


Risk factors and impact of early anastomotic biliary complications after liver transplantation: UK registry analysis

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Abstract

Background: Biliary leaks and anastomotic strictures are common early anastomotic biliary complications (EABCs) following liver transplantation. However, there are no large multicentre studies investigating their clinical impact or risk factors. This study aimed to define the incidence, risk factors and impact of EABC.

Methods: The NHS registry on adult liver transplantation between 2006 and 2017 was reviewed retrospectively. Adjusted regression models were used to assess predictors of EABC, and their impact on outcomes.

Results: Analyses included 8304 liver transplant recipients. Patients with EABC (9.6 per cent) had prolonged hospitalization (23 versus 15 days; $P < 0.001$) and increased chance for readmission within the first year (56 versus 32 per cent; $P < 0.001$). Patients with EABC had decreased estimated 5-year graft survival of 75.1 versus 84.5 per cent in those without EABC, and decreased 5-year patient survival of 76.9 versus 83.3 per cent; both $P < 0.001$. Adjusted Cox regression revealed that EABCs have a significant and independent impact on graft survival (leak hazard ratio (HR) 1.344, $P = 0.015$; stricture HR 1.513, $P = 0.002$; leak plus stricture HR 1.526, $P = 0.036$) and patient survival (leak HR 1.215, $P = 0.136$, stricture HR 1.526, $P = 0.001$; leak plus stricture HR 1.509; $P = 0.043$). On adjusted logistic regression, risk factors for EABC included donation after circulatory death grafts, graft aberrant arterial anatomy, biliary anastomosis type, vascular anastomosis time and recipient model of end-stage liver disease.

Conclusion: EABCs prolong hospital stay, increase readmission rates and are independent risk factors for graft loss and increased mortality. This study has identified factors that increase the likelihood of EABC occurrence; research into interventions to prevent EABCs in these at-risk groups is vital to improve liver transplantation outcomes.

Introduction

Liver transplantation is the definitive treatment option for patients with end-stage liver failure with average 5-year survival rates around 80 per cent in the UK¹. The success of liver transplantation has led to increasing demand for organs. However, the supply of high-quality grafts is limited. This has led to the increased use of marginal grafts from extended-criteria donors and donation following circulatory death (DCD) donors²⁻⁴. These organs pose an increased risk of primary non-function and higher rates of both vascular and biliary anastomotic complications⁴⁻⁶.

Biliary complications are the most commonly reported complications following liver transplantation⁷. Incidence has been estimated to be approximately 10 to 15 per cent in deceased donor transplants⁸ and may be as high as 15 to 30 per cent in living donor transplant recipients⁹. These complications are often

associated with split grafts, concomitant vascular complications, prolonged ischaemia, reperfusion injury, cytomegalovirus (CMV) infection, primary sclerosing cholangitis (PSC) and the type of biliary reconstruction¹⁰⁻¹⁴. More than half of all biliary complications are early complications occurring at the anastomotic site. Approximately 30 per cent represent early anastomotic strictures and around 20 per cent are bile leaks⁷. These early anastomotic biliary complications (EABCs) are the focus of this study.

There are a number of biliary reconstruction options for surgeons including end-to-end choledocho-choledochostomy (CDCD) anastomosis, Roux-en-Y hepaticojejunostomy, T-tube, or stented anastomosis. Currently, end-to-end ductal anastomosis is the most commonly used biliary reconstruction in liver transplantation, however the impact of anastomosis technique on biliary complication rates remains poorly described.

A number of single-centre studies have previously investigated the impact of EABC on morbidity and mortality^{15–17}. However, these are underpowered to investigate the impact of EABC on long-term graft survival and mortality. Furthermore, small studies are unable to adjust for sufficient confounders, and therefore cannot evaluate whether EABCs are independent predictors of poor outcome, or simply markers of poor grafts and complex transplants. Whereas registry analyses have been performed to investigate economic implications, there have been, to the authors' knowledge, no large multicentre analyses investigating the clinical impact of early biliary complications¹⁸.

There is a significant volume of research examining the best way to manage biliary complications after transplantation^{19–21} but robust studies describing how best to prevent them are lacking. Many clinicians feel the development of a biliary complication is a multifactorial problem and may be indicative of a poor graft or poor preservation. However, a formal analysis of risk factors for EABC development using a sufficiently large database has not been performed. As increasingly marginal organs are transplanted it is important to identify risk factors that are amenable to intervention.

The aim of this study is to investigate the incidence, impact and risk factors associated with EABC with a view to better informing surgeons which donor/recipient combinations and operative factors may increase the risk of developing this common complication.

Methods

National UK data on adult liver transplantation from eight transplant centres between 2006 and 2017 collected and validated by the National Health Service Blood and Transplant (NHSBT) transplant registry were reviewed. Data were provided in an anonymized form (patient-identifiable information and transplant unit not provided) as per NHSBT approvals, and individual ethical approval was not required for this project. All adult liver transplants were included. The NHSBT registry records occurrence of surgical complications within 3 months as a dichotomous variable. EABCs were therefore recorded as the development of a leak and/or stricture within the first 3 months after transplantation. For analysis the cohort was split into four groups; no EABC, leak only, stricture only and leak plus stricture.

Data was cleaned, and values which were deemed impossible were removed (summary of removed data points is in [Table S1](#)). Of this final cohort, 68 patients were noted as either to have no biliary stricture (67 patients) or not reported (1 patient), despite having a form of biliary stricture treatment. The authors assumed this was a mistake in the data and characterized these participants as having a stricture. Sensitivity analysis was performed where graft survival, patient survival and predictors were re-analysed with these 68 mismatches excluded, or included in the no stricture groups; the results did not change significantly.

Statistical analysis

All patients included had a minimum of 12 months' follow-up. Initial crude analyses compared donor, recipient, operative and early outcomes in the four biliary complication groups. Pearson's χ^2 test was used for categorical variables. If cell counts were too low, then Monte Carlo estimates of Fisher's exact tests were used. For continuous data, normality was evaluated using Kolmogorov–Smirnov tests. Analysis of variance (ANOVA) and Kruskal–Wallis tests were then applied as appropriate. Data results are mean (s.d.) or median (range), depending on normality.

Post-hoc tests with Bonferroni correction were applied. All tests were two-sided. The common closure date of the study was June 2018; graft and patient survival were censored at 10 years. Unadjusted graft and patient survival were calculated using Kaplan–Meier plots and P values were derived with the log-rank test. Graft survival was death censored, and graft loss was defined as retransplant or death due to liver failure.

A rigorous approach was taken to build the adjusted multivariable Cox regression models for graft and patient survival. Donor, graft, recipient, operative and postoperative factors available from NHSBT registry were initially screened, and a broad selection criterion was applied. Variables were selected if they had previously been reported to affect graft or patient survival^{22,23}, were significantly correlated with EABCs, or were associated with survival on univariable Cox regression in the study cohort ($P < 0.200$). Multiple imputation was used to generate 20 imputed datasets, as described below. Cox regression with backward likelihood ratio stepwise selection was then performed to identify key variables. Variables retained in more than 90 per cent of imputed datasets were included in a final adjusted multivariable model using pooled data from all 20 imputations. Sensitivity analyses were performed which included variables retained in more than 50 per cent of imputed models, and none of the extra variables was significant in the final models.

