

Liver transplantation as last-resort treatment for patients with bile duct injuries following cholecystectomy: a multicenter analysis

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Abstract

Background Liver transplantation (LT) has been used as a last resort in patients with end-stage liver disease due to bile duct injuries (BDI) following cholecystectomy. Our study aimed to identify and evaluate factors that cause or contribute to an extended liver disease that requires LT as ultimate solution, after BDI during cholecystectomy.

Methods Data from 8 high-volume LT centers relating to patients who underwent LT after suffering BDI during cholecystectomy were prospectively collected and retrospectively analyzed.

Results Thirty-four patients (16 men, 18 women) with a median age of 45 (range 22-69) years were included in this study. Thirty of them (88.2%) underwent LT because of liver failure, most commonly as a result of secondary biliary cirrhosis. The median time interval between BDI and LT was 63 (range 0-336) months. There were 23 cases (67.6%) of postoperative morbidity, 6 cases (17.6%) of post-transplant 30-day mortality, and 10 deaths (29.4%) in total after LT. There was a higher probability that patients with concomitant vascular injury (hazard ratio 10.69, $P=0.039$) would be referred sooner for LT. Overall survival following LT at 1, 3, 5 and 10 years was 82.4%, 76.5%, 73.5% and 70.6%, respectively.

Conclusion LT for selected patients with otherwise unmanageable BDI following cholecystectomy yields acceptable long-term outcomes.

Keywords Bile duct injury, cholecystectomy, liver transplantation, end-stage liver disease, cholangitis

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Introduction

The vast majority of injuries of the extrahepatic biliary system are iatrogenic, occurring most frequently during laparoscopic (LC) or open cholecystectomy (OC) [1,2]. The exact incidence of common bile duct injury (BDI) post-cholecystectomy remains elusive, yet the currently available data addressing BDI during OC show that the incidence is relatively low, approximately 0.1-0.2% [2,3]. Specifically with regard to BDI during LC, the incidence of injuries as evidenced by national databases ranges from 0.1-0.55% (for major traumas), while the incidence of microbubbles with bile leakage is approximately 0.3%, resulting in a total of 0.85% [2]. In a series of 12,397 LCs, Scott *et al* reported severe BDI in 0.3%, minor injuries in 0.1% and cholorrhea in 0.4% of patients, with a total morbidity of 4% and mortality of 0.08% [4].

A plethora of factors associated with BDI have been identified; a surgical technique with insufficient exposure and failure to identify structures before ligation and division seem to be the most significant causes of major injuries [5,6]. In an analysis of 252 laparoscopic BDI, the authors showed that the main cause of the error was a visual misinterpretation in 97% of the cases, while technical errors accounted for only 3% [7]. Moreover, while in the past BDI were considered more likely to occur in patients suffering from pancreatitis, cholangitis or acute cholecystitis, recent studies have shown that approximately 70% of BDI occur in cases where the only indication for cholecystectomy is symptomatic gallstones. [6]. The clinical course of patients with BDI would ideally be less complicated if they were promptly recognized at the time of surgery, but unfortunately this occurs only in about 25% of cases [6,8]. Moreover, in many patients there is a delayed referral to a specialized hepatobiliary (HPB) surgery center, despite actual signs of injury [9,10]. Management of patients with BDI post cholecystectomy is critical, whilst inadequate management of complex BDI with concurrent vascular injury has been associated with increased morbidity and mortality [11,12]. Early complications may include biliary peritonitis, systemic sepsis and multiple organ failure, and patients may later progress into end-stage liver disease (ESLD) [13,14].

In that setting, liver transplantation (LT) has been implemented as a last-resort strategy in a limited number of patients with ESLD secondary to usually multiple failed attempts to manage their BDI [8,15,16]. However, the outcomes in these patients remain ill-determined, mainly because of the small number of cases reported worldwide. To that end, the objective of our multicenter study was to identify and evaluate factors that cause or contribute to the progression to severe liver disease after BDI, ultimately requiring LT, and to assess the outcomes of patients transplanted for this indication.

