Duct-to-duct biliary reconstruction with or without an intraductal removable stent in liver transplantation: The BILIDRAIN-T multicentric randomised trial

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Background & Aims: Biliary complications (BC) following liver transplantation (LT) are responsible for significant morbidity. No technical procedure during reconstruction has been associated with a risk reduction of BC. The placement of an intraductal removable stent (IRS) during reconstruction followed by its endoscopic removal showed feasibility and safety in a preliminary study. This multicentric randomised controlled trial aimed at evaluating the impact of an IRS on BC following LT.

Methods: This multicentric randomised controlled trial was conducted in 7 centres from April 2015 to February 2019. Randomisation was done during LT when a duct-to-duct anastomosis was confirmed with at least 1 of the stump diameters ≤7 mm. In the IRS group, a custom-made segment of a T-tube was placed into the bile duct to act as a stake during healing and was removed endoscopically 4 to 6 months post LT. The primary endpoint was the incidence of BC (fistulae and strictures) within 6 months post LT. The secondary criteria were complications related to the IRS placement or extraction, including endoscopic retrograde cholangio-pancreatography (ERCP)-related complications.

Results: In total, 235 patients were randomised: 117 in the IRS group and 118 in the control group. BC occurred in 31 patients (26.5%) in the IRS group *vs.* 24 (20.3%) in the control group (*p* = 0.27), including 16 (13.8%) and 15 (12.8%) strictures, respectively. IRS migration occurred in 24 patients (20.5%), cholangitis in 1 (0.9%), acute pancreatitis in 2 (1.8%), and difficulty during endoscopic extraction in 19 (19.4%). No predictive factor for BC was identified.

Conclusions: IRS does not prevent BC after LT and may require specific endoscopic expertise for removal.

Trial registration number (ClinicalTrials.gov): NCT02356939 (https://clinicaltrials.gov/ct2/show/NCT02356939?term=NCT02356939&draw=2&rank=1).

Lay summary: Liver transplantation is a life-saving treatment for many patients with end-stage liver disease. However, it can be associated with complications involving the bile duct reconstruction. Herein, the placement of a specific stent called an intraductal removable stent was trialled as a way of reducing bile duct complications in patients undergoing liver transplantation. Unfortunately, it did not help preventing such complications.

Introduction

Biliary tract reconstruction is the final technical step of liver transplantation (LT) and still impacts post-LT outcome.[1,2] In fact, the incidence of biliary complications (BC) following LT remains high, ranging from 10 to 50% of patients despite an increasing experience worldwide.[2–4] These complications, mainly represented by bile leaks and strictures, are responsible for readmissions and additional procedures such as endoscopic or radiologic interventional manoeuvres, which bring their own specific risks (bleeding, pancreatitis, and cholangitis), and eventually surgical repair in case of failures of these latter mini-

invasive treatments.[5–7] Although biliary leaks occur in the early postoperative period (within 3 months), biliary strictures mainly occur within 5 to 8 months and up to 1 year in the great majority[3,4] with a reported incidence ranging from 5 to 30%.[2,4]

A small bile duct diameter has been identified as a risk factor for BC in several studies, including a prospective trial.[8–11] The diameter cut-off associated with significant increase in BC varied from 5 mm in living donor studies analysing partial grafts from living donors[9–11] to 7 mm in a prospective trial including whole cadaveric grafts.[8]

To prevent BC, the placement of an external T-tube has been largely debated.[12–17] The goal is to facilitate biliary healing through a 'tutoring' and 'decompressive' effect and keep an easy access to the biliary tract to perform a cholangiography, until its removal 6 to 8 weeks post LT.[18] However, several studies,[12–15,17] including 3 randomised trials,[13–15] have shown not only an absence of difference of BC with or without the T-tube but also a specific morbidity, such as cholangitis, and biliary leaks at the time of removal related to the external aspect of the drainage. Based on these results, and on the emergence of safe endoscopic management of BC, numerous teams do not use external biliary drainage anymore.[19–23] So far, one could conclude that no intraoperative technique has shown efficacy in BC prevention during LT.

A novel technique of using an intraductal removable stent (IRS) placed during biliary reconstruction in LT and removed by endoscopy within 6 months postoperative has been recently proposed.[24] The rationale is to prevent BC while avoiding side effects related to an external T-tube. Contrary to the T-tube that is removed early within 2 months post LT, the IRS would allow a longer stenting effect on biliary anastomosis[24] without the drawbacks of an external drainage. A preliminary study showed the feasibility and safety of the technique on 20 patients with a small graft bile duct (<5 mm).[24] No technical failure and no procedure-related complication were recorded during drain removal, and BC occurred in 4 patients, which all received a partial graft. A similar technique using ureteral stents had been described in 2000 in 77 patients with early endoscopic removal (4 to 6 weeks) and acceptable outcome (18% BC).[25] However, the early removal may theoretically counterbalance the stenting effect on biliary stenosis formation.