Multiple binary logistic regression was used to identify significant predictors of biliary leak and biliary stricture. A model was built using an identical approach to that described above. Results displayed are adjusted hazard ratios (aHR) or adjusted odds ratios (aOR) with 95 per cent confidence intervals.

Variables with the largest proportion of missing data were donor bilirubin (29.0 per cent), recipient diabetes (23.2 per cent), single versus multiple hepatic artery anastomosis (18.0 per cent), graft hepatic artery anatomy (16.6 per cent), vascular anastomosis time (16.1 per cent), waiting list time (14.0 per cent), UK model for end-stage liver (UKELD, 13.6 per cent), model for end-stage liver disease (MELD, 13.6 per cent), donor cardiovascular disease (5.6 per cent) and donor hypertension (5.2 per cent). All remaining variables had missing data in less than 5 per cent of cases (full report of missing data in [Table S2](#)). Missing data were dealt with by multiple imputation using the fully conditional specification technique applied to generate 20 imputed datasets.

For all tests performed $P < 0.050$ was deemed significant. All analyses were performed in SPSSTM version 26 (IBM Corp, Armonk, New York, USA), and figures were generated using GraphPad PrismTM version 6 (GraphPad Software, San Diego, California USA).

Results

The initial database included 8780 adult liver transplant recipients. The following patients were excluded: multivisceral transplants (148 patients), missing data on leak and stricture (198 patients), missing graft survival data (30 patients), intraoperative deaths (35 patients), or graft loss on day 0 or 1 (65 patients). The last two groups were excluded to minimize immortal time bias, as leak or stricture would never be recorded. This left 8304 participants for the main analyses. [Table 1](#) summarizes the demographics of this cohort.

Overall, EABCs were reported in 799 (9.6 per cent) patients: 344 (4.14 per cent) experienced a biliary leak, 335 (4.03 per cent) a biliary stricture and 120 (1.44 per cent) had both leak and stricture.

Table 1 Demographic information for the entire dataset

	Cohort demographics (n = 8304)
Donor characteristics	
Donor age (years) [†]	50.0 (6–86)
Cold ischaemic time (min) [*]	511.8 (163.5)
Donor type	
DBD	6476 (78.0)
DCD	1677 (20.2)
Living	111 (1.3)
Domino	40 (0.5)
Recipient and transplant characteristics	
Recipient age (years) [†]	54.0 (18–75)
Recipient MELD [‡]	16.6 (6.84)
Biliary anastomosis type	
CDCD	6599 (80.2)
Roux-en-Y	1261 (15.3)
T-tube	330 (4.0)
Stent	40 (0.5)
Early anastomotic biliary complication	
No biliary complication	7505 (90.4)
Biliary leak only	344 (4.14)
Biliary stricture only	335 (4.03)
Both leak and stricture	120 (1.44)

Values in parentheses are percentages unless indicated otherwise; * values are mean (s.d.); † values are median (range). DBD, donation following brainstem death; DCD, donation following circulatory death; MELD, model for end-stage liver disease; CDCD, choledocho-choledochostomy.

Clinical demographics

The cohort was split into these four groups: those with no biliary complication, leak only, stricture only and a combination of leak and stricture. These groups were well matched for most clinical demographics (Tables 2–4).

Donor demographics are described in Table 2. Donor age differed between groups on unadjusted analysis, with post-hoc tests revealing significantly lower age in the biliary leak group compared with no biliary complication. Grafts from DCD, living donors and domino all had higher rates of EABC, as did split or reduced grafts, grafts from diabetic donors and grafts from donors with ethnicity 'other'.

Table 3 describes recipient demographics between groups. Female recipients or those with primary biliary cirrhosis or biliary atresia experienced more biliary complications, whilst those patients transplanted for acute liver failure had fewer EABCs. Post-hoc tests revealed that those in the leak alone group had significantly higher MELD than those with no EABCs.

Perioperative factors are shown in Table 4. The type of biliary anastomosis was associated with differing rates of EABC. On post-hoc tests, vascular anastomosis time (also termed second warm ischaemic time) was higher in the leak and leak plus stricture groups than in the no EABC group. Association of additional variables stored in the registry with EABCs can be found in Table S3. All variables in any of these tables displaying significant differences across the four groups were selected as potential variables for inclusion into Cox regression models.

Association with other early postoperative complications

There is a strong association between EABCs and most other early complications recorded by NHSBT (Table 5). EABC rates were significantly higher in patients experiencing any of the following early complications: acute rejection, renal failure requiring dialysis, hepatic artery thrombus, active CMV infection, fungal

infection, early sepsis. Data on these other complications are collected at the same time as EABC, and the database does not contain information on exactly when, or in which order, these complications develop. All of these early postoperative complications were therefore included as potential confounders in the adjusted models.

Association with 1-year outcomes

Association between occurrence of EABC and outcomes at 1 year is displayed in Table 6. Patients experiencing any EABC spent approximately 50 per cent longer in hospital on their initial admission when compared with the rest of the cohort (23 versus 15 days; $P < 0.001$). They were also over 75 per cent more likely to need readmission to hospital in the first year after transplantation (56 per cent versus 32 per cent; $P < 0.001$). Recipients with a biliary stricture were significantly more likely to have ongoing renal dysfunction 1 year after transplant compared with those with no biliary complication.

Liver function tests at 1 year were also deranged in the EABC groups (Table 6). On post-hoc tests, alkaline phosphatase was significantly higher in all three EABC groups when compared with the no EABC group. Median aspartate aminotransferase and alanine transaminase were significantly different between groups, and numerically higher in the EABC groups. However, none of the comparisons reached statistical significance on post-hoc tests.

Graft survival

Figure 1 displays unadjusted analysis of graft survival in Kaplan-Meier plots. Patients experiencing EABC had significantly worse graft survival (Fig. 1a,b). Overall, estimated 5-year graft survival was 84.5 (95 per cent c.i. 83.5–85.5) per cent in patients without an EABC, and 75.1 (95 per cent c.i. 71.3 to 78.5) per cent in the any biliary complication group; $P < 0.001$ (Fig. 1a). In the case of leak, the authors did not find a significant difference in graft survival for patients managed conservatively, radiologically or surgically (Fig. 1c). The vast majority (437 of 455; 96 per cent) of patients with a stricture received treatment. There were no graft-survival differences seen between endoscopic and surgical management of stricture (Fig. 1d). However, these are unadjusted analyses and selection bias will exist.

In the final adjusted multivariable Cox regression model (Table 7) early anastomotic biliary complications were significant independent risk factors for graft loss (leak only aHR 1.344 (95 per cent c.i. 1.059 to 1.705), $P = 0.015$; stricture only aHR 1.513 (1.171 to 1.956), $P = 0.002$; leak plus stricture aHR 1.526 (1.028 to 2.264), $P = 0.036$). Early biliary complications were retained as significant predictors of graft survival in all 20 of the imputed datasets.

