73-1.72)
46–60	0.99 (0.66-1.49)	0.95 (0.63-1.43)	0.96 (0.64-1.44)
>60	1.02 (0.68-1.53)	0.98 (0.65-1.47)	0.98 (0.65-1.47)
Male	1.05 (0.95-1.15)	1.05 (0.95-1.15)	1.05 (0.96-1.15)
Race			
White	Reference	Reference	Reference
Black	1.36 (1.18-1.58)[3]	1.38 (1.20-1.60)[3]	1.37 (1.19-1.59)[3]
Hispanic	0.81 (0.71-0.93)[1]	0.81 (0.71-0.93)[1]	0.81 (0.71-0.93)[1]
Other race	0.85 (0.69-1.04)	0.85 (0.69-1.04)	0.85 (0.69-1.04)
ABO type			
A	Reference	Reference	Reference
AB	0.87 (0.70-1.07)	0.87 (0.71-1.08)	0.86 (0.70-1.06)
B	0.87 (0.76-1.00)	0.87 (0.76-1.00)	0.87 (0.76-1.00)
O	0.97 (0.89-1.07)	0.97 (0.88-1.06)	0.97 (0.89-1.07)
Laboratory MELD at transplant	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (1.00-1.01)
Cause of ESLD			
HCC	Reference	Reference	Reference
HCV	0.85 (0.75-0.96)[1]	0.85 (0.75-0.96)[1]	0.85 (0.75-0.96)[1]
HBV	0.65 (0.44-0.96)[1]	0.65 (0.44-0.96)[1]	0.64 (0.43-0.94)[1]
Metabolic	0.56 (0.40-0.78)[2]	0.56 (0.40-0.78)[2]	0.55 (0.40-0.77)[2]
Alcoholic	0.64 (0.54-0.76)[3]	0.64 (0.53-0.75)[3]	0.63 (0.53-0.75)[3]
Other	0.63 (0.56-0.71)[3]	0.64 (0.56-0.72)[3]	0.63 (0.56-0.71)[3]
Cold ischemic time, hours			
0–6	Reference	Reference	Reference
7–12	1.05 (0.95-1.15)	1.05 (0.95-1.15)	1.06 (0.97-1.17)
>12	0.93 (0.71-1.22)	0.93 (0.71-1.22)	0.94 (0.71-1.23)
Not reported	1.02 (0.90-1.15)	1.02 (0.90-1.15)	1.02 (0.90-1.16)
Warm ischemic time, min			
0–30	Reference	Reference	Reference
>30	1.04 (0.93-1.17)	1.04 (0.93-1.17)	1.03 (0.92-1.16)
Not reported	1.11 (0.96-1.27)	1.11 (0.96-1.27)	1.09 (0.95-1.25)
Previous transplant	1.26 (1.03-1.54)[1]	1.27 (1.04-1.56)[1]	1.27 (1.04-1.56)[1]
Peritonitis	1.01 (0.86-1.18)	1.00 (0.86-1.18)	1.01 (0.86-1.18)
Previous abdominal surgery	0.97 (0.88-1.06)	0.97 (0.89-1.06)	0.98 (0.89-1.07)
Portal vein thrombosis	0.96 (0.83-1.09)	0.96 (0.84-1.10)	0.96 (0.84-1.10)
Diabetes	1.19 (1.09-1.31)[2]	1.19 (1.09-1.30)[2]	1.18 (1.08-1.29)[2]
On life support	1.07 (0.75-1.51)	1.05 (0.74-1.49)	1.06 (0.75-1.51)
Donor characteristics			
Donor age, y	1.01 (1.01-1.01)[3]	1.01 (1.01-1.01)[3]	1.01 (1.01-1.01)[3]
Donor cause of death			
Cerebrovascular/stroke	0.95 (0.85-1.07)	0.95 (0.85-1.07)	0.96 (0.86-1.08)

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TABLE 5. (CONTINUED)