Patients and methods

Fifteen LT centers were contacted and asked to provide information about patients who underwent LT after

suffering from BDI during cholecystectomy. A questionnaire containing information regarding the following parameters was sent to all contributing centers: age, sex, the indication for cholecystectomy (cholecystitis vs. cholelithiasis), the type of approach for cholecystectomy (LC vs. OC), whether cholecystectomy was carried out in urgent or elective settings, whether BDI was recognized intraoperatively or postoperatively, the manifestation of BDI (biliary fistula or cholestasis), whether there was a concomitant vascular injury during cholecystectomy, the type of BDI according to Strasberg's classification [17], the treatment of BDI before LT (liver resection, bilioenteric anastomosis or repair through percutaneous transhepatic cholangiography [PTC] or endoscopic retrograde cholangiopancreatography [ERCP]), the time interval between BDI and its treatment before LT, the time interval between BDI and LT, the main indication for LT (liver failure vs. recurrent cholangitis), and morbidity, mortality, and survival after LT.

Statistical analysis

Data were expressed as median (min-max) for quantitative data and as absolute numbers and percentages for qualitative data. Survival times were expressed as median with standard error (SE) and 95% confidence intervals (CI). Categorical variables were compared using the chi-square and Fisher's exact test. Logistic regression with the forward conditional method was used for multivariate analysis when the dependent outcome was a binary variable. Kaplan-Meier curves were used for the assessment of the time interval between bile duct injury and LT, as well as the assessment of survival after LT, while comparisons of survival among different groups were made using the log-rank test. Cox regression with the forward conditional method was used for multivariate survival analysis. All the tests were 2-tailed. Results were considered statistically significant if the P-value was less than 0.05. Statistical analysis was performed using the 25th edition of Statistical Package for Social Sciences (SPSS) (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

Eight centers provided data for 34 patients (16 men and 18 women) who underwent LT as a last-resort treatment after BDI during cholecystectomy and were included in our study. Thirty of them (88.2%) were referred for LT because of liver failure and the remaining 4 (11.8%) because of recurrent cholangitis. The median age was 45 years (min-max: 22-69). Median follow-up period post LT was 57 months (min-max: 0-158). Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Characteristics	Value
Sex	Male: 16, Female: 18
Age	Median (min-max): 45 years (22-69)
Acute cholecystitis	Yes: 17, No: 9, N/A: 8
Type of cholecystectomy	Laparoscopic: 14, Open: 20
Setting of cholecystectomy	Elective: 18, Urgent: 6, N/A: 10
Recognition of BDI	Intraoperative: 8, Postoperative: 15, N/A: 11
Manifestation of BDI	Cholorrhea: 14, Cholestasis: 12, N/A: 8
Concomitant vascular injury	Yes: 8, No: 26
Strasberg's classification	E2: 7, E3: 8, E4: 6, N/A: 13
Treatment of BDI	ERCP: 6, PTC: 2, Bilioenteric anastomosis: 21, liver resection: 1, N/A: 4
Time between BDI and primary treatment	Median (min-max): 2 months (0-97)
Indication for LT	Liver failure: 30, Recurrent cholangitis: 4
Time between BDI and LT	Median (min-max): 63 months (0-336)
Postoperative complications	23 (67.6%)
Major complications (Clavien-Dindo \geq 3b)	12 (35.3%)
30-day mortality	6 (17.6%)
Overall mortality	10 (29.4%)

BDI, bile duct injury; LT, liver transplantation; PTC, percutaneous transhepatic cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; N/A, not available