When analysing graft survival there was significant interaction between DCD transplants and biliary complications ($P = 0.015$), prompting subgroup analysis. On adjusted analysis the detrimental effects of biliary complications were exaggerated in DCD grafts (leak only aHR 1.290 (95 per cent c.i. 0.713 to 2.333), $P = 0.401$; stricture only aHR 1.733 (1.054 to 2.849), $P = 0.030$; leak plus stricture aHR 2.806 (1.587 to 4.961), $P < 0.005$) compared with donation after brain death (DBD) grafts (leak only aHR 1.349 (1.031 to 1.765), $P = 0.029$; stricture only aHR 1.459 (1.073 to 1.984), $P = 0.016$; leak plus stricture aHR 1.219 (0.702 to 2.119), $P = 0.482$).

A model without other early postoperative complications, but otherwise identical to the model in Table 7, was constructed. In this model the effect size of all of these biliary complications remained significant and was larger: leak aHR 1.790 (95 per cent c.i. 1.418 to 2.261), $P < 0.001$, stricture aHR 1.700 (1.318 to 2.192),

Table 2 Donor factors associated with early anastomotic biliary complications

Donor factor	No biliary complication (n = 7505)	Biliary leak alone (n = 344)	Biliary stricture alone (n = 335)	Both leak and stricture (n = 120)	P [‡]
Donor age*	50 (6–86) (n = 7504)	45 (6–83)	48 (11–85)	49.5 (18–79)	0.001 [¶]
Donor sex					
Male	3927 (90.2)	174 (4.0)	189 (4.3)	65 (1.5)	0.428
Female	3575 (90.6)	170 (4.3)	146 (3.7)	55 (1.4)	
Cold ischaemic time (min)[†]	512(162) (n = 7436)	522(183), (n = 336)	498(169), (n = 329)	509(189), (n = 117)	0.298 [¶]
Total warm ischaemic time in DCD grafts (min)[†]	27.0(8.2) (n = 818)	29.0(10.7) (n = 33)	27.6(7.1) (n = 50)	27.9(8.8) (n = 18)	0.536 [¶]
Donor type					
DBD	5887 (90.9)	264 (4.1)	245 (3.8)	80 (1.2)	<0.001 [§]
DCD	1505 (89.7)	61 (3.6)	82 (4.9)	29 (1.7)	
Living	78 (70.3)	15 (13.5)	7 (6.3)	11 (9.9)	
Domino	35 (87.5)	4 (10.0)	1 (2.5)	0 (0)	
Steatosis					
No steatosis	4087 (90.4)	196 (4.3)	181 (4.0)	57 (1.3)	0.709
Mild	2302 (90.7)	98 (3.9)	104 (4.1)	35 (1.4)	
Moderate	835 (91.4)	29 (3.2)	36 (3.9)	14 (1.5)	
Severe	72 (93.5)	1 (1.3)	4 (5.2)	0 (0)	
Transplant type					
Whole liver	6926 (91.2)	267 (3.5)	307 (4.0)	95 (1.3)	<0.001
Reduced or split liver	579 (81.7)	77 (10.9)	28 (3.9)	25 (3.5)	
Ethnicity					
White	7028 (90.6)	309 (4.0)	308 (4.0)	109 (1.4)	0.008 [§]
Asian	160 (89.9)	8 (4.5)	8 (4.5)	2 (1.1)	
Black	106 (91.4)	4 (3.4)	4 (3.4)	2 (1.7)	
Other	150 (80.2)	18 (9.6)	14 (7.5)	5 (2.7)	
Donor BMI[†]	26.1(4.8) (n = 7395)	25.5(4.7) (n = 328)	26.2(5.1) (n = 327)	26.6(4.8) (n = 109)	0.076 [¶]
Donor past medical history					
Diabetic	426 (91.2)	7 (1.5)	28 (6.0)	6 (1.3)	0.005
Non-diabetic	6777 (90.6)	311 (4.2)	290 (3.9)	99 (1.3)	
Hypertensive	1916 (91.1)	67 (3.2)	98 (4.7)	23 (1.1)	0.027
Non-hypertensive	5221 (90.5)	249 (4.3)	217 (3.8)	81 (1.4)	
History of alcohol abuse	607 (90.7)	23 (3.4)	30 (4.5)	9 (1.3)	0.669
No alcohol abuse	4927 (90.8)	214 (3.9)	200 (3.7)	84 (1.5)	
CVS disease	712 (91.6)	24 (3.1)	30 (3.9)	11 (1.4)	0.549
No CVS disease	6392 (90.6)	293 (4.2)	280 (4.0)	93 (1.3)	
History of liver disease	82 (83.7)	8 (8.2)	6 (6.1)	2 (2.0)	0.064 [§]
No liver disease	7036 (90.8)	305 (3.9)	310 (4.0)	102 (1.3)	
Smoker	3715 (90.9)	169 (4.1)	153 (3.7)	49 (1.2)	0.409
Non-smoker	3515 (90.6)	145 (3.7)	164 (4.2)	56 (1.4)	

Values in parentheses are percentages unless otherwise indicated. Percentages displayed describe biliary complication rate for each donor factor (within-row percentages). *Values are median (range); †values are mean(s.d.). ‡ χ^2 test, except §Monte Carlo simulations of Fishers exact test, ¶one-way ANOVA. Raw data are given, a summary of missing data is found in Table S2. Further donor factors are displayed in Table S3.

Table 3 Recipient factors associated with early anastomotic biliary complications

Recipient factor	No biliary complication (n = 7505)	Biliary leak alone (n = 344)	Biliary stricture alone (n = 335)	Both leak and stricture (n = 120)	P [‡]
Recipient age*	54 (17–75)	54 (17–73)	53 (19–73)	55 (20–72)	0.224
Recipient sex					
Male	4675 (90.8)	196 (3.8)	197 (3.8)	83 (1.6)	0.045
Female	2829 (89.8)	148 (4.7)	138 (4.4)	37 (1.2)	
Indication					
Non-biliary	6185 (90.5)	267 (3.9)	285 (4.2)	97 (1.4)	0.013 [§]
PBC	600 (88.2)	36 (5.3)	35 (5.1)	9 (1.3)	
PSC	692 (91.4)	39 (5.2)	14 (1.8)	12 (1.6)	
Biliary atresia	28 (84.8)	2 (6.1)	1 (3.0)	2 (6.1)	
Listed as super-urgent	910 (91.1)	37 (3.7)	42 (4.2)	10 (1.0)	0.527
Not listed as super-urgent	6595 (90.3)	307 (4.2)	293 (4.0)	110 (1.5)	
Liver failure grade					
Not acute	6335 (90.4)	288 (4.1)	275 (3.9)	106 (1.5)	0.022
Hyperacute	618 (92.9)	22 (3.3)	18 (2.7)	7 (1.1)	
Acute	224 (89.2)	8 (3.2)	17 (6.8)	2 (0.8)	
Subacute	148 (87.1)	10 (5.9)	12 (7.1)	0	
MELD[†]	16.6(6.8) (n = 6493)	17.7(7.5) (n = 295)	16.2(6.8) (n = 285)	16.5(7.3) (n = 104)	0.048 [¶]

Values in parentheses are percentages unless otherwise indicated. Percentages displayed describe biliary complication rate for each recipient factor (within-row percentages). *Values are median (range); †values are mean(s.d.). ‡ χ^2 test, except §Monte Carlo simulations of Fishers exact test, ¶one-way ANOVA. Raw data are given, a summary of missing data is found in Table S2. Further recipient factors are displayed in Table S3. PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MELD, model for end-stage liver disease.

