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ORIGINAL ARTICLE

Incidence of and risk factors for ischemic-type biliary lesions following orthotopic liver transplantation

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Summary

Ischemic-type biliary lesions (ITBL) account for a major part of patients' morbidity and mortality after orthotopic liver transplantation (OLT). The exact origin of this type of biliary complication remains unknown. This study retrospectively evaluated 1843 patients. Patients with primary sclerosing cholangitis were excluded from this study. The diagnosis of ITBL was established only when all other causes of destruction of the biliary tree were ruled out. Donor age ($P = 0.028$) and cold ischemic time (CIT) ($P = 0.002$) were found to be significant risk factors for the development of ITBL. Organs that were perfused with University of Wisconsin (UW) solution developed ITBL significantly more often than Histidine–Tryptophan–Ketoglutarate (HTK)-perfused organs ($P = 0.036$). The same applied to organs harvested externally and shipped to our center versus those that were procured locally by our harvest teams ($P < 0.001$). Pressure perfusion via the hepatic artery significantly reduced the risk of ITBL ($P = 0.001$). The only recipient factor that showed a significant influence was Child-Pugh score status C ($P = 0.021$). Immunologic factors had no significant impact on ITBL. The clinical consequences of this study for our institution have been the strict limitation of CIT to <10 h and the exclusive use of HTK solution. We further advocate that all organ procurement teams perform pressure perfusion on harvested organs.

Introduction

Biliary complications remain a major source of morbidity and mortality following orthotopic liver transplantation (OLT) [1,2]. Early post-OLT biliary complications are mostly of a technical nature, such as insufficiency of the bile duct anastomosis or dislocation of a T-tube [3]. Biliary complications that develop months or years after liver transplantation can be divided into those affecting the anastomotic site or the ampulla of Vater and those affecting the intra- or extrahepatic parts of the donor biliary tree. Anastomotic strictures can be treated endoscopically with high success rates. In contrast, nonanastomotic strictures represent a major therapeutic problem [4,5]. Endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography (PTC) represent the gold standards of diagnostic procedures (see Images 1–3) [6]. Though the terms 'nonanastomotic biliary strictures', 'intrahepatic biliary strictures' or 'ischemic-type biliary lesion' (ITBL) are often used as synonyms for hilar or intrahepatic, diffuse bile duct strictures, necroses or ectasia/dilation, these diagnoses include a variety of forms of biliary lesion – hepatic artery thrombosis for example – with known etiologies, [7]. In this study, we intentionally focused exclusively on biliary lesions with no known genesis. The diagnosis of ITBL should be applied only in the

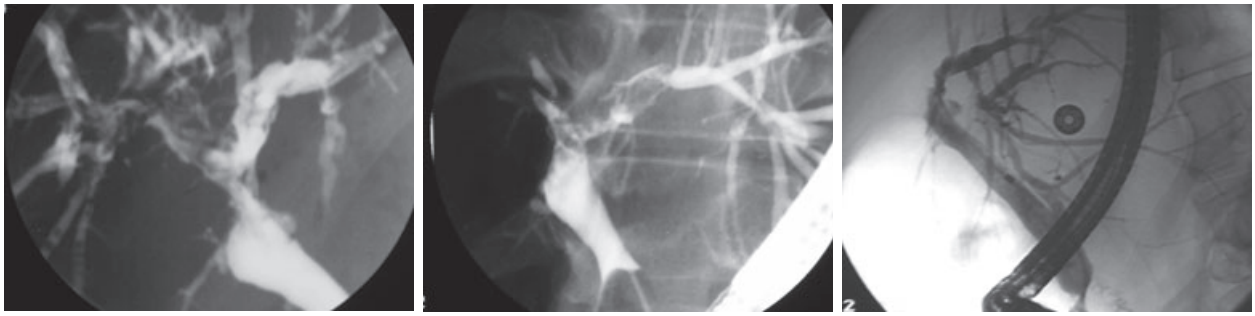

Figure 1 Cholangiographs show a typical image of intrahepatic destruction of the biliary tree in terms of ITBL. Hepatic artery was proved to be patent by angiography. The patient received over 15 endoscopic interventions between 2002 and 2005. The right hepatic lobe showed almost complete atrophy over time. The patient is in good health and without any episode of cholangitis for almost 2 years.