Time between BDI and LT

The median time interval between BDI and LT was 63 months (min-max: 0-336). Patients who suffered BDI during LC required LT earlier (median time 19 months, SE 11.2, 95%CI 0-41) than patients who suffered BDI during OC (median time 113 months, SE 27.6, 95%CI 58.9-167.1) ($P<0.001$) (Fig. 1A). Furthermore, the time between BDI and LT was shorter if there was a concomitant vascular injury at the time of cholecystectomy (median time 12 months, SE 12.7, 95%CI 0-36.9) than if there was not (median time 75 months, SE 28.2, 95%CI 19.8-130.2) ($P<0.001$) (Fig. 1B). In addition, there was an association between the type of BDI according to the Strasberg classification and the time period until LT. In particular, the median time interval between BDI and LT was 46 months for E2 injuries (SE 22.3, 95%CI 2.4-89.6), 113 months for E3 injuries (SE 43.8, 95%CI 27.1-198.9) and 19 months for E4 injuries (SE 11, 95%CI 0-40.6) ($P=0.007$) (Fig. 1C). However, Cox regression analysis revealed that the only independent risk factor associated with a shorter time interval between BDI and LT was the presence of a concomitant vascular injury (hazard ratio 10.69, 95%CI 1.134-100.8, $P=0.039$). Results concerning time until LT are listed in Table 2.

Table 2 Time between BDI and LT

Parameter	Univariate analysis (median times)	Multivariate analysis
Sex	Male: 52 months Female: 75 months $P=0.314$	$P=0.318$
Age (years)	≤ 50 : 67 months >50 : 44 months $P=0.226$	$P=0.509$
Acute cholecystitis	No: 19 months Yes: 58 months $P=0.267$	$P=0.695$
Type of cholecystectomy	Open: 113 months Laparoscopic: 19 months $P<0.001$	$P=0.35$
Setting of cholecystectomy	Elective: 58 months Urgent: 12 months $P=0.214$	$P=0.078$
Recognition of BDI	Intraoperative: 29 months Postoperative: 51 months $P=0.827$	$P=0.927$
Manifestation of BDI	Cholorrhea: 58 months Cholestasis: 52 months $P=0.266$	$P=0.734$
Concomitant vascular injury	No: 75 months Yes: 12 months $P<0.001$	HR 10.69 95%CI 1.134-100.8 $P=0.039$
Strasberg's classification	E2: 46 months E3: 113 months E4: 19 months $P=0.007$	$P=0.264$
Treatment of BDI	PTC/ERCP: 51 months Bilioenteric anastomosis: 108 months $P=0.935$	$P=0.337$
Time between BDI and treatment	≤ 1 month: 44 months >1 month: 52 months $P=0.341$	$P=0.933$
Indication for LT	Recurrent cholangitis: 25 months Liver failure: 59 months $P=0.604$	$P=0.902$

BDI, bile duct injury; LT, liver transplantation; PTC, percutaneous transhepatic cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; HR, hazard ratio; CI, confidence interval

Postoperative outcomes after LT

Twenty-three patients (67.6%) had postoperative complications following LT. Patients who suffered BDI during OC had higher postoperative morbidity rates (17/20; 85%) than patients who suffered BDI during LC (6/14; 42.9%) ($P=0.023$). Moreover, patients who underwent LT more than 2 years after BDI were more likely to experience postoperative complications (19/25; 76%) than patients who underwent LT within 2 years after BDI (2/7; 28.6%) ($P=0.032$). Nevertheless,