The aim of this multicentric randomised controlled trial was thus to compare the incidence of BC, that is, stenosis and leakage, after duct-to-duct biliary reconstruction performed with or without an IRS placement in LT. The secondary endpoint was to assess the incidence of complications related to the IRS and its extraction by endoscopy.

Patients and methods
Study design and study population
The study rationale, design, and methods of the BILIDRAINT trial, a randomised, superiority, unblinded controlled trial, have been published.[26] Briefly, the trial enrolled patients >18 years of age eligible for LT. All patients gave their written consent for participation. Patients were not enrolled in case biliary reconstruction was decided to be a hepaticojejunostomy for anatomical/biliary disease reasons and/or because of the presence of latex, polymer, or rubber allergy. Definitive inclusion was performed in the operating room during LT and depended on the fulfilment of the following 'definitive inclusion criteria':

1) duct-to-duct biliary reconstruction confirmed and a complete biliary tract of the donor, 2) graft or recipient biliary duct diameter ≤7 mm, and 3) graft not from a donor deceased from cardiac arrest. Definitive inclusion and randomisation were performed during LT in the operating room online through the CleanWeb® software. A randomisation list was performed by an independent statistician with blocks of varying size and a 1:1 ratio and stratified by centre.

The inclusion period was set at 2 years, for a total study duration of 2.5 years, in 7 LT centres in France. The follow-up was set at 6 months postoperative to screen the majority of BC.

Study outcomes
The primary outcome was the incidence of BC, which included biliary strictures and leakage, within 6 months post LT.

A biliary leakage was defined by the presence of bile in the abdominal drainage and/or an intra-abdominal collection requiring drainage with bilious content. A biliary stenosis was defined by a size discrepancy between the 2 sides of the bile duct anastomosis on specific imaging (magnetic resonance cholangiography [MRC] and endoscopic retrograde cholangio-pancreatography [ERCP]) associated with an upstream bile tract distention, with a clinical and biological cholestasis, after excluding other cholestasis causes (rejection and viral reactivation). The diagnosis of biliary stenosis was reviewed for each case by an independent expert committee. Graft loss and death were considered as events.

Secondary outcomes included were the incidence of complications related to the IRS and its extraction by endoscopy: cholangitis, stent migration, extraction difficulties, acute pancreatitis, digestive perforation, and haemorrhage. Graft and patients' survival at 6 months were also analysed as secondary endpoints. Arterial and BC (ABC)-free survival at 6 months was analysed as a supplementary endpoint.[27]

A data monitoring committee (DMC) provided trial oversight and assessed the safety profile of the trial. Independent clinical research associates monitored the sites and gathered the data. All events were analysed and adjudicated by an independent, 3-person, clinical evaluation committee.

In the IRS group, the surgeon would place a custom-made segment of an 8-French T-tube in the biliary duct without suture fixation after measuring the duct diameter using a sterile graduated ruler. To homogenise the technique, a short movie describing the steps of IRS placement was published online by the investigating team (Supplementary information at https://youtu.be/BY29ybb-01M). The stent was placed across the anastomosis, with the lower end sitting on the papilla without crossing it (Fig. 1). The technique of biliary reconstruction was left to the surgeon's preference.

Post-LT follow-up was performed according to each centre's usual practice. Clinical, biological, and radiological data were collected at Day 1, Day 7, Day 15, Month 1, Month 3, and Month 6. An MRC was performed 6 months post LT (after endoscopic removal in the IRS group).

In the IRS group, an ERCP was planned between the fourth and sixth months post transplantation, requiring a short stay in the hospital, a general anaesthesia, and clinical and biological tests including plasmatic lipase dosage at Day 1.

Any adverse event related to IRS was immediately reported for further investigation, and potentially severe adverse events were previously defined for early identification: severe
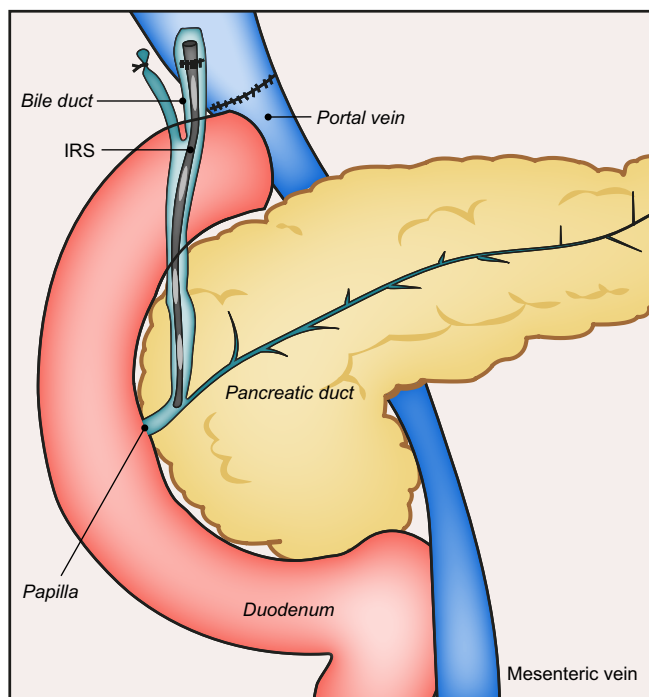
Fig. 1. IRS placement across biliary anastomosis. The stent is a custom-made segment (2 cm) of an 8-French T-tube inserted in the biliary duct across the anastomosis without suture fixation. The lower end is sitting on the papilla without crossing it. Courtesy of Dr. R. Brustia. IRS, intraductal removable stent.