absence of such pathologies as post-OLT hepatic artery thrombosis, ABO-incompatibility, recurrence of primary sclerosing cholangitis (PSC) or chronic ductopenic rejection. It is important to rule out the aforementioned circumstances before making the diagnosis of ITBL. PSC Patients can obviously develop ITBL, but there seem to be no diagnostic tool to differentiate between ITBL and PCS recidivism. For this reason, we excluded 90 patients that were transplanted for PSC from this study. Patients with ITBL present without characteristic or pathognomonic clinical symptoms. Malaise, subfebrile temperatures, slightly elevated alkaline phosphatase (AP) and gamma glutamyltransferase (γGT) or light bilirubinemia can be the leading clinical findings but also shivering, high temperature, jaundice or even septic shock. The reported incidence of ITBL following OLT varies between 1.4% and 26% [8–11]. While this could be merely a consequence of differing definitions or diagnostic interpretations, the bitter fact remains that a diagnosis of ITBL significantly reduces both the patient's and the graft's chances of survival [12] Fig. 1.

Unfortunately, consistent data on the causes of ITBL are rare. In order to establish strategies for its treatment or prevention, possible risk factors for the development of ITBL have to be clearly addressed.

The aim of this retrospective, single-center study was to investigate 1843 OLT patients with regard to the incidence and risk factors of ITBL.

Materials and methods

In this retrospective study, 1843 consecutive OLTs were reviewed. Ninety patients who were transplanted with the diagnosis of PSC were excluded from the evaluation. All OLTs were carried out at the transplant center of the Humboldt University of Berlin between December 1988 and December 2005. All patients were reviewed and re-examined ½, 1, 3, 5, 7, 10, and 13 years (where applicable) post-transplantation in a standardized follow-up program. Patient follow-up performance was 99.8%. Patients were divided into two groups: group 1 comprised organ recipients without ITBL, and group 2 recipients with ITBL.

The diagnosis of ITBL was suspected when either ERC or PTC showed typical signs of segmental or diffuse intra- or extrahepatic strictures, necrosis, abscesses or destructions of the biliary tree. Diagnosis of ITBL was established only after hepatic artery thrombosis, ABO-incompatibility, biliary anastomotic stricture or other reasons for biliary destruction (e.g. chronic ductopenic rejection, ABO incompatibility) were ruled out.

Hepatic artery patency was ensured in all cases of ITBL either with Doppler ultrasound, computed tomography-based angiography (angio-CAT scan), magnetic resonance imaging-based angiography (angio-MRI) or conventional angiography.

Patients routinely underwent liver biopsies at our institution. When the pathologist diagnosed dominant cholangitis or cholestasis, further diagnostics were initiated, including ERC, PTC or magnetic resonance cholangiopancreatography (MRCP).

Donor factors studied were as follows: age, gender, serum sodium level, duration of stay on intensive care unit (ICU) prior to organ harvest and causes of brain death.

The following criteria were used to identify risk factors related to graft and allocation factors: cold ischemic time (CIT), choice of perfusion solution, shipped versus non-shipped organs, gravity versus pressure perfusion, urgency of transplantation, necessity of retransplantation, transplantation following initial non functioning of organ, split-liver transplantation, living versus deceased donor and the use of blood products for transplantation (packed red cells and fresh-frozen plasma). There have been no incidences with non heart-beating donors at our institution. Resulting from differences in harvesting techniques