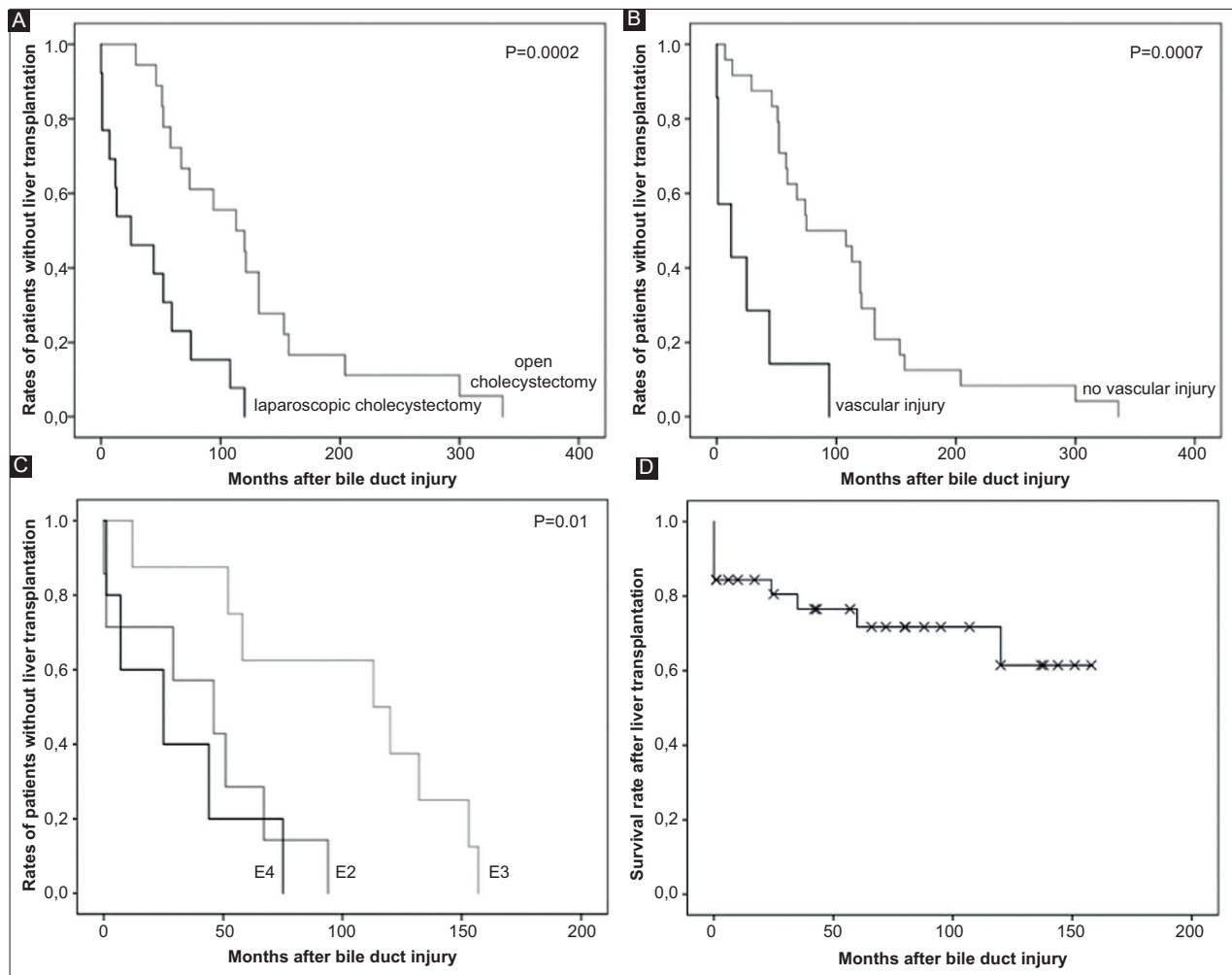


Figure 1 (A) Time between BDI and LT according to type of cholecystectomy; (B) Time between BDI and LT according to vascular injury; (C) Time between BDI and LT according to type of bile duct injury; (D) Overall survival after LT
BDI, bile duct injury; LT, liver transplantation

logistic regression analysis showed no independent risk factor for postoperative morbidity after LT. Twelve patients (35.3%) had major complications (Clavien-Dindo classification [18] 3b or higher) after LT. Patients older than 50 years had lower rates of major complications post LT (2/15; 13.3%) when compared with younger patients (10/19; 52.6%) (P=0.017). Nonetheless, logistic regression analysis revealed no independent risk factor for major complications post LT.

Six patients (17.6%) died within the first month post LT. However, no association was found between postoperative mortality and any of the tested parameters in either uni- or multivariate analysis. Results regarding postoperative outcomes after LT are shown in Table 3.