cholangitis, ERCP-related severe acute pancreatitis, ERCP-related haemorrhage, and ERCP-related duodenal perforation.

Extraction difficulties were reported as an IRS extraction manoeuvre unusually long and/or complicated as described by the endoscopist. Reasons for difficulty were classified in catheterism difficulty and/or extraction difficulty.

Statistical analysis

As described previously, the inclusion of 248 patients would provide a power of at least 80%, with a 2-sided alpha of 5%, for rejection of the null hypothesis of no difference, considering an expected incidence of BC of 25% in the non-IRS group and a 60% reduction of BC (10%) in the IRS group. No interim analysis was planned, and all analyses were performed on an intention-to-treat basis.

Baseline characteristics were expressed as number (percentage) for categorical variables and mean (standard deviation) or median (IQR) for continuous variables depending on their distribution. The frequency of occurrence of BC was compared between groups using a Chi-square test. Two-sided 95% CIs were estimated using the exact method. The analysis was performed among both the as-randomised population, which included all randomised patients with missing outcome data replaced using worst-case imputation (BC), and the per-protocol population, which included all patients without a major protocol violation (including eligibility criteria not fulfilled or IRS migration). Because the trial was conducted at multiple sites, site effect was accounted for in a *post hoc* sensitivity analysis using a generalised linear regression mixed model with binary distribution and a logit link function with strategy as a fixed effect and centre as a random effect.

Exploratory analysis was performed using a linear generalised regression mixed model with binary distribution (logit link) to study the following risk factors of BC: occurrence of arterial complication before BC, warm ischaemia time, graft diameter, receiver diameter, and thread size ($\geq$6/0). Site was considered as a random effect. The results were expressed as odd ratios with 95% CIs. The log linearity hypothesis was not achieved for 1) warm ischaemia time that was therefore dichotomised around the clinically relevant value of 30 min and 2) graft and receiver diameters that were categorised based on quartiles.

Survivals were estimated using the Kaplan–Meier method, and groups were compared using a log-rank test. Greenwood's variance estimate was used to calculate 2-sided 95% CIs. A stratified Cox proportional hazards model was used to study the effect of surgery strategy on ABC-free survival considering the following adjustment factors: warm ischaemia time, reconstruction technique, and thread size. The results were expressed as hazard ratios with 95% CIs. The stratification variable was the site of inclusion. The risk proportionality hypothesis was verified by testing the interaction between interest variable and time. For each model, unadjusted analysis was first performed to select variables of clinical interest at the *p* value threshold of 0.2. Then, a full adjusted regression model was built before a stepwise backward selection: all variables with a *p* value <0.05 kept in the final model except the randomisation group, which was forced as an adjustment variable.

Premature discontinuation of research was censored at the last follow-up visit available. Missing data for secondary outcomes were not replaced. All superiority tests were 2-sided, and *p* values <0.05 were considered significant. No adjustment was planned for multiplicity, and there was no prespecified hierarchy for secondary efficacy outcomes. Statistical analyses were performed using SAS V.9.4 software (SAS Institute Inc.).

Ethical approval

This trial was approved by the *Comité de Protection des Personnes* (CPP) Ile de France III - 3170 (file ref.: 2014-A00866-41).

Results

Study population

Between April 2015 to July 2018, a total of 467 patients were enrolled at 7 centres, of whom 235 patients (117 in the IRS group and 118 in the control group) met the randomisation criteria at the time of LT (Fig. 2).

Baseline parameters were well balanced between the 2 groups, as well as donor characteristics (Table 1). Hepatocellular carcinoma (HCC) was present in 136 (57.9%) patients (Table 1). Mean cold ischaemia time was 432.8 ± 116.8 min in the IRS group and 430.9 ± 116.7 min in the control group.