	Group 1: Diagnosis aHR (95% CI)	Group 2: Diagnosis + procedure or surgery aHR (95% CI)	Group 3: Diagnosis + surgery aHR (95% CI)
Anoxia	0.99 (0.87-1.12)	0.99 (0.87-1.12)	0.98 (0.87-1.11)
Head trauma	Reference	Reference	Reference
CNS tumor	0.74 (0.28-1.99)	0.75 (0.28-2.02)	0.72 (0.27-1.94)
Other	0.76 (0.50-1.16)	0.76 (0.50-1.15)	0.77 (0.51-1.16)
Partial/split liver	0.64 (0.43-0.95)[1]	0.64 (0.43-0.96)[1]	0.67 (0.45-0.99)[1]
Donor type			
Living	1.47 (0.81-2.65)	1.47 (0.82-2.66)	1.50 (0.83-2.69)
DCD	1.06 (0.92-1.21)	1.06 (0.93-1.21)	1.08 (0.94-1.23)
DBD	Reference	Reference	Reference

Group 1: any diagnosis of biliary complication; group 2: patients with a diagnosis of biliary complication who require either an endoscopic or a radiographic procedure; group 3: patients with a biliary complication diagnosis who required a surgical revision.
[1]$P < 0.05$–0.002.
[2]$P = 0.001$–0.0002.
[3]$P < 0.0001$.
[a]HR, adjusted hazard ratio; CI, confidence interval; CNS, central nervous system; DBD, donation after brain death; DCD, nonheart beating donor; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease.

half of the LT recipients diagnosed with BCs require endoscopic or radiological intervention (group 2) or surgical correction (group 3), each of which has decreased. Despite modest improvements, the implications of BCs on patient outcome remain significant because they increase the risk of death and graft failure. In addition, BCs dramatically increase the cost of LT.

Despite improved donor selection, expedited procurement techniques, minimized ischemia time, selection of preservative solution, and recipient surgical technique, the incidence of BCs has not substantially improved nationally. Our analysis demonstrated an increasing incidence of BCs with each succeeding 3-y period until the most recent period, which saw limited improvement. One potential explanation for the increasing rate of BCs is increased severity of illness (reflected in higher MELD) of patients at transplant. In the post-MELD era, single-center studies have demonstrated that biliary strictures were significantly more common than in the pre-MELD era (15.4% versus 6.4%; $P < 0.001$).[12] A systematic review of 14 411 DDLTs found a MELD score of >25, and transplants for primary sclerosing cholangitis were significantly associated with BCs.[13] Despite recent allocation reforms, which have resulted in greater risk of BC, as MELD scores at transplant continue to rise in many locations and broader sharing has increased cold ischemic time, it is reassuring that, in this series, we do not see an ongoing increase in incidence.[14,15]

DCD organs have historically been associated with a greater incidence of BCs. In a retrospective analysis from 2018, Senter-Zapata et al[16] reported that recipients of DCD DDLTs had a greater incidence of BCs than DBD DDLTs (36% versus 22.4%; $P = 0.037$) and, particularly, a higher incidence of leaks (12.0% versus 4.9%; $P = 0.043$). Although BCs and, particularly, NAS/ischemic cholangiopathy were more common with use of DCD grafts than DBD grafts in the past, this difference has steadily decreased. Careful selection of DCD donors regarding age, limiting functional warm ischemic time to <30 min, and emphasizing efficiency to minimize cold ischemia time have contributed to improved outcomes in the last decade. Novel preservation strategies have been evaluated to further reduce the incidence of biliary strictures. A systematic review and meta-analysis combined results from 10 prospective cohorts, and 2 randomized controlled trials that studied machine perfusion versus static cold storage of liver allografts demonstrated significantly lower rates of BCs ($P = 0.006$) and ischemic cholangiopathy ($P = 0.02$) when hypothermic machine perfusion was used, although this has not yet been widely disseminated in clinical practice.[17]