Table 4 Operative factors associated with early anastomotic biliary complications

Operative factor	No biliary complication (n = 7505)	Biliary leak alone (n = 344)	Biliary stricture alone (n = 335)	Both leak and stricture (n = 120)	P [†]
Transplant year					
2006–2009	2034 (91.3)	99 (4.4)	67 (3.0)	27 (1.2)	0.086
2010–2013	2357 (89.9)	103 (3.9)	119 (4.5)	44 (1.7)	
2014–2017	3114 (90.2)	142 (4.1)	149 (4.3)	49 (1.4)	
Biliary anastomosis					
CDCD	5967 (90.4)	235 (3.6)	291 (4.4)	106 (1.6)	<0.001 [‡]
Roux	1153 (91.4)	70 (5.6)	27 (2.1)	11 (0.9)	
T-tube	282 (85.5)	34 (10.3)	12 (3.6)	2 (0.6)	
Stent	35 (87.5)	4 (10)	1 (2.5)	0	
Donor HA anatomy					
Single	4997 (90.2)	218 (3.9)	238 (4.3)	87 (1.6)	0.114
Accessory	1222 (88.2)	71 (5.1)	71 (5.1)	22 (1.6)	
HA anastomosis					
Single	5255 (89.9)	238 (4.1)	258 (4.4)	93 (1.6)	0.831
Multiple	860 (89.1)	45 (4.7)	45 (4.7)	15 (1.6)	
Vascular anastomosis time (mins)*	39 (10–217) (n = 6258)	41 (17–181) (n = 276)	38 (13–95) (n = 290)	42 (13–102) (n = 109)	0.002 [§]

Values in parentheses are percentages unless indicated otherwise. Percentages displayed describe biliary complication rate for each operative factor (within-row percentages). *Values are median (range). [†] χ^2 test, except [‡]Monte Carlo simulations of Fishers exact test, [§]Kruskall–Wallis test. Raw data are given, a summary of missing data is found in [Table S2](#). CDCD, choledocho-choledochostomy, Roux, Roux-en-Y hepaticojejunostomy; HA, hepatic artery.

Table 5 Early postoperative complications (within 3 months) associated with early anastomotic biliary complications

Postoperative factor	No biliary complication (n = 7505)	Biliary leak alone (n = 344)	Biliary stricture alone (n = 335)	Both leak and stricture (n = 120)	P*
Acute rejection episodes					
0	6160 (91.1)	257 (3.8)	255 (3.8)	91 (1.3)	<0.001
1	1055 (89.0)	63 (5.3)	48 (4.0)	20 (1.7)	
≥2	212 (80.6)	21 (8.0)	25 (9.5)	5 (1.9)	
Postoperative RRT					
Nil	5956 (90.7)	256 (3.9)	256 (3.9)	100 (1.5)	0.002 [†]
Transient filtration	870 (90.4)	46 (4.8)	37 (3.8)	9 (0.9)	
Short-term dialysis	571 (88.4)	31 (4.8)	34 (5.3)	10 (1.5)	
Long-term dialysis	21 (67.7)	6 (19.4)	3 (9.7)	1 (3.2)	
HA thrombus	233 (82.9)	30 (10.7)	11 (3.9)	7 (2.5)	<0.001
No HA thrombus	7272 (90.7)	314 (3.9)	324 (4.0)	111 (1.4)	
PV thrombus	227 (87.6)	13 (5.0)	13 (5.0)	6 (2.3)	0.410
No PV thrombus	7278 (90.5)	330 (4.1)	322 (4.0)	112 (1.4)	
CMV infection	583 (82.7)	63 (8.9)	51 (7.2)	8 (1.1)	<0.001
No CMV infection	6900 (91.1)	280 (3.7)	284 (3.7)	111 (1.5)	
Fungal infection	147 (79.9)	25 (13.6)	8 (4.3)	4 (2.2)	<0.001
No fungal infection	7335 (90.6)	317 (3.9)	326 (4.0)	116 (1.4)	
Early sepsis	2467 (84.9)	217 (7.5)	173 (6.0)	50 (1.7)	<0.001
No sepsis	4997 (93.4)	127 (2.4)	160 (3.0)	68 (1.3)	

Values in parentheses are percentages. Percentages displayed describe biliary complication rate for each postoperative factor (within-row percentages). * χ^2 test, except [†]Monte Carlo simulations of Fishers exact test. Raw data are given, a summary of missing data is found in [Table S2](#). RRT, renal replacement therapy; HA, hepatic artery; PV, portal vein; CMV, cytomegalovirus.

$P < 0.001$) and leak plus stricture aHR 1.657 (1.120 to 2.451), $P = 0.011$).

Further sensitivity analyses were performed where the following factors were included in the model: MELD/UKELD, super-urgent listing, portal vein thrombus, aberrant hepatic artery anatomy. These factors did not have significant effects on the outcome of the analysis and were not significant in an adjusted model.

Patient survival

Patient survival data was available for 8063 participants. [Figure 2](#) displays unadjusted analysis of patient survival in Kaplan–Meier plots. Patients with EABC had increased mortality ([Fig. 2a,b](#)). Overall, estimated 5-year patient survival was 83.3 (95 per cent c.i. 82.1 to 84.3) per cent in patients without an EABC, and 76.9 (72.9 to 80.4) per cent in the any biliary complication group;

$P < 0.001$, ([Fig. 2a](#)). For both leak and stricture the chosen treatment modality did not significantly impact patient survival ([Fig. 2c,d](#)); these analyses on the effect of treatment modality are unadjusted, and large selection biases probably exist.

In the adjusted Cox regression model ([Table 8](#)) stricture (aHR 1.526 (95 per cent c.i. 1.183 to 1.968), $P = 0.001$) and leak plus stricture (aHR 1.509 (1.013 to 2.248), $P = 0.043$) were both independent predictors of increased patient mortality. Leak only was a significant predictor of patient survival on univariable analysis (HR 1.406 (95 per cent c.i. 1.098–1.799), $P = 0.007$), but significance was lost on adjusted Cox regression (aHR 1.215 (95 per cent c.i. 0.941 to 1.568), $P = 0.136$).