Overall survival after LT

The median surveillance period after LT was 57 months (min-max: 0-158). Ten patients (29.4%) died during the surveillance period after LT. Overall survival rates were 82.4% (28/34) at

1 year, 76.5% at 3 years (26/34), 73.5% at 5 years (25/34), and 70.6% at 10 years (24/34) after LT (Fig. 1D). Patients older than 50 years old had longer overall survival post LT (median survival not reached yet) than younger patients (median survival 60 months, SE 18.7, 95%CI 48.2-121.6) (P=0.041). Furthermore, patients who received treatment for BDI within the first month (bilioenteric anastomosis or treatment through PTC or ERCP) had shorter overall survival after LT (median survival 35 months, SE 45.8, 95%CI 0-124.8) than patients who received treatment more than 1 month after BDI (median survival not reached yet) (P=0.026). However, Cox regression analysis did not reveal any independent prognostic factor of overall survival after LT. Results concerning overall survival post LT are listed in Table 4.

Discussion

LT for patients who suffered from BDI during cholecystectomy was first reported almost 30 years ago [19],

Table 3 Postoperative outcomes after LT

Parameter	Complications		Major complications		Mortality	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Sex						
Male	11/16		7/16		3/16	
Female	12/18		5/18		3/16	
P-value	0.897	>0.99	0.331	0.303	>0.99	0.389
Age (years)						
≤50	15/19		10/19		5/19	
>50	8/15		2/15		1/15	
P-value	0.151	0.14	0.017	0.1	0.196	0.107
Acute cholecystitis						
No	5/9		3/9		2/9	
Yes	11/17		4/17		1/17	
P-value	0.692	0.121	0.661	0.165	0.268	>0.99
Type of cholecystectomy						
Open	17/20		8/20		4/20	
Laparoscopic	6/14		4/14		2/14	
P-value	0.023	>0.99	0.717	0.819	>0.99	0.292
Setting of cholecystectomy						
Elective	11/18		4/18		2/18	
Urgent	4/6		3/6		1/6	
P-value	>0.99	0.439	0.307	0.898	>0.99	0.49
Recognition of BDI						
Intraoperative	5/8		2/8		2/8	
Postoperative	9/15		4/15		1/15	
P-value	>0.99	0.54	>0.99	0.477	0.269	0.107
Manifestation of BDI						
Cholorrhea	11/14		7/14		4/14	
Cholestasis	6/12		3/12		0/12	
P-value	0.218	0.54	0.248	0.554	0.1	0.389
Concomitant vascular injury						
No	20/26		9/26		4/26	
Yes	3/8		3/8		2/8	
P-value	0.079	0.221	>0.99	0.477	0.609	0.49
Strasberg's classification						
E2	5/7		3/7		1/7	
E3	5/8		1/8		1/8	
E4	3/6		2/6		1/6	
P-value	0.856	0.472	0.491	0.588	>0.99	0.574
Treatment of BDI						
PTC/ERCP	6/8		4/8		0/8	
Bilioenteric anastomosis	15/21		7/21		5/21	

(Contd...)

Table 3 (Continued)

Parameter	Complications		Major complications		Mortality	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
P-value	>0.99	0.54	0.433	0.819	0.283	0.292
Time between BDI and treatment						
≤1 month	5/7		4/7		3/7	
>1 month	8/10		4/10		1/10	
P-value	>0.99	>0.99	0.637	0.819	0.25	0.197
Indication for LT						
Recurrent cholangitis	3/4		2/4		0/4	
Liver failure	20/30		10/30		6/30	
P-value	>0.99	0.121	0.602	0.165	>0.99	0.725
Time between BDI and LT						
≤2 years	2/7		2/7		2/7	
>2 years	19/25		9/25		3/25	
P-value	0.032	>0.99	>0.99	0.898	0.296	0.598

BDI, bile duct injury; LT, liver transplantation; PTC, percutaneous transhepatic cholangiography; ERCP, endoscopic retrograde cholangiopancreatography

but outcomes at that time were dismal and long-term results disappointing. Reports from the 1970s showed that approximately 8% of patients with BDI ultimately suffered from biliary cirrhosis due to failed attempts to manage biliary outflow obstruction, with associated increased mortality. At the time, LT was not a pursuable option [20]. More recently published series have shown that approximately 4-19% of BDI patients are eligible for LT, mainly due to secondary biliary cirrhosis (SBC), with acceptable reported post-transplant long-term outcomes [8,21,22]. Nonetheless, it should be taken into account that the exact denominator of patients with BDI might be higher than reported; thus, the exact proportion of patients led to LT remains poorly determined.