at various transplant centers, we differentiated between organs received by shipment and those that were procured by one of the center's own teams. Beginning in 1996, our center has routinely performed pressure perfusion of the hepatic artery during organ harvesting. Arterial pressure perfusion is generated by the use of a pressure bag with a mean pressure of ca. 150 mmHg; the portal perfusion is caused by gravity. We presumed that all shipped organs were harvested without the use of pressure perfusion techniques, while understanding that – in very rare cases – this might not be true. Since 2004, Histidine–Tryptophan–Ketoglutarate (HTK) has replaced University of Wisconsin (UW) solution as the standard for perfusion. High-urgency transplantation was understood to denote all patients experiencing either acute liver failure or fulminant post-transplantation complications and, as a result, granted UNOS 1 status on the Eurotransplant waiting list. Retransplantation encompassed all patients receiving a second, third or fourth graft. Living donors included right (segments 5–8), left (segments 2–4) and left-lateral (segments 2–3) splits. All LDLT livers were perfused with HTK. Only intra-operative blood product usage was included for evaluation. Pre- and postoperative demand for plasma or blood products was excluded.

Recipient factors investigated included: gender, age, model of end-stage liver disease (MELD) score, Child-Pugh score (CPS), blood group, underlying disease and technique of bile duct reconstruction. MELD scores were calculated with the UNOS meld calculator (http://www.unos.org/resources/meldPeldCalculator.asp). CPS was calculated according to the established formula [13]. Underlying diseases were grouped into 11 groups of diagnosis including hepatitis B-related cirrhosis [HBV, including co-infection with the delta virus and patients with hepatocellular carcinoma (HCC)], hepatitis C-related cirrhosis (HCV, including co-infections with HBV and HCC), malignant liver tumors (including HCC, cholangiocellular carcinoma (CCC) and hepatoblastoma but excluding HBV-, HCV- and PSC-related HCC or CCC), primary biliary cirrhosis (PBC), PSC (including HCC or CCC), acute liver failure (ALF, including viral), autoimune hepatitis (AIH), metabolic liver disease (Met, including alpha-1 antitrypsin deficiency, Wilson's disease, hemochromatosis, cystic liver disease, Byler's disease), alcohol-induced liver cirrhosis (alc), others and retransplantation (reTx, including first, second and third retransplantations).

Immunologic factors were evaluated as follows: primary immunosuppression, cytomegalovirus infection (CMV), acute cellular rejection and anti CD-3 monoclonal antibody treatment (OKT III). Only calcineurin-inhibitor-based immunosuppressive protocols were evaluated. There was no differentiation between double, triple or quadruple immunosuppressive regimens. CMV Infection was defined as present in the case of antiviral treatment (CMV hyperimmunoglobulin, Ganciclovir) following biopsy-proven CMV tissue-invasive disease (e.g. hepatitis, gastritis, retinitis or colitis), pp65 APAAP-positive blood test and CMV-related leukopenia for PCR-positive cases (noninvasive CMV disease). For the purposes of this study, PCR-positive serology without medical treatment was defined as a negative CMV infection. Acute cellular rejection, as established by histologic findings, were divided into four grades according to the Banff criteria of acute rejection (aR): (aR0) no evidence of rejection; (aRI) mild periportal mononuclear infiltrate with minimal endotheliitis and minimal bile duct injury without hepatocyte necrosis; (aRII) moderate periportal mononuclear infiltrate extending beyond the portal triad, marked endotheliitis, marked bile duct injury and single cell hepatocyte necrosis; (aRIII) the same alterations as described in II plus severe injuries and massive hepatocyte necrosis [14,15]. OKT-III (murine anti-CD3 monoclonal antibody) treatment included all OKT-III treatments of 5–7 days.

In order to evaluate the incidence of ITBL over a period of time and among different transplant periods, calculations were made of yearly incidences between 1988 and 2004, as well as within each set of 100 consecutive transplantations.