Again, the authors re-analysed the data with the exclusion of other early postoperative complications. Interestingly, in this analysis the effect of leak only on patient survival reached statistical significance (leak aHR 1.506 (95 per cent c.i. 1.327 to

Table 6 Outcomes at 1-year separated by biliary complication

Outcomes at 1-year	No biliary complication (n = 7505)	Biliary leak alone (n = 344)	Biliary stricture alone (n = 335)	Both leak and stricture (n = 120)	P†
Duration of hospital stay in days (index admission)*	15 (4–378) (n = 7020)	26 (7–119) (n = 303)	20.5 (6–108) (n = 310)	26 (8–402) (n = 113)	<0.001‡
Readmissions (1-year)					
0	4195 (67.6)	127 (46.5)	114 (42.5)	41 (40.2)	<0.001
1	1143 (18.4)	70 (25.6)	67 (25.0)	22 (21.6)	
>1	870 (14)	76 (27.8)	87 (32.5)	39 (38.2)	
Renal dysfunction (1-year)	1393 (22.8)	55 (20.3)	75 (28.4)	16 (16)	0.040
No renal dysfunction	4729 (77.2)	216 (79.7)	189 (71.6)	84 (84)	
1-year blood results					
Bilirubin (µmol/l)*	10 (1–977) (n = 6183)	10 (3–790) (n = 268)	10 (2–676) (n = 267)	10 (3–455) (n = 102)	0.344‡
ALP (unit/l)*	126 (10–1995) (n = 6146)	140.5 (11–1917) (n = 266)	168.5 (44–1306) (n = 266)	205 (9–1749) (n = 99)	<0.001‡
ALT (unit/l)*	26 (3–1371) (n = 3613)	28 (6–1238) (n = 174)	27 (6–332) (n = 178)	37.5 (8–274) (n = 92)	0.045‡
AST (unit/l)*	23 (2–1814) (n = 3565)	27 (6–780) (n = 152)	27 (8–2219) (n = 149)	38 (13–179) (n = 31)	0.001‡

Values in parentheses are percentages except where indicated otherwise. Percentages represent the chances of renal dysfunction or readmission in each of the biliary complication groups (within column percentage). *Values are median (range). †χ² test, except ‡Kruskal-Wallis test. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase.

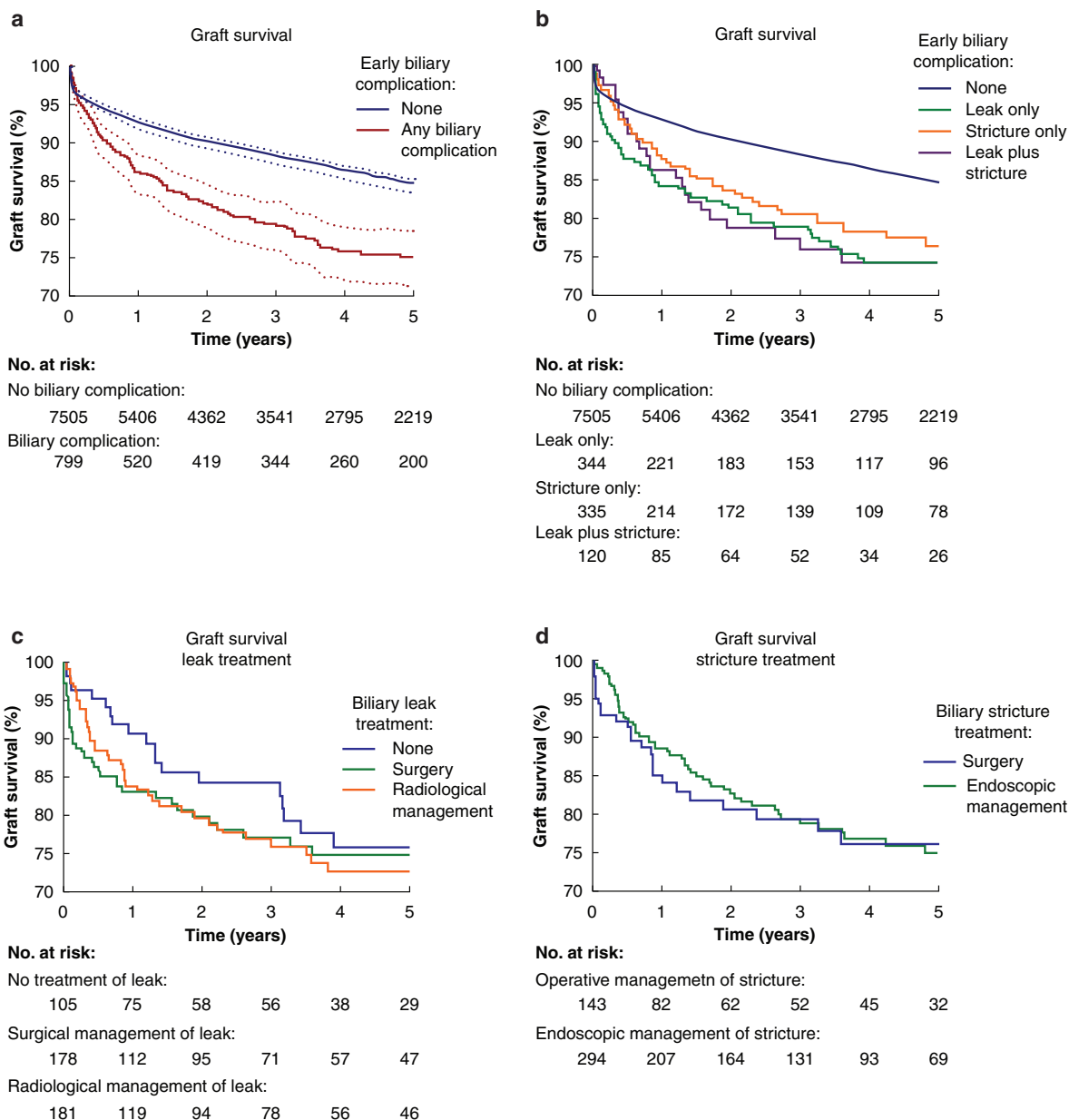


Fig. 1 Impact of early anastomotic biliary complications on graft survival

Each panel is a Kaplan–Meier graph, with numbers at risk displayed. P values are the result of log-rank tests. **a** P < 0.001. Shaded areas represent 95 per cent confidence intervals. **b** P < 0.001. **c** P = 0.883. **d** P = 0.683

Table 7 Graft survival Cox regression using pooled data from all 20 imputed datasets (n = 8304 per imputation).