Whilst concomitant major vascular injuries may lead to acute liver failure, long-term damage to the liver parenchyma is difficult to predict in patients with BDI. Vascular injuries or unresolved partial biliary obstruction may result in acute liver failure, liver atrophy, chronic intrahepatic infection, abscess formation or SBC. Consequently, careful evaluation is mandated in these patients. Liver resection has been advocated in a selected number of patients with BDI, the majority being patients with continuous sepsis in obstructed segments or those whose drainage of extrahepatic bile ducts is not adequate because of conduit or fibrosis damage [23,24].

According to a recent review of 1756 BDIs following cholecystectomy, 99 patients (5.6%) were reported to require hepatectomy, 16 of whom had concomitant arterial injury [24]. Occasionally, early liver resection is required for combined arterial injury, portal vein injury and biliary trauma, yet the outcomes are poor [25]. The right lobe is usually affected by sepsis and atrophy, as is the right hepatic duct, because the right artery is more likely to be damaged

during cholecystectomy [25]. In our series, no patient initially underwent liver resection, possibly highlighting that it may represent a more effective approach in treating these patients and preventing them from requiring LT.

Currently available data on patients undergoing LT after BDI following cholecystectomy are scanty and mainly derive from case reports and small case series [15,23,26-28]. Ardiles *et al* conducted a retrospective multicenter national survey in Argentina, aiming to collect clinical data on patients referred for LT as a consequence of iatrogenic BDI during a 14-year period [8]; 16 patients (6 LC and 10 OC) were led to LT, after a mean interval of 71 months from BDI occurrence during cholecystectomy, with the most common indication being SBC (93.7%). Authors observed that the percentage of LT performed for BDI declined over the study period. The reported 5- and 10-year survival rates were 68% and 45%, respectively [8]. In the largest published series, from the Spanish Liver Transplantation Study Groups, during a 24-year period 24 patients underwent LT because of BDI following cholecystectomy [16]. The authors reported that 12 and 13 patients initially suffered from BDI after LC and OC, respectively, whereas the median time from index surgery to LT was 3 years, significantly lower than the respective interval of 5.25 years in our series. Similarly to the previous mentioned and our study, the most common indication leading to LT was SBC (74% of patients). Seven patients underwent emergent LT for acute liver failure after BDI associated with a vascular injury, with only 1 survivor. In the same study, associated vascular injuries were more commonly encountered in patients who had initially undergone LC, similarly to our study where 87.5% of concomitant vascular injuries were sustained during a laparoscopic approach. Overall post-LT mortality was 42%

Table 4 Overall survival after LT

Parameter	Univariate analysis (median times)	Multivariate analysis
Sex	Male: not reached yet Female: not reached yet P=0.386	P=0.592
Age (years)	≤50: 60 months >50: not reached yet P=0.041	P=0.475
Acute cholecystitis	No: not reached yet Yes: not reached yet P=0.565	P=0.103
Type of cholecystectomy	Open: not reached yet Laparoscopic: not reached yet P=0.306	P=0.705
Setting of cholecystectomy	Elective: not reached yet Urgent: not reached yet P=0.827	P=0.238
Recognition of BDI	Intraoperative: not reached yet Postoperative: not reached yet P=0.421	P=0.475
Manifestation of BDI	Cholorrhea: not reached yet Cholestasis: not reached yet P=0.188	P=0.886
Concomitant vascular injury	No: not reached yet Yes: 120 months P=0.709	P=0.768
Strasberg's classification	E2: not reached yet E3: not reached yet E4: not reached yet P=0.996	P=0.746
Treatment of BDI	PTC/ERCP: not reached yet Bilioenteric anastomosis: not reached yet P=0.23	P=0.157
Time between BDI and treatment	≤1 month: 35 months >1 month: not reached yet P=0.026	P=0.116
Indication for LT	Recurrent cholangitis: not reached yet Liver failure: not reached yet P=0.253	P=0.739
Time between BDI and LT	≤2 years: not reached yet >2 years: not reached yet P=0.795	P=0.274

BDI, bile duct injury; LT, liver transplantation; PTC, percutaneous transhepatic cholangiography; ERCP, endoscopic retrograde cholangiopancreatography

and 7.7% for LC and OC patients, respectively, with a 5-year survival of 68% [16].