Statistical analysis

All statistical calculations were performed in SPSS 11.3 (SPSS Inc. Chicago, CA, USA). Descriptive statistics were used to summarize the donor and recipient characteristics. Cross-tabulation, the chi-squared test and Fisher's exact test were performed for independent variables. Nonparametric variables were evaluated with the Mann–Whitney *U*-test and asymptotic significance was also calculated. Multivariate analysis was carried out using a logistic regression model. All of the tests performed were two-sided. *P*-values of $P < 0.05$ were considered to be statistically significant. All calculations were performed in association with the Department of Biometrical Medicine.

Results

The overall incidence of post liver-transplantation ITBL was 3.9% (65/1688) at our institution.

Analysis of donor factors

Donor age had a significant impact on the development of ITBL ($P = 0.028$). This difference was also significant in a multivariate analysis ($P = 0.037$). However, there

Table 1. Donor characteristics: Donor age was significantly different between groups, showing an almost five year older average age in the ITBL group.

	Donor characteristics			
Variables	Group 1 patients w/o ITBL	Group 2 patients with ITBL	Incidence of ITBL (%)	*P*-value
Donor age (years)	38.9 ± 16.9	43.6 ± 16.9		0.028
Donor gender				
Male	1048 (62.1)	38	3.6	ns
Female	640 (37.9)	27	4.2	ns
Mean donor serum Na^+ (mmol/1)	149 ± 11.3	146.8 ± 10		ns
Cause of brain death				
Subarachnoidal bleeding	698 (41.4)	27	3.9	ns
Trauma	613 (39.9)	26	4.2	ns
Intracerebral bleeding	10 (0.7)	0		ns
Hypoxia	90 (5.3)	4	4.4	ns
Brain tumor	20 (1.2)	0		ns
Cardiac infarction	8 (0.5)	0		ns
Cerebral infarction	86 (5.1)	5	5.8	ns
others	163 (9.6)	3	1.8	
Stay on the ICU prior to Organ harvesting (days)	3.89 ± 4.99	2.96 ± 2.9		ns

Values in parenthesis are expressed in percentage.

Table 2. Allocation characteristics: Cold ischemic time was significantly longer in the ITBL group. Graft that were perfused with W-solution developed significantly more often ITBL than those perfused with HTK. All shipped organS were gravity perfused. Both factors, shipped organ and gravity perfusion, correlate significantly more often with the developement of ITBL.

	Allocation characteristics			
Variables	Group 1 patients w/o ITBL	Group 2 patients with ITBL	Incidence of ITBL (%)	*P*-value
n	1688	65	3.9	
Cold ischemia (min)	558 + 218	652 + 242		0.002
Perfusion solution				
University of Wisconsin	1421 (85.7)	63	4.4	
HTK – Belzer's	209 (12.6)	2	1	0.036
others	28 (1.7)	0		
UW Perfusate via hepatic artery (liter)	3.3 ± 2.1	3.7 ± 1.5		ns
UW Perfusate via portal vein (liter)	2.0 ±0.6	2.5 ± 0.8		ns
HTK Perfusate via hepatic artery (liter)	5.8 ±0.7	8.8 ± 2.5		ns
HTK Perfusate via portal vein (liter)	3.6 ±0.6	5.0		ns
Non-shipped organs	1041 (61.7)	24	2.3	
Shipped organs	647 (38.3)	41	6.3	<0.001
Pressure-perfused organs	618 (56.1)	13	2.1	
Gravity-perfused organs	484 (43.9)	30	6.2	0.001
High urgency transplantation	191 (10.3)	6	3.1	ns
Retransplantation	201 (10.9)	10	5.0	ns
Transplantation following INF	61 (3.3)	0		ns
whole organ	1546 (91.7)	63	4.1	
Split organ (cadaver or living)	142 (8.3)	2	1.3	ns
Cadaver donation	1594 (94.4)	63	4.0	
Living donation	94 (5.6)	2	2.1	ns
Fresh-frozen plasma product during transplantation	10.2 ± 8.4	10.2 ± 8.3		ns
Packed red blood cells during tansplantation	7.1 ± 7.2	6.5 ± 7.9		ns

Values in parenthesis are expressed in percentage.

were no significant differences between groups concerning the causes of brain death. Grafts from donors that died of cerebral infarction and hypoxia had a slightly increased incidence of ITBL ($P > 0.05$). None of the ITBL patients had received a graft of a donor who died of cardiac infarction. Organs of donors that developed ITBL had a

shorter period of ICU. This difference did not reach significance. Donor characteristics are shown in Table 1.