LDLT transplant has been associated with higher rates of BCs because of the need to reconstruct multiple small bile ducts with potentially compromised vascular supplies. The current data confirm the strong association between donor type and the incidence of BC: 51.4% after LDLT compared with 36.0% and 19.2% after DCD and DBD DDLT, respectively. Multiple investigations have demonstrated that BCs significantly increase morbidity and mortality among LDLT recipients.[18,19] Although no randomized controlled trials have compared RYHJ to duct-to-duct anastomosis in LDLT, retrospective evaluation had suggested that RYHJ can minimize BCs in LDLT, especially in right lobe grafts when ducts are <4 mm.[19] Potential use of microsurgical techniques, commonly used for arterial reconstruction, can be applied for biliary reconstruction, as a recent report demonstrated a decreased rate of BCs in LDLT when these techniques were used (8.9% microsurgical versus 21.9% conventional).[20]

Although most BCs can be successfully treated, long-term graft and patient survival may be reduced. In this national analysis, LT with BCs, particularly those requiring interventions, experienced a higher incidence of all-cause graft failures and deaths, which suggests that, despite the benefit of minimally invasive management with endoscopy, BCs portend a significant risk. These results are consistent with a recent national readmission database analysis of outcomes in posttransplant biliary strictures, which found that posttransplant biliary strictures were associated with increased rates of rejection, graft failure, cholangitis, and readmission.[21] Unfortunately, strategies to reduce or eliminate BCs using internal or external stenting (T-tubes) have had mixed results. Systemic reviews demonstrate that external T-tubes contribute to biliary

leaks upon removal in 5% to 33% of cases.[5] Another study demonstrated an increased incidence of biliary leaks in adult LT patients with T-tubes or internal stents when compared with patients who were stent-free (53% versus 26%; $P = 0.049$).[16] Conversely, internal stenting was found to help prevent biliary strictures in pediatric and LDLT when duct diameter was ≤2 mm and a RYHJ was used.[19,22]

In both the institutional data and national Medicare data, BCs resulted in substantial increases in the cost of LT care. The development of BC resulted in a 2-fold increase in the cost of LT in the institutional data, resulting in greater estimated losses for the hospital. Nationally, BC resulted in up to $104 743 in incremental risk first-year mean Medicare spending for LT for patients requiring surgical revision. Decreasing the incidence of BCs would result in significant financial savings for payers and transplant programs while improving patient survival and quality of life.

This analysis has limitations. First, the claims and clinical chart review validation were performed in a single institution, and other institutional clinical and coding practices might affect the sensitivity and specificity of claims analysis. However, these data suggest that using administrative datasets provides a reproducible and accurate assessment of quality outcomes without the expense and burden of manual chart review. Second, the national data used Medicare claims. Medicare patients may differ from LT patients with private insurance coverage. Medicare claims offer the advantage of identification of procedures performed at any US facility, and the robust effects suggest that the association between BC and posttransplant outcomes and claims accurately identifies patients with clinically significant events. Finally, we clustered all BCs and did not distinguish between leaks and strictures. However, there is substantial overlap, given the association of early biliary leaks with long-term strictures. The benefit of national data derived from diagnosis codes likely exceeds the potential benefit of further separation because the *International Statistical Classification of Disease and Related Health Problems*–9/10 codes are not specific enough to appropriately classify patients. Furthermore, the combined BC classification was highly correlated with important clinical outcomes, including graft failure and patient death.

In conclusion, BCs remain an important complication of DDLT and LDLT, with clinical and cost implications. Although most of these complications are successfully treated, BCs increase cost, reduce graft survival, and diminish patient quality of life. Focused quality-improvement plans are needed to limit avoidable causes of BCs, and administrative data can be used to effectively assess and monitor performance in multicenter analyses. Insights from these analyses may elucidate practices that reduce the incidence and long-term consequences of this persistent Achilles heel of LT.