Technical parameters during LT had a broadly similar distribution between groups (Table 1). Warm arterial ischaemia time was 44.0 [36.0; 55.0] min in the IRS group and 40.0 [35.0; 50.0] min in the control group. Arterial anastomosis was described as 'difficult' in 3 (6.3%) cases in the IRS group and 4 (8.3%) cases in the control group. Graft bile duct diameter was 6.5 ± 1.6 mm in the IRS group and 6.4 ± 1.7 mm in the control
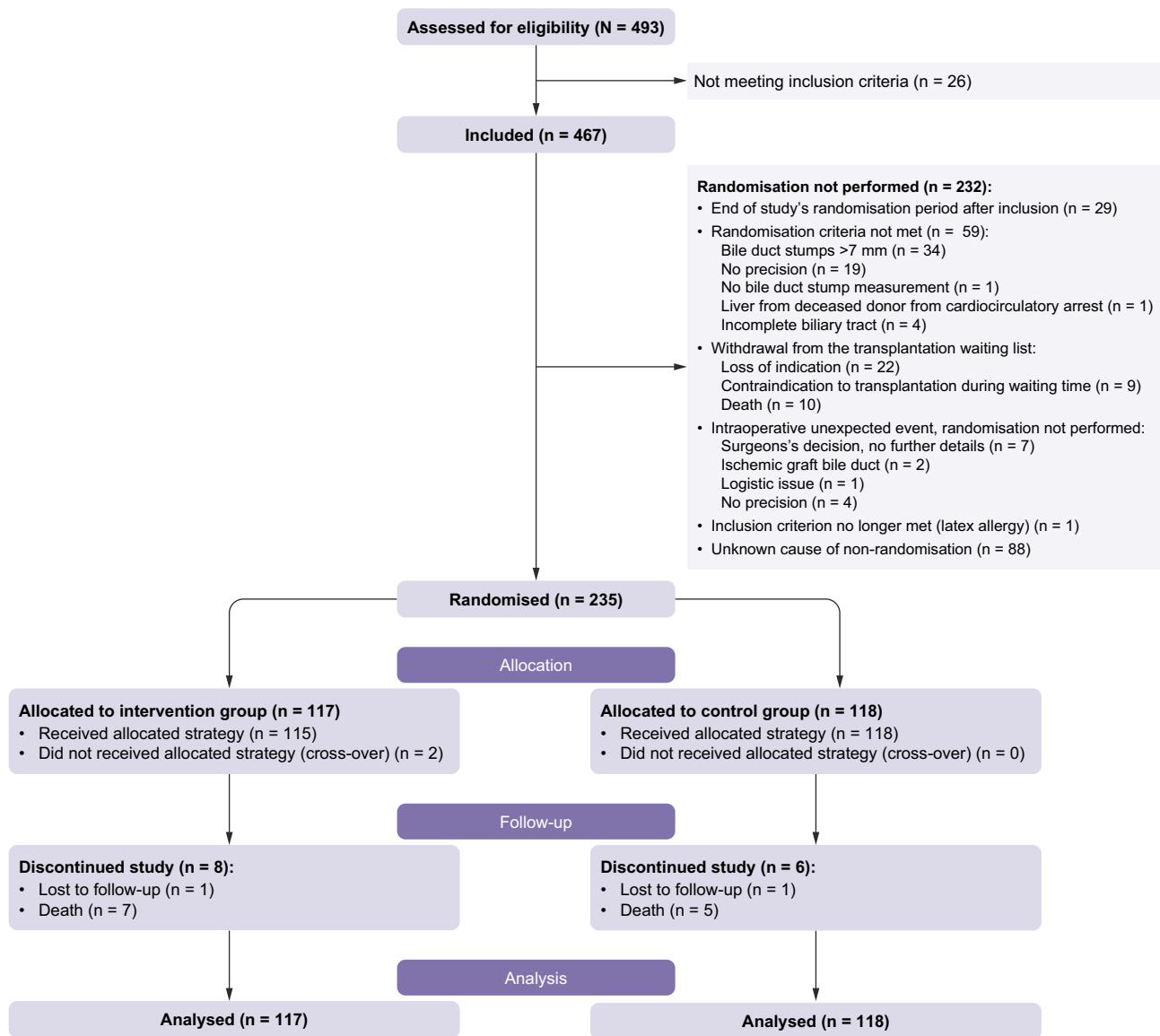
Fig. 2. CONSORT diagram of enrolment and follow-up.

group, *vs.* a recipient bile duct diameter of 7.0 ± 2.7 mm in the IRS group and 6.7 ± 2.3 mm in the control group. Running suture was preferred in 64 (31.7%) biliary anastomosis *vs.* separate stiches in 59 (29.2%) and a mixed technique in 79 (39.1%).

Primary outcome
BC occurred in 31 patients (26.5%) in the IRS group *vs.* 24 (20.3%) in the control group (*p* = 0.27), including 16 (13.8%) and 15 (12.8%) stenosis and 9 (7.8%) and 6 (5.1%) fistulae in the IRS and control groups, respectively (Table 2). Among the 15 patients with fistulae, 5 (33.3) also developed stenosis, including 2/9 (22.2%) in the IRS group and 3/6 (50.0%) in the control group.