Analysis of allocation and graft factors

Grafts that developed ITBL had a significantly longer CIT with a mean of 652 ± 242 min vs. 558 ± 218 min ($P = 0.002$). A multivariate analysis included CIT as a significant factor with $P = 0.002$. Grafts that were perfused and preserved with UW solution showed a significantly higher incidence of ITBL as compared with grafts that were perfused and preserved with HTK solution ($P = 0.036$). With an incidence of 6.3%, as compared with 2.3% ($P < 0.001$), shipped organs developed ITBL significantly more often than organs procured by one of our harvesting teams. Furthermore, while such teams procured 60% of the organs studied, 65.3% of all organs with ITBL were shipped ones. This difference was statistically significant in a multivariate analysis ($P = 0.001$). Organs that were harvested with arterial pressure perfusion developed significantly less ITBL ($P = 0.001$). Graft and allocation characteristics are shown in Table 2.

Analysis of recipient factors

Child-Pugh score had a significant impact on the risk of developing ITBL. Patients with CPS-C had a significantly increased incidence of 6.5% ($P = 0.021$). Recipient age and gender were not risk factors for ITBL. Neither MELD score nor recipient's blood group showed any statistically significant impact on the development of ITBL. Data are depicted in Table 3.

Neither the underlying disease, rejection episodes, CMV status of donor or recipient nor technique of bile

Table 3. Recipient characteristics.

	Recipient characteristics			
Variables	Group 1 patients w/o ITBL	Group 2 patients with ITBL	Incidence of ITBL (%)	*P*-value
n	1688	65	3.9	
Recipient gender				
Male	977 (57.9)	41	4.2	ns
Female	711 (42.1)	24	3.4	
Mean recipient age (years)	47.4 + 14.1	47.9 + 10.1		ns
MELD score (mean + SD)	20.3 + 9.9	20.6 + 9.1		ns
Child-Pugh score				
CPS-A	226 (13.4)	6	3.2	ns
CPS-B	723 (42.8.5)	23	3.4	ns
CPS-C	403 (23.9)	26	6.5	0.021
Recipient blood group				
EGA	789 (46.7)	29	3.7	ns
BOB	225 (13.3)	7	3.1	ns
BGAB	118 (7.0)	6	5.0	ns
BGO	556 (32.9)	23	4.1	ns
Underlying disease				
Hepatitis B-related cirrhosis	170 (10)	9	5.3	ns
Hepatitis C-related cirrhosis	210 (12.4)	9	4.3	ns
Hepatocellular carcinoma	252 (14.9)	7	2.8	ns
Primary biliary cirrhosis	109 (6.3)	2	1.9	ns
Acute liver failure	105 (6.2)	4	3.8	ns
Autoimmune hepatitis	59 (3.5)	0	0	
Metabolic liver diseases	72 (4.2)	1	1.4	ns
Alcohol-induced cirrhosis	318 (18.8)	17	5.3	ns
Others	194 (11.5)	7	3.6	ns
Retransplantation	194 (11.5)	7	3.6	ns
Biliary reconstruction				
Side-to-side	1379 (86.1)	61	4.2	ns
Choledochojejunostomy	41 (6.0)	1	2.4	ns
Choledochoduodenostomy	17 (2.5)	0		
Cobrahead; spatulated	5 (0.3)	0		
End-to-side	18 (2.7)	1	5.3	ns
End-to-end	52 (3.2)	1	1.9	ns

Values in parenthesis are expressed in percentage.

Table 4. Immunologic factors.