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REFERENCES

1. Navez J, Iesari S, Kourta D, et al. The real incidence of biliary tract complications after adult liver transplantation: the role of the prospective routine use of cholangiography during post-transplant follow-up. *Transpl Int*. 2021;34:245–258.
2. Keane MG, Devlin J, Harrison P, et al. Diagnosis and management of benign biliary strictures post liver transplantation in adults. *Transplant Rev (Orlando)*. 2020;35:100593.
3. Seehofer D, Eurich D, Veltzke-Schlieker W, et al. Biliary complications after liver transplantation: old problems and new challenges. *Am J Transplant*. 2013;13:253–265.
4. Simoes P, Kesar V, Ahmad J. Spectrum of biliary complications following live donor liver transplantation. *World J Hepatol*. 2015;7:1856–1865.
5. Moy BT, Birk JW. A review on the management of biliary complications after orthotopic liver transplantation. *J Clin Transl Hepatol*. 2019;7:61–71.
6. Villa NA, Harrison ME. Management of biliary strictures after liver transplantation. *Gastroenterol Hepatol (N Y)*. 2015;11:316–328.
7. Daniel K, Said A. Early biliary complications after liver transplantation. *Clin Liver Dis (Hoboken)*. 2017;10:63–67.
8. Gunawansa N, McCall JL, Holden A, et al. Biliary complications following orthotopic liver transplantation: a 10-year audit. *HPB (Oxford)*. 2011;13:391–399.
9. Noack K, Bronk SF, Kato A, et al. The greater vulnerability of bile-duct cells to reoxygenation injury than to anoxia—implications for the pathogenesis of biliary strictures after liver-transplantation. *Transplantation*. 1993;56:495–499.
10. Axelrod DA, Dzebisashvili N, Lentine KL, et al. Variation in biliary complication rates following liver transplantation: implications for cost and outcome. *Am J Transplant*. 2015;15:170–179.
11. Axelrod DA, Dzebisashvilli N, Lentine KL, et al. National assessment of early biliary complications after liver transplantation: economic implications. *Transplantation*. 2014;98:11261226–11261235.
12. Magro B, Tacelli M, Mazzola A, et al. Biliary complications after liver transplantation: current perspectives and future strategies. *Hepatobiliary Surg Nutr*. 2021;10:76–92.
13. Nemes B, Gaman G, Doros A. Biliary complications after liver transplantation. *Expert Rev Gastroenterol Hepatol*. 2015;9:447–466.
14. Fleming JN, Taber DJ, et al. The effect of Share 35 on biliary complications: an interrupted time series analysis. *Am J Transplant*. 2019;19:221–226.
15. Jia J, Nie Y, Li J, et al. A systematic review and meta-analysis of machine perfusion vs. static cold storage of liver allografts on liver transplantation outcomes: the future direction of graft preservation. *Front Med (Lausanne)*. 2020;7:135.
16. Senter-Zapata M, Khan AS, Subramanian T, et al. Patient and graft survival: biliary complications after liver transplantation. *J Am Coll Surg*. 2018;226:484–494.
17. Mittler J, Chavin KD, Heinrich S, et al. Surgical duct-to-duct reconstruction: an alternative approach to late biliary anastomotic stricture after deceased donor liver transplantation. *J Gastrointest Surg*. 2021;25:708–712.

18. Gad EH, Alsebaey A, Lotfy M, et al. Complications and mortality after adult to adult living donor liver transplantation: a retrospective cohort study. *Ann Med Surg (Lond)*. 2015;4:162–171.
19. Wang SF, Huang ZY, Chen XP. Biliary complications after living donor liver transplantation. *Liver Transpl*. 2011;17:1127–1136.
20. Lin TS, Concejero AM, Chen CL, et al. Routine microsurgical biliary reconstruction decreases early anastomotic complications in living donor liver transplantation. *Liver Transpl*. 2009;15:1766–1775.
21. Kohli DR, Desai MV, Kennedy KF, et al. Patients with post-transplant biliary strictures have significantly higher rates of liver transplant failure and rejection: a nationwide inpatient analysis. *J Gastroen Hepatol*. 2021;36:2008–2014.
22. Shirouzu Y, Okajima H, Ogata S, et al. Biliary reconstruction for infantile living donor liver transplantation: Roux-en-Y hepaticojejunostomy or duct-to-duct choledochocholedochostomy? *Liver Transpl*. 2008;14:1761–1765.