Variable	Univariable		Adjusted	
	Hazard ratio	P	Hazard ratio	P
Biliary complication				
None	1	–	1	–
Leak only	1.761 (1.398–2.217)	<0.001	1.344 (1.059–1.705)	0.015
Stricture only	1.571 (1.220–2.023)	<0.001	1.513 (1.171–1.956)	0.002
Leak plus stricture	1.726 (1.169–2.547)	0.006	1.526 (1.028–2.264)	0.036
Indication				
Non-biliary	1	–	1	–
Primary biliary cirrhosis	0.796 (0.633–1.002)	0.052	0.868 (0.687–1.098)	0.238
Primary sclerosing cholangitis	1.517 (1.277–1.802)	<0.001	1.624 (1.356–1.943)	<0.001
Biliary atresia	1.918 (0.956–3.847)	0.067	2.126 (1.050–4.302)	0.036
Liver failure grade				
Not acute	1	–	1	–
Hyperacute	0.905 (0.730–1.121)	0.362	0.710 (0.549–0.917)	0.009
Acute	1.241 (0.923–1.669)	0.152	1.310 (0.958–1.793)	0.091
Subacute	0.653 (0.405–1.055)	0.082	0.751 (0.461–1.223)	0.250
Transplant year	0.987 (0.968–1.006)	0.190	0.960 (0.941–0.980)	<0.001
Type of transplant				
Whole	1	–	1	–
Reduced	0.789 (0.457–1.364)	0.397	0.801 (0.199–3.229)	0.755
Split	1.149 (0.936–1.411)	0.184	1.642 (1.299–2.075)	<0.001
Type of graft				
DBD	1	–	1	–
DCD	1.460 (1.273–1.675)	<0.001	1.818 (1.557–2.122)	<0.001
Living	0.963 (0.531–1.746)	0.902	1.559 (0.337–7.216)	0.570
Domino	1.793 (0.930–3.458)	0.081	2.914 (1.497–5.673)	0.002
Previous non-liver transplants				
0	1	–	1	–
1	3.173 (1.702–5.913)	<0.001	4.113 (2.047–8.262)	<0.001
2	4.783 (0.673–33.992)	0.110	6.723 (0.936–48.306)	0.058
Previous liver transplants				
0	1	–	1	–
1	1.648 (1.379–1.970)	<0.001	1.802 (1.485–2.100)	<0.001
>1	2.616 (1.785–3.834)	<0.001	3.753 (2.540–5.545)	<0.001
Donor age	1.007 (1.003–1.010)	<0.001	1.013 (1.009–1.017)	<0.001
Donor diabetes	1.361 (1.088–1.703)	0.007	1.480 (1.181–1.855)	0.001
Donor smoker	1.147 (1.021–1.287)	0.021	1.196 (1.061–1.348)	0.003
CIT (per 10 mins)	1.004 (1.000–1.007)	0.041	1.005 (1.001–1.009)	0.015
Acute rejection episodes				
0	1	–	1	–
1	1.123 (0.961–1.311)	0.145	1.189 (1.014–1.394)	0.033
>1	1.379 (1.051–1.809)	0.020	1.381 (1.049–1.818)	0.021
Postoperative RRT				
Nil	1	–	1	–
Transient filtration	1.802 (1.536–2.113)	<0.001	1.907 (1.599–2.273)	<0.001
Short-term dialysis	2.448 (2.069–2.898)	<0.001	2.430 (2.039–2.896)	<0.001
Long-term dialysis	4.460 (2.473–8.043)	<0.001	3.551 (1.915–6.585)	<0.001
HA thrombus	12.212 (10.433–14.296)	<0.001	10.749 (9.122–12.665)	<0.001
Fungal infection	2.025 (1.493–2.748)	<0.001	1.484 (1.086–2.029)	0.013

Values in parentheses are 95 per cent confidence intervals. These variables were selected using a backwards stepwise approach. Interaction term between previous liver and non-liver transplants included in model but not displayed. DBD, donation following brainstem death; DCD, donation following circulatory death; CIT, cold ischaemic time; RRT, renal replacement therapy; HA, hepatic artery.

1.709), $P=0.001$). The effect size of other groups was also exaggerated: stricture aHR 1.626 (95 per cent c.i. 1.430 to 1.848), $P<0.001$ and leak plus stricture aHR 1.610 (1.315 to 1.972), $P=0.018$).

In contrast to the analysis on graft survival, there was no significant interaction between DCD versus DBD and biliary complications when analysing patient survival; the detrimental effects of biliary stricture on patient survival were similar across these groups. Sensitivity analyses were performed as described for graft survival, and the main results remained unchanged.

Predictors of biliary complications

Predictors of EABCs in whole deceased donor liver transplantation (excluding split and reduced grafts) were identified using

multiple logistic regression and are displayed in [Table 9](#). Several risk factors were identified for biliary leak. DCD grafts, grafts with aberrant arterial anatomy and grafts from female donors all had higher risk of leak. Recipients with higher MELD and Asian recipients also had higher chance of leak. UKELD was not a retained predictive factor. Recipients who had had three or more previous liver transplants (12 patients) had a higher chance of leak. There was no evidence that patients with one to two previous liver transplants had a higher risk of leak.

Two 'intraoperative' factors were predictors of anastomotic leak. Patients where a T-tube was used in the biliary anastomosis were more likely to suffer a leak when compared with standard CDCD anastomosis. An increasing vascular anastomosis time (also termed reperfusion time) was also associated with a higher