After excluding 24 patients with IRS migration, 1 patient with missing primary endpoint and 2 patients without IRS (per-protocol analysis), BC occurred in 19 patients in the IRS group (18.4%) and 23 (19.7%) in the control group. Similar results were found in *post hoc* sensitivity analyses accounting for site effects.

In patients alive without graft loss or with BC before graft loss or before death, there was no significant predictive factor for BC in multivariate exploratory analysis (Table 3).

Secondary outcome
Complications related to IRS are displayed in Table 2. IRS migration occurred in 24 patients (20.5%), cholangitis in 1 (0.9%), severe acute pancreatitis in 2 (1.8%), and extraction difficulties during ERCP in 19 (19.4%). Concomitant IRS-related complications and BC occurred in 11 (9.6%), including 9 (7.8%) associated migration and BC.

The only case of cholangitis occurred immediately after ERCP and was resolutive within 24 h. The 2 cases of severe acute pancreatitis occurred within 24 h after ERCP.

Extraction difficulties were related to complex catheterism in 15 cases (79%) and difficulty for IRS extraction in itself in 4 cases (21%). Difficulty for IRS extraction was responsible for redo-ERCP for extraction in 2 (1.7%) cases.

Table 1. Baseline characteristics of the randomised population.

Variable	All patients N = 235		IRS n = 117		Control n = 118	
Recipient characteristics	n[a]		n[a]		n[a]	
Age at LT (years)	235	59.9 [53.5–64.5] (21.1–71.6)	117	59.8 [54.4–63.4] (21.1–71.2)	118	60.6 [53.2–65.4] (27.5–71.6)
Sex	235		117		118	
Male		190 (80.9)		90 (76.9)		100 (84.7)
Female		45 (19.1)		27 (23.1)		18 (15.3)
BMI (kg/m²)	233	26.9 ± 4.6 (16.6–40.7)	117	27.3 ± 4.5 (18.7–40.7)	116	26.5 ± 4.6 (16.6–40.7)
ASA score	176		89		87	
1		34 (19.3)		17 (19.1)		17 (19.5)
2		85 (48.3)		48 (53.9)		37 (42.5)
3		53 (30.1)		23 (25.8)		30 (34.5)
4		4 (2.3)		1 (1.1)		3 (3.4)
Cardiovascular history	235	113 (48.1)	117	56 (47.9)	118	57 (48.3)
Atheromatous lesions	235	37 (15.7)	117	21 (17.9)	118	16 (13.6)
High blood pressure	235	85 (36.2)	117	41 (35.0)	118	44 (37.3)
Diabetes	235	87 (37.0)	117	40 (34.2)	118	47 (39.8)
CMV positive status	235	134 (57.0)	117	65 (55.6)	118	69 (58.5)
Indication for LT						
Alcohol abuse	235	148 (63.0)	117	69 (59.0)	118	79 (66.9)
NASH	235	55 (23.4)	117	27 (23.1)	118	28 (23.7)
Hepatitis B infection	235	16 (6.8)	117	10 (8.5)	118	6 (5.1)
Hepatitis C infection	235	39 (16.6)	117	18 (15.4)	118	21 (17.8)
Hemochromatosis	235	10 (4.3)	117	3 (2.6)	118	7 (5.9)
Primary sclerosing cholangitis	235	2 (1.7)	117	2 (1.7)	118	4 (3.4)
Primary biliary cirrhosis	235	4 (1.7)	117	2 (1.7)	118	2 (1.7)
Secondary biliary cirrhosis	235	1 (0.4)	117	0 (0)	118	1 (0.4)
Metabolic other than NASH	235	10 (4.3)	117	6 (5.1)	118	4 (3.4)
Other indication for LT	235	23 (9.8)	117	12 (10.2)	118	11 (9.3)
Hepatocellular carcinoma	235	136 (57.9)	117	67 (57.3)	118	69 (58.5)
Portal thrombosis	235	7 (2.9)	117	2 (1.7)	118	5 (4.2)
Donor characteristics						
Donor age	234	56.7 ± 18.5 (16.0–95.0)	117	55.2 ± 19.2 (16.0–88.0)	117	58.1 ± 17.8 (16.0–95.0)
Donor sex	234		117		117	
Male		140 (59.8)		74 (63.2)		66 (56.4)
Female		94 (40.2)		43 (36.8)		51 (43.6)
CMV status positive	234	114 (48.7)	117	53 (45.3)	117	61 (52.1)
Death cause	234		117		117	
Traumatic		50 (21.4)		26 (22.2)		24 (20.5)
Vascular		133 (56.8)		66 (56.4)		67 (57.3)
Other		51 (21.8)		25 (21.4)		26 (22.2)
Graft characteristics						
Cold ischaemia time (min)	234	431.8 ± 116.5 (210.0–899.0)	116	432.8 ± 116.8 (210.0–899.0)	118	430.9 ± 116.7 (212.0–782.0)
% steatosis	89	10.0 [5.0–30.0] (1.0–90.0)	44	10.0 [5.0–20.0] (1.0–70.0)	45	10.0 [5.0–30.0] (1.0–90.0)
Preservation solution	223		113		110	
IGL-1®		115 (51.6)		58 (51.3)		57 (51.8)
Celsior®		7 (3.1)		4 (3.5)		3 (2.7)
Custodiol®		37 (16.6)		18 (15.9)		19 (17.3)
Scott®		40 (17.9)		21 (18.6)		19 (17.3)
UW		24 (10.8)		12 (10.6)		12 (10.9)
LT intraoperative parameters						
Arterial warm ischaemia time (min)	219	43.0 [35.0–54.0] (1.0–550.0)	110	44.0 [36.0–55.0] (1.0–550.0)	109	40.0 [35.0–50.0] (1.0–145.0)
Multiple arteries	229	29 (12.7)	115	14 (12.2)	114	15 (13.2)
Arterial anastomosis technically difficult	96	7 (7.3)	48	3 (6.3)	48	4 (8.3)
Graft bile duct diameter (mm)	191	6.4 ± 1.7 (4.0–12.0)	89	6.5 ± 1.6 (4.0–12.0)	102	6.4 ± 1.7 (4.0–12.0)
Recipient bile duct diameter (mm)	190	6.8 ± 2.5 (2.0–20.0)	88	7.0 ± 2.7 (2.0–20.0)	102	6.7 ± 2.3 (3.0–16.0)
Biliary reconstruction under magnifying glasses	101	77 (76.2)	47	34 (72.3)	54	43 (79.6)
Anastomosis type	151		71		80	
Hepatico-choledocal		30 (19.9)		11 (15.5)		19 (23.8)
Choledoco-choledocal		121 (80.1)		60 (84.5)		61 (76.3)