	Immunologic risk factors			
Variables	Group 1 patients w/o ITBL	Group 2 patients with ITBL	Incidence of ITBL (%)	*P*-value
Initial immunosuppression				
Tacrolimus	1058 (62.7)	41 (63.1)	3.9	ns
Cyclosporin A	572 (33.9)	24 (36.9)	4.2	
Others	58 (3.4)			
CMV infection				
Positive	622 (36.8)	23	3.7	ns
Negative	320 (19.0)	10	3.1	ns
Unknown	746 (44.2)	32	4.2	ns
Maximum grade of rejection				
No rejection	1169 (67.4)	36	3.1	ns
First grade	235 (14.7)	14	5.9	ns
Second grade	246 (15.8)	12	4.9	ns
Third grade	38 (2.3)	3	7.9	ns
Number of rejection episodes				
0 rejection	1169 (69.3)	37	3.1	ns
1 rejection	401 (23.8)	23	5.7	ns
2 rejections	86 (5.1)	3	3.4	ns
3 or more rejections	32 (1.9)	2	6.2	ns
OKT-3 therapy	93 (5.5)	7	7.5	ns

Values in parenthesis are expressed in percentage.

duct anastomosis had an effect on the development of ITBL (Table 4).

No increase or decrease of ITBL incidence could be documented over the last 15 years.

Discussion

This study reviews data from 1843 liver-transplant patients. After exclusion of 90 patients that were transplanted for PSC, we examined 1771 liver-transplant patients demonstrating a low incidence of ITBL (3.9%). Six relevant and statistically significant risk factors for the development of ITBL were identified. These factors comprised CIT, donor age, shipped organs, pressure perfusion technique during organ procurement, type of perfusion solution and CPS. In a multivariate analysis, only CIT and shipped organs remained statistically significant. Surprisingly, some commonly reported risk factors, including cardiac death or hypoxemia, did not prove to be relevant factors as per the findings in this study.

The reported incidence of post-OLT ITBL varied between from 1.4% up to as high as 26% [10,16–21]. One reason for these differences could be the lack of a clear, standardized definition for ITBL. Some centers equate all kinds of nonanastomotic intrahepatic biliary strictures with ITBL [2]. We accepted the diagnosis of ITBL only if all other known causes for biliary complications had been ruled out. An incidence of 3.9% of 1843 liver-transplant patients demonstrates a respectably low morbidity following OTL. Furthermore, it is substantiated by a strict and clear diagnostic protocol and can be assumed to be representative for this disease. However, even well trained pathologists have difficulties differentiating between chronic rejection, recurrence of PSC and ITBL [22–25]. All studies evaluating ITBL contain this diagnostic and definition bias. Surely therefore, the variability and indeed the complexity of pathologic findings are the major reasons for the extreme inconsistency among data concerning ITBL. For this reason, we excluded all PSC patients from this study in order to render the definition of ITBL with more precision.

Cold ischemic time has been described in many studies as a relevant risk factor for the development of ITBL. Grafts that were preserved for more than 11–13 h have been shown to have a significantly increased risk for the development of ITBL [1,12,26]. However, there have been several contraditory studies published. A retrospective study of 1113 patients, for example, showed no impact of CIT on ITBL [10]. Likewise, a study of 288 adult liver-transplant recipients with an extended CIT up to 15 h did not show any adverse effect on the outcome and did not correlate with a higher incidence of ITBL [27]. Two further retrospective studies of 100 and 154 patients showed no impact of CIT on the development of ITBL [28,29]. One can only speculate why these data are so much at odds with conventional wisdom. Steatosis of the graft might be a relevant cofactor. Unfortunately, neither in the aforementioned studies, nor in conjunction

with our own transplantations, were graft biopsies examined. This represents an area in potential need of further study.

Another explanation might be the interrelation between ischemia and reperfusion injury. It has been shown in numerous experimental and clinical studies that the length of CIT correlates with the magnitude of ischemia/reperfusion injury [30,31]. Biliary injury could be a result of endothelium reperfusion injury. Damage to peribiliary arterioles could consequently lead to ischemic damage to biliary epithelium. So far, this explanation remains speculative. Some centers have ceased accepting grafts with total CIT of more than 13 h and their results have improved [2]. In our own experience, a threshold of 10 h of CIT turned out to be significant regarding ITBL. We strongly advocate minimizing CIT to <10 h.