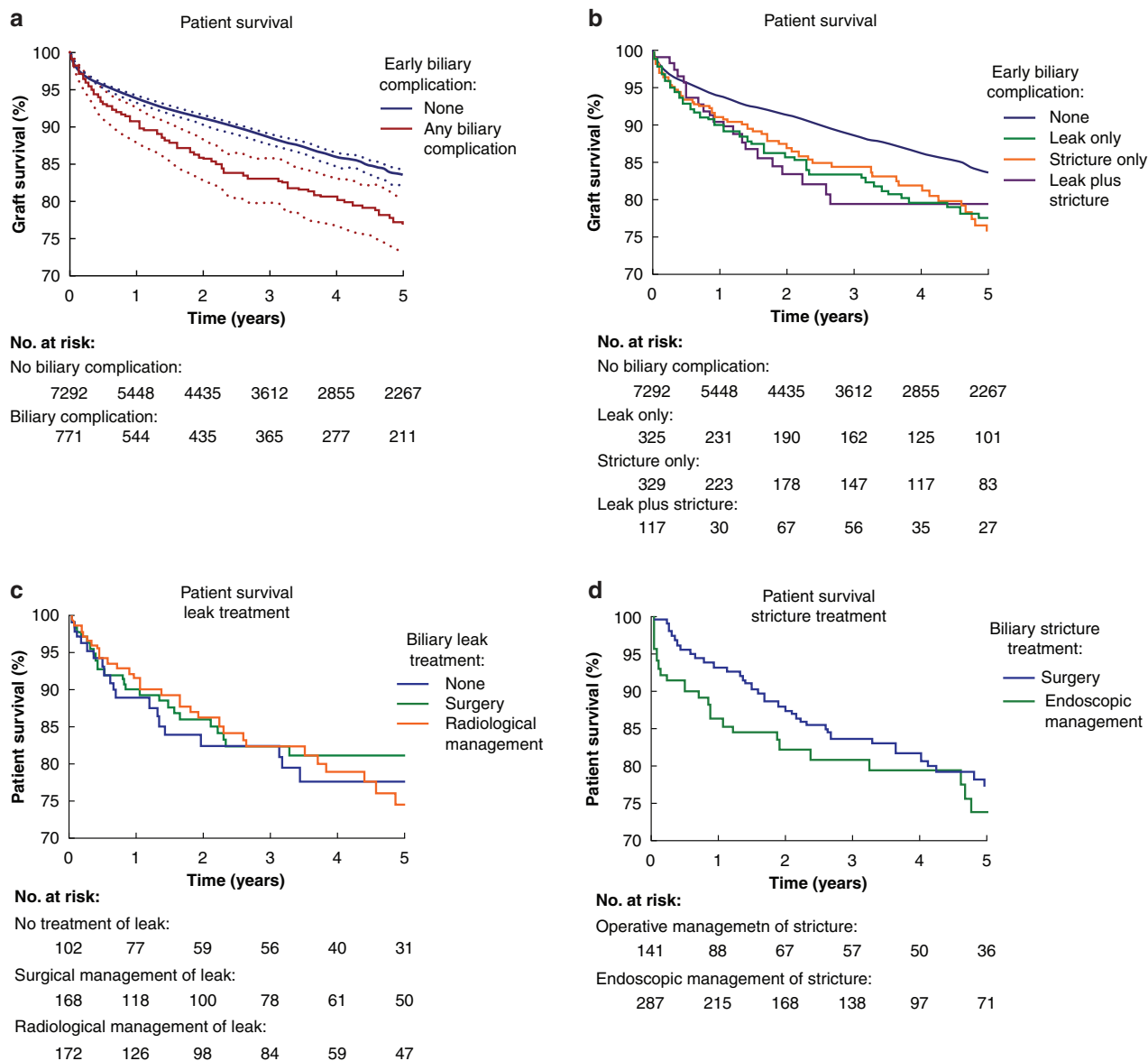


Fig. 2 Impact of early anastomotic biliary complications on patient survival

Each panel is a Kaplan–Meier graph, with numbers at risk displayed. *P* values are the result of log-rank tests. **a** $P < 0.001$. Shaded areas represent 95 per cent confidence intervals. **b** $P < 0.001$. **c** $P = 0.637$. **d** $P = 0.155$

risk of biliary leak; every 10-min addition increased the risk of leak by approximately 10.5 per cent. Overall, the effect of stents on either leak or stricture is uncertain, due to the small number of stents used in whole deceased donor grafts (24 patients).

Fewer risk factors for biliary stricture could be identified. Again, DCD grafts had higher risk of biliary stricture when compared with DBD grafts (aOR 1.31 (95 per cent c.i. 1.04 to 1.64), $P = 0.022$). Roux anastomosis was associated with decreased risk of stricture when compared with standard CDCD anastomosis (aOR 0.56 (95 per cent c.i. 0.39 to 0.80), $P = 0.001$).

The authors also performed logistic regression models on the entire cohort, including split and reduced grafts. These models returned similar results to above, with the addition of split grafts as a significant predictor of leak (aOR 2.92 (95 per cent c.i. 2.21 to 3.87), $P < 0.001$), and reduced grafts as a risk factor for both leak (aOR 4.69 (95 per cent c.i. 3.02 to 7.29), $P < 0.001$) and stricture (aOR 3.01 (1.83 to 4.95), $P < 0.001$) when compared with whole grafts.

Despite identifying significant risk factors, the r^2 of both of these models was low (0.024 and 0.008 for leak and stricture models respectively), indicating that these complications are difficult to predict using information available to transplanting surgeons. Building a clinically useful scoring system was not possible using the variables collected in the NHSBT registry.

Discussion

In this manuscript the authors present the first national registry analysis investigating the clinical impact and risk factors for EABCs. Prior to this study, there were no large multicentre analyses to provide clinically relevant data to transplant clinicians. EABCs are common after liver transplantation (9.6 per cent), and associated with increased duration of hospital stay and increased readmissions to hospital in the first year. The present study shows for the first time that the detrimental impacts of EABC on graft survival and mortality remain significant when adjusted for

Table 8 Patient survival Cox regression using pooled data from all 20 imputed datasets (n = 8063 per imputation)

Variable	Univariable		Adjusted	
	Hazard ratio	P	Hazard ratio	P
Biliary complication				
None	1		1	
Leak only	1.406 (1.098–1.799)	0.007	1.215 (0.941–1.568)	0.136
Stricture only	1.523 (1.186–1.957)	0.001	1.526 (1.183–1.968)	0.001
Leak plus stricture	1.579 (1.062–2.347)	0.024	1.509 (1.013–2.248)	0.043
Indication				
Non-biliary	1		1	
Primary biliary cirrhosis	0.773 (0.621–0.962)	0.021	0.754 (0.604–0.940)	0.012
Primary sclerosing cholangitis	0.900 (0.733–1.104)	0.310	0.988 (0.804–1.215)	0.910
Biliary atresia	0.789 (0.296–2.107)	0.637	1.473 (0.582–3.728)	0.443
Recipient age	1.021 (1.015–1.026)	<0.001	1.025 (1.019–1.030)	<0.001
Transplant year	0.957 (0.938–0.977)	<0.001	0.937 (0.918–0.957)	<0.001
Previous non-liver transplants				
0	1		1	
1	2.737 (1.366–5.487)	0.005	1.592 (0.765–3.312)	0.214
2	5.348 (0.752–38.014)	0.094	10.094 (3.702–27.520)	0.021
Previous liver transplants				
0	1		1	
1	0.603 (0.453–0.802)	0.001	0.520 (0.386–0.700)	<0.001
2	0.941 (0.470–1.887)	0.865	1.176 (0.603–2.294)	0.650
>2	3.723 (1.395–9.938)	0.009	6.195 (2.918–13.154)	<0.001
Donor age	1.010 (1.007–1.014)	<0.001	1.011 (1.007–1.014)	<0.001
Postoperative RRT				
Nil	1		1	
Transient filtration	1.820 (1.558–2.127)	<0.001	1.914 (1.623–2.256)	<0.001
Short-term dialysis	2.225 (1.877–2.636)	<0.001	2.183 (1.823–2.614)	<0.001
Long-term dialysis	8.860 (5.243–14.973)	<0.001	7.518 (4.550–12.422)	<0.001
HA thrombus	2.439 (2.171–2.739)	<0.001	2.427 (1.924–3.062)	<0.001
Fungal infection	2.113 (1.569–2.846)	<0.001	1.654 (1.214–2.254)	0.001
Sepsis	1.380 (1.232–1.544)	<0.001	1.152 (1.021–1.300)	0.022

Values in parentheses are 95 per cent confidence intervals. These variables were selected using a backwards stepwise approach. RRT, renal replacement therapy; HA, hepatic artery.

a wide range of donor, graft, recipient, operative and other early postoperative complications. Risk factors for EABC, including DCD grafts, grafts with aberrant arterial anatomy, choice of biliary anastomosis, vascular anastomosis time and recipient MELD, were identified. Many of these risk factors are related to increased ischaemia, either before, during or after transplantation (DCD, increased vascular anastomosis time and aberrant arterial anatomy respectively).

NHSBT does not record exactly how these EABCs were diagnosed. However, routine or protocol magnetic resonance cholangiopancreatography (MRCP) to look for subclinical complications is not performed in the majority of transplant units in the UK. The incidence of EABC described in this study is similar to that described in previous series^{7–9} indicating that the present analysis is based on the incidence of clinically significant EABCs, rather than EABCs picked up on imaging alone. Two findings support this. First, the rate of anastomotic stricture in this study is far lower than the anastomotic stricture rate when routine MRCP is performed after transplantation, an incidence which exceeds 40 per cent²⁴. Second, 96 per cent of the patients recorded as anastomotic stricture in this study required treatment.