(continued on next page)

Table 1 (continued)

Variable	All patients N = 235		IRS n = 117		Control n = 118	
Recipient characteristics	n[a]		n[a]		n[a]	
Suture type:	202		100		102	
Separate stitches		59 (29.2)		32 (32.0)		27 (26.5)
Mixed		79 (39.1)		37 (37.0)		42 (41.2)
Running suture		64 (31.7)		31 (31.0)		33 (32.4)
Thread size	191		91		100	
4/0		1 (0.5)		0 (0)		1 (1.0)
5/0		26 (13.6)		9 (9.9)		17 (17.0)
6/0		155 (81.2)		77 (84.6)		78 (78.0)
7/0		7 (3.7)		3 (3.3)		4 (4.0)
8/0		2 (1.0)		2 (2.2)		0 (0)
Operative time (min)	227	392.7 ± 87.2 (198.0–722.0)	113	393.3 ± 73.1 (247.0–600.0)	114	392.1 ± 99.5 (198.0–722.0)
Blood loss (ml)	144	1,000.0 [600.0–1,600.0] (0.0–7,000.0)	70	1,000.0 [700.0–1,600.0] (0.0–7,000.0)	74	975.0 [500.0–1,600.0] (100.0–6,900.0)
Red packed cells transfusion	235	153 (65.1)	117	75 (64.1)	118	78 (66.1)
Reperfusion syndrome	96	56 (58.3)	48	29 (60.4)	48	27 (56.3)
Per-LT haemorrhagic shock	96	16 (16.7)	48	7 (14.6)	48	9 (18.8)
Abdominal drainage	211	183 (86.7)	103	92 (89.3)	108	91 (84.3)

Continuous data presented as mean ± SD or median (IQR).
ASA, American Society of Anesthesiologists; CMV, cytomegalovirus; IRS, intraductal removable stent; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; P, percentile.
[a] Number of available data. Categorical data presented as n (%).

Early allograft dysfunction, according to the criteria by Olthoff *et al.*,[28] occurred in 9 (7.7%) cases, including 2 in the IRS group. Arterial complications occurred in 11 (9.4%) in the IRS group and 9 (7.7%) in the control group, including 5 (4.3%) and 2 (1.7%) thrombosis and 8 (6.8%) and 6 (5.1%) stenosis in the IRS and control groups, respectively.

Overall survival, graft survival, and ABC-free survival
Overall survival probability at 6 months post LT was 94.0% (95% CI 87.7–97.1) and 95.8% (95% CI 90.1–98.2) in the IRS and control groups, respectively (*p* = 0.54) (Fig. 3).

Graft survival probability at 6 months post LT was 98.3% (95% CI 93.2–99.6) and 99.2% (95% CI 94.1–99.9) in the IRS and control groups, respectively (*p* = 0.55).