Inferior outcomes in these patients are at least partially due to the elevated degree of difficulty in performing LT in these patients, which can be particularly challenging. They are highly likely to have undergone a significant number of endoscopic or/and surgical procedures and therefore their

anatomy, both biliary and vascular, is far from normal [15,29]. Additionally, the presence of multiple adhesions formed as a result of severe inflammation and/or multiple surgical interventions can be very difficult to manage [30]. Notably, 3 of the patients included in our analysis had 2 or more redo hepaticojejunostomy anastomoses. In the first published series of 4 patients who underwent LT for BDI, because of a combination of advanced cirrhosis, severe portal hypertension and dense abdominal adhesions, none of the patients survived the procedure [19]. When comparing patients who underwent LT for ESLD secondary to BDI during cholecystectomy with patients who underwent LT for other indications during the same study period, Santibanes *et al* showed that, although morbidity and long-term survival were similar in the 2 groups, the former group had significantly more protracted operative times, were more challenging and had higher blood transfusion requirements [30]. Based on our analysis, patients who underwent LT more than 2 years after the BDI were more likely to experience postoperative complications, possibly indicating the presence of tenacious adhesions compromising hilar dissection, poorer performance status, recurrent cholangitis and potential sepsis, as well as ischemic damage with vanishing ducts, compared to those who underwent LT within 2 years after the BDI.

To the best of our knowledge, our study presents the largest reported cohort of patients who underwent LT as a last resort because of BDI during cholecystectomy. Nonetheless, several limitations must be taken into account before solid conclusions can be drawn. First, the retrospective nature of our study and the small number of patients included constitute significant limitations. Since these patients underwent LT in a specialized center other than the one in which the original BDI occurred, it was not possible to evaluate confounding factors such as surgeon's experience and surgical expertise, which could correlate with the complexity of the injury. Collecting accurate data for such patients was very challenging; the majority follow a long and transient course from cholecystectomy to LT, which may involve admissions and interventional procedures in more than 2 hospitals, or even in different countries, which may not be reported adequately. Additionally, the indications and criteria for LT may vary between reference centers. The limited number of patients included made it harder to determine significant associations between predictors and analyzed outcomes.

Long-lasting unsuccessful management of BDI can be detrimental by making LT challenging, thus highlighting the need for these patients to be referred more promptly to specialized HPB/LT units. Despite the relatively high related morbidity and mortality, LT for patients with ESLD secondary to otherwise unmanageable BDI following cholecystectomy seems to confer acceptable long-term survival compared to other indications. However, this is a real scenario that represents one of the most dreadful outcomes of a supposedly straightforward surgical procedure such as cholecystectomy.

Summary Box

What is already known:

- The vast majority of extrahepatic biliary system injuries are iatrogenic, occurring most frequently during laparoscopic (LC) or open cholecystectomy (OC)
- Long-term damage to the liver parenchyma is difficult to predict in patients with poorly managed BDI
- Liver transplantation (LT) has been used as a last resort in patients with end-stage liver disease due to bile duct injuries (BDI) following cholecystectomy

What the new findings are:

- Overall survival rates after LT were 82.4% at 1 year, 76.5% at 3 years, 73.5% at 5 years and 70.6% at 10 years
- The time interval between BDI and LT was shorter if there was a concomitant vascular injury at the time of cholecystectomy
- Despite the relatively high related morbidity and mortality, LT for patients with end-stage liver disease secondary to otherwise unmanageable BDI following cholecystectomy seems to confer acceptable long-term survival compared to other indications

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