In this study, donor age was shown to be a relevant risk factor as well. This inference is in contrast to Guichelaar's study on 749 patients [1]. And although Nakamura and Buis report of a markedly increased donor age of organs that later develop ITBL, they could not show that donor age has a significant impact on ITBL (1113 pts., $P = 0.09$; 487 pts., $P = 0.16$) [10,32].

Why did organs that were harvested by local teams show significantly less ITBL than organs shipped to our transplant center? It was impossible to investigate the exact procurement procedures of all shipped grafts because of lack of adequate documentation. There were four main differences between the shipped and non-shipped organs. Shipped organs had a longer mean CIT (632 min ± 188 min vs. 514 min ± 227 min, $P < 0{,}001$ and were on average older (37.7 ± 16.3 vs. 41.0 ± 17.8, $P < 0.001$). Furthermore, most, if not all, shipped organs did not receive arterial pressure perfusion, nor was careful rinsing done of the bile duct with perfusion solution a standard procedure of all external harvesting teams. As a consequence of these findings, we strongly advocate the use of arterial pressure perfusion during organ procurement.

Furthermore, additional arterial back table perfusion could significantly reduce the rate of ITBL ($P = 0.001$) [21]. It is hypothesized that gravity perfusion via the hepatic artery does not completely rinse the peribiliary plexus, causes blood to stagnate locally in these tiny, incompletely flushed vessels and thus leads to micro thrombi of these arterioles. Consequently, local ischemia is provoked, leading to fibrosis and biliary strictures, including ITBL [33].These explanations, while being quite compelling, will remain speculative until flow measurements and histopathologic examinations of the peribiliary plexus are more comprehensively studied.

An incomplete rinsing of the peribiliary plexus, attributable to UW solution's very high viscosity, might provide an explanation for why ITBL develops more often under UW preservation than under that of the much less viscose HTK ($P = 0.036$). Interestingly, a prospective study of 52 OLT-patients identified *type of preservation solution* (UW!) and not CIT as the major determinant of ITBL [34]. Canelo *et al.* [35] reported in a retrospective analysis of 123 liver-transplant patients that ITBL developed exclusively under UW preservation. Buis *et al.* [32] examined the impact of preservation solution on the development of ITBL within 487 patients and found significantly less ITBL in organs that were perfused with HTK. In contrast, Testa *et al.* [36] reported data on 30 adult living-donor liver transplantations describing more biliary complications under HTK perfusion as compared with UW. We nevertheless recommend the use of HTK preservation, provided that CIT can be contained to <10 h.

The only recipient factor that showed any impact on the development of ITBL was CPS. Patients that were transplanted with CPS status C had an incidence of ITBL of 6.4% ($P = 0.021$). This finding is congruent with data from 347 liver-transplant recipients wherein UNOS status (this includes CPS) was identified as an independent risk factor for higher rates of mortality and postoperative complications (including ITBL) [37].

In conclusion, ITBL remains a consistent cause of morbidity and mortality among liver-transplant recipients. While the exact pathomechanisms that lead to ITBL remain unclear and inconsistencies plague much of the published data, this study nevertheless identified graft and allocation factors as the main contributors, along with CPS, to the development of ITBL. Therefore, the authors urge all efforts to be taken to minimize these risk factors by aggressively reducing CIT and avoiding the use of gravity arterial perfusion and UW preservation solution. This will minimize the rate of ITBL, reduce patient morbidity and prevent major costs.

Authorship

CH, JP, GP, PN: designed research/study. CH: performed research/study. JP, GP, UN, WV-S, PN: contributed important reagents. CH, WV-S: collected data. CH, AP, PN: analysed data. CH, JP, PN: wrote the paper.

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