ABC-free survival probability at 6 months post LT was 74.2% (95% CI 64.7–81.6) and 77.9% (95% CI 68.7–84.7) in the IRS and control groups, respectively (*p* = 0.45). There was no significant predictive factor for ABC-free survival in the multivariate Cox model (Table 4). Median times of follow-up were 6.1 [5.9–6.5] months for overall survival and graft survival and 6.0 [5.4–6.3] months for ABC-free survival.

Discussion
In this large randomised controlled trial that included 235 patients, the placement of an IRS during biliary reconstruction did not reduce BC after LT. This is the first randomised trial that evaluated the potential protective effect of an internal stent on BC occurrence. Despite decades of experience, this trial confirms that the post-LT BC rate remains high, and the use of an IRS could not modify this rate. Although no failure to remove the IRS occurred, the difficulty to remove the drain (19.4%) highlights the need for specific endoscopic expertise at the time of IRS removal.

A first and unexpected finding of this study was the spontaneous migration rate of the IRS. Consequently, the high proportion of IRS migration (n = 24, 20.5%) may have changed the ability to prevent strictures and leaks in the IRS group. This is why we also performed a per-protocol analysis on BC excluding patients with IRS migration that did not show a difference in favour of IRS.

The 2 main complications associated with biliary reconstruction, that is, anastomotic stricture and internal leakage, were found to be independent of the presence of an IRS in the current study. The 23.4% overall rate of BC, including 31 (13.2%) biliary strictures and 15 (6.4%) biliary fistulae, follow those reported in previous studies assessing an external T-tube in the prevention of BC. Although still debated, no clear preventive effect of an external T-tube on BC has ever been demonstrated so far.[12–15,17] Three randomised trials[13–15] did not find any difference in BC with or without the T-tube, and 1 meta-analysis concludes with 'no clear evidence' regarding its use.[29] Two other randomised studies found decreased BC in patients with a T-tube,[8,16] but a similar stricture rate was found in 1 study[16] and a higher biliary stricture rate in another, relying exclusively on imaging – and not clinics or biology – for diagnosis.[8] In contrast, the IRS was designed to be left in place much longer than an external T-tube (4 to 6 months vs. 6 weeks) and therefore to really act as a stake during most of the healing phase. Thus, several reasons can explain the current results. First, we chose to include only patients with at least 1 of the 2 biliary stumps ≤7 mm in diameter, a small diameter being previously reported as a risk factor for BC. A cut-off of 7 mm was chosen according to previous reports including similar patients (LT from whole organs), so the number of expected BC would be higher than that in the general LT population. To homogenise the technique among the 7 LT centres, a short movie was published online (Supplementary information). However, technical bias related to the 'customised' aspect of the technique, and to the subjectivity of each surgeon's interpretation, may persist.

For logistics and feasibility purposes, we did not impose the IRS material (rubber or latex) to the different LT centres. The diameter was not imposed either so that the surgeons would

Table 2. Post-LT outcome of 235 patients included according to their randomisation group (IRS, n = 117 *vs*. control, n = 118).

Variable	IRS n = 117		Control n = 118		Difference [95% CI]
	n[a]	n (%)	n[a]	n (%)	
Primary outcome: BC	117	31 (26.5)[b]	118	24 (20.3)[b]	6.2 [-4.9 to17.1]
Biliary fistula	116	9 (7.8)	117	6 (5.1)	2.6 [-4.3 to 9.7]
Biliary stenosis	116	16 (13.8)	117	15 (12.8)	1.0 [-8.1 to 10.2]
Secondary outcome: post-LT complications					
Death	117	7 (6.0)	118	5 (4.2)	1.7 [-4.4 to 8.3]
Early allograft dysfunction	59	2 (3.4)	58	7 (12.1)	-8.7 [-20.3 to -1.3]
Graft loss	116	1 (0.9)	117	0 (0)	0.9 [-2.5 to 4.8]
Retransplantation	117	2 (1.7)	118	1 (0.8)	0.9 [-3.2 to 5.3]
Haemorrhage	116	15 (12.9)	118	6 (5.1)	7.8 [0.3 to 15.9]
Intra-abdominal collection	116	18 (15.5)	117	26 (22.2)	-6.7 [-17.0 to 3.5]
Arterial stenosis	117	8 (6.8)	117	6 (5.1)	1.7 [-4.9 to 8.6]
Arterial thrombosis	117	5 (4.3)	117	2 (1.7)	2.6 [-2.3 to 8.2]
Portal complications	116	7 (6.0)	117	7 (6.0)	0.1 [-6.8 to 6.8]
Caval complications	116	4 (3.4)	118	4 (3.4)	0.1 [-5.6 to 5.6]
Wound complications	116	14 (12.1)	118	28 (23.7)	-11.7 [-21.6 to -1.4]
Other abdominal complication	116	29 (25.0)	117	16 (13.7)	11.3 [0.9 to 21.7]
Ileus		7 (6.0)		4 (3.4)	2.6 [-3.4 to 9.1]
Other		22 (19.0)		12 (10.3)	8.7 [-0.5 to 18.2]
Infectious complication	116	52 (44.8)	118	53 (44.9)	-0.1 [-13.1 to 12.8]
Cholangitis	116	4 (3.4)	117	5 (4.3)	-0.8 [-6.8 to 5.0]
Toxic/drug-related complication	116	30 (25.9)	118	32 (27.1)	-1.3 [-12.7 to 10.2]
Rejection	116	8 (6.9)	118	8 (6.8)	0.1 [-7.0 to 7.3]
CMV reactivation	116	14 (12.1)	118	12 (10.2)	1.9 [-6.5 to 10.6]
HCV reactivation	116	2 (1.7)	118	0 (0)	1.7 [-1.5 to 6.2]
Secondary outcome: complications related to IRS		n % [95% CI]			
Infectious cholangitis	113	1 0.9 [0.0–4.8]	–		
Extraction difficulties	98	19 19.4 [12.1–28.6]	–		
ERCP-related haemorrhage	104	5 4.8 [1.6–10.9]	–		
ERCP-related duodenal perforation	109	1 0.9 [0.0–5.0]	–		
ERCP-related severe acute pancreatitis	109	2 1.8 [0.2–6.5]	–		
IRS spontaneous migration	117	24 20.5 [13.6–29.0]			
Association of BC and IRS-related complications	–	11 9.6 [4.9–16.5]			
Association of BC and migration		9 7.8 [3.6–14.3]			