Several risk factors were identified for EABC. DCD grafts were the only common risk factor for both leak and stricture. Additional risk factors for leak included grafts with aberrant arterial anatomy, increasing recipient MELD, the use of a T-tube for biliary anastomosis, and increasing vascular anastomosis time in the recipient. The use of a Roux-en-Y anastomosis appeared to decrease stricture risk. However, although the authors could

identify significant risk factors, the r^2 of these models was low, and it was not possible to predict accurately whether an individual patient would develop an EABC. This suggests factors not coded in the NHSBT registry may play a key role, such as damage to biliary epithelium caused during retrieval and preservation, mismatch in bile duct diameter, suturing technique used and type of CDCD anastomosis²⁵. It also suggests that technical error, which cannot be coded in the database, may be a factor in EABC occurrence⁸.

Previous smaller studies have suggested that EABCs are associated with morbidity and increased mortality^{7,15–17}. Performing analyses using a large registry has allowed the present study to expand on this work and to quantify the negative effects, whilst adjusting for multiple confounders. It has shown for the first time that EABCs are independent predictors of graft loss and mortality, even when adjusting for a large range of donor and recipient factors.

One strength of the present study is the inclusion of postoperative complications as confounders. As EABCs are associated with other early postoperative complications, it could be argued that the detrimental effects seen in previous studies were simply explained by EABC being markers of the other complications which are known to be detrimental (such as acute rejection). For the first time, this study has shown that the effects of EABCs on graft and patient survival are independent of other postoperative complications.

In some situations, EABCs will probably be the cause of other complications, such as sepsis. Therefore, the model adjusted for

Table 9 Predictors of biliary leak and stricture in whole deceased donor liver transplants, using pooled data from all 20 imputed datasets (n = 7555)

	Simple logistic regression		Adjusted	
	Odds ratio	P	Odds ratio	P
Biliary leak risk factors				
Recipient MELD	1.02 (1.00–1.03)	0.019	1.02 (1.00–1.03)	0.023
Vascular anastomosis time (per minute)	1.01 (1.00–1.02)	0.001	1.01 (1.00–1.02)	0.001
DCD graft (DBD as comparator)	1.19 (0.93–1.52)	0.168	1.42 (1.10–1.84)	0.007
Aberrent hepatic artery anatomy	1.37 (1.05–1.78)	0.020	1.37 (1.05–1.79)	0.021
Female donor	1.22 (0.99–1.51)	0.067	1.24 (1.00–1.54)	0.047
Biliary anastomosis				
CDCD	1		1	
Roux	1.28 (0.96–1.70)	0.091	1.15 (0.84–1.58)	0.394
T-tube	1.99 (1.21–3.28)	0.007	2.06 (1.23–3.42)	0.006
Stent	1.57 (0.37–6.63)	0.536	1.54 (0.36–6.53)	0.561
Previous liver transplants				
0	1		1	
1	1.34 (0.94–1.92)	0.104	1.21 (0.82–1.79)	0.347
2	1.26 (0.51–3.12)	0.624	1.12 (0.44–2.88)	0.810
≥3	6.95 (1.87–25.79)	0.004	6.07 (1.56–23.69)	0.009
Recipient ethnicity				
White	1		1	
Asian	0.64 (0.40–1.02)	0.058	0.61 (0.38–0.97)	0.038
Black	0.91 (0.48–1.74)	0.783	0.85 (0.44–1.63)	0.622
Other	0.60 (0.24–1.46)	0.256	0.58 (0.24–1.43)	0.236
Biliary stricture risk factors				
DCD graft (DBD as comparator)	1.37 (1.09–1.71)	0.007	1.31 (1.04–1.64)	0.022
Biliary anastomosis				
CDCD	1		1	
Roux	0.54 (0.38–0.77)	0.001	0.56 (0.39–0.80)	0.001
T-tube or stent	0.71 (0.37–1.36)	0.305	0.75 (0.39–1.44)	0.390

Values in parentheses are 95 per cent confidence intervals. Odds ratios from simple and multiple binary logistic regression are given. These variables were selected using a backwards stepwise approach. MELD, model for end-stage liver disease; DCD, donation following circulatory death; DBD, donation following brainstem death; CDCD, choledocho-choledochostomy; Roux, Roux-en-Y hepaticojejunostomy.

these postoperative complications and may underestimate the effect size of EABCs. To address this limitation, the authors performed sensitivity analyses without other early complications; in these models both leak and stricture (alone or in combination) had a significant impact on both graft loss and mortality, and the effect size estimates were larger.

Further limitations include the selection bias that is inherent to any registry analysis. Missing data have the potential to introduce bias in any registry; the authors adopted well accepted techniques to deal with missing data^{26,27}. Finally, the study was limited by the granularity of the registry. Some factors that the authors wanted to investigate were not recorded in the database and therefore could not be analysed, such as bile duct size, exact arterial anatomy, smoking after transplant and occurrence of non-anastomotic ischaemic-type biliary lesions.

This study has several implications for current clinical practice and future research. The biliary anastomosis has long been considered the least difficult of the liver transplant anastomoses²⁸. In many units there is a tendency for this either to be left to junior or less experienced surgeons, or be completed by a less focused senior surgeon, who is fatigued after performing the vascular anastomoses. This could explain the seemingly paradoxical finding that complications at the biliary anastomosis are more common than complications at the vascular anastomoses, which are considered more technically challenging⁷. The authors hope this study will cause a shift in mind-set, prompting surgeons to give the same care and attention to the biliary anastomosis as they do to the vascular anastomoses.

Future research should focus on methods to prevent biliary complications, especially in the high-risk groups that this study has identified. In several specialties enhanced recovery after surgery (ERAS) protocols are common place^{29,30}, and in the setting of liver transplantation small studies have suggested that ERAS is feasible and that early enteral nutrition reduces rates of EABC^{31,32}. Further studies looking to optimize ERAS protocols in liver transplantation and investigating the effect on EABC occurrence would be valuable. In addition, further studies looking at radiological screening of high-risk groups and different management options are required.

As DCD grafts are at increased risk of both leak and stricture, and there are increasing reports of extensive biliary epithelial damage following retrieval and storage, improving preservation and optimizing organs is another potential avenue for EABC prevention^{25,33}. The use of dynamic machine-perfusion techniques for organ preservation and optimization is seeing growing international interest. However, a systematic review described no evidence that any commonly used machine-perfusion technique was able to reduce EABC rate, which was also demonstrated in a recent randomized trial of normothermic machine perfusion^{24,34}. It has been reported that hypothermic oxygenated perfusion is able to ameliorate ischaemic-type biliary lesions, suggesting it is able to prevent damage to biliary epithelium³³. Randomized trials of hypothermic oxygenated perfusion are ongoing, and will add key evidence as to whether this dynamic-preservation modality is able to reduce the rate of EABCs³⁵.

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Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

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