BC, biliary complications; CMV, cytomegalovirus; ERCP, endoscopic retrograde cholangio-pancreatography; HCV, hepatitis C virus; IRS, intraductal removable stent; LT, liver transplantation.
[a] Number of available data.
[b] One missing piece of data was imputed by BC.

adapt it to the anastomosis. The tailored IRS material made from T-tubes would not have been a problem, as T-tubes are specific drains for bile duct drainage in the first place. However, despite the efforts for technique homogenisation through the online video, some surgeons may have placed a too-small-diameter IRS owing to local constraints (unavailable T-tube of adequate diameter and misevaluation). Unfortunately, this intraoperative information is usually unreported.

Moreover, the size discrepancy between the graft and the donor's bile duct was not specifically evaluated and may play a role in the development of a biliary stenosis or in the migration of the IRS. Second, although biliary strictures were defined as a composite criterion including radiologic features with clinical or biological impact, the realisation of a systematic magnetic resonance cholangiopancreatography at 6 months may have uncovered size discrepancies diagnosed and treated as stenosis even

though the diagnosis for biliary stricture in the protocol was composite in the first place (imaging and biology).

There was no prognostic factor identified for BC, and there was no impact of any technical aspect of biliary reconstruction, such as thread decimal or suture type. In addition, arterial complications or prolonged warm ischaemia time were not identified as prognostic factors for BC; however, the number of arterial thrombosis was relatively small (2.9%). These results suggest a greater influence of non-technical factors on BC. The choice of a 6-month endpoint for follow-up was made to detect most anastomotic strictures while keeping an acceptable timing for the study course. Of course, this design may miss late strictures, although rare.[10] However, in the IRS group, the follow-up after extraction (1 to 2 months) may be seen as too short, and longer follow-up may be required to draw definitive conclusions on the proportion of anastomosis strictures. Nevertheless, the

Table 3. Multivariate logistic regression on biliary complications.

Variable	n	Unadjusted analysis OR [95% CI]	p value	n	Full adjusted analysis OR (95% CI)	p value
IRS	181	1.67 [0.76–3.67]	0.20	181	1.81 [0.81–4.03]	0.15
Arterial complication (before biliary complications) (yes *vs.* no)	181	0.47 [0.06–3.84]	0.48			
Warm ischaemia time (≥30 *vs.* <30 min)	168	1.16 [0.24–5.60]	0.85			
Thread size (≥6/0 *vs.* <6/0)	181	0.50 [0.19–1.32]	0.16	181	0.45 [0.17–1.22]	0.11
Recipient bile duct diameter (mm)	151		0.74			
≤5		1				
[5–6]		1.44 [0.46–4.44]				
[6–7]		0.71 [0.18–2.82]				
>7		1.07 [0.31–3.73]				
Graft bile duct diameter (mm)	151		0.87			
≤5		1				
[5–6]		1.64 [0.47–5.78]				
[6–7]		1.26 [0.32–4.94]				
>7		1.60 [0.38–6.80]				

Analysis performed on patients alive without graft loss or with biliary complications before graft loss or before death.
IRS, intraductal removable stent; OR, odds ratio.

current results of the trial may suffice to draw conclusions on the use of an IRS.

Finally, the significant proportion of extraction difficulties encountered during ERCP (19.4% of patients in the IRS group) must be highlighted. These results are in contrast with those of our preliminary study where all of the 20 patients had undergone a successful IRS extraction.[24] However, in the preliminary study, all patients were referred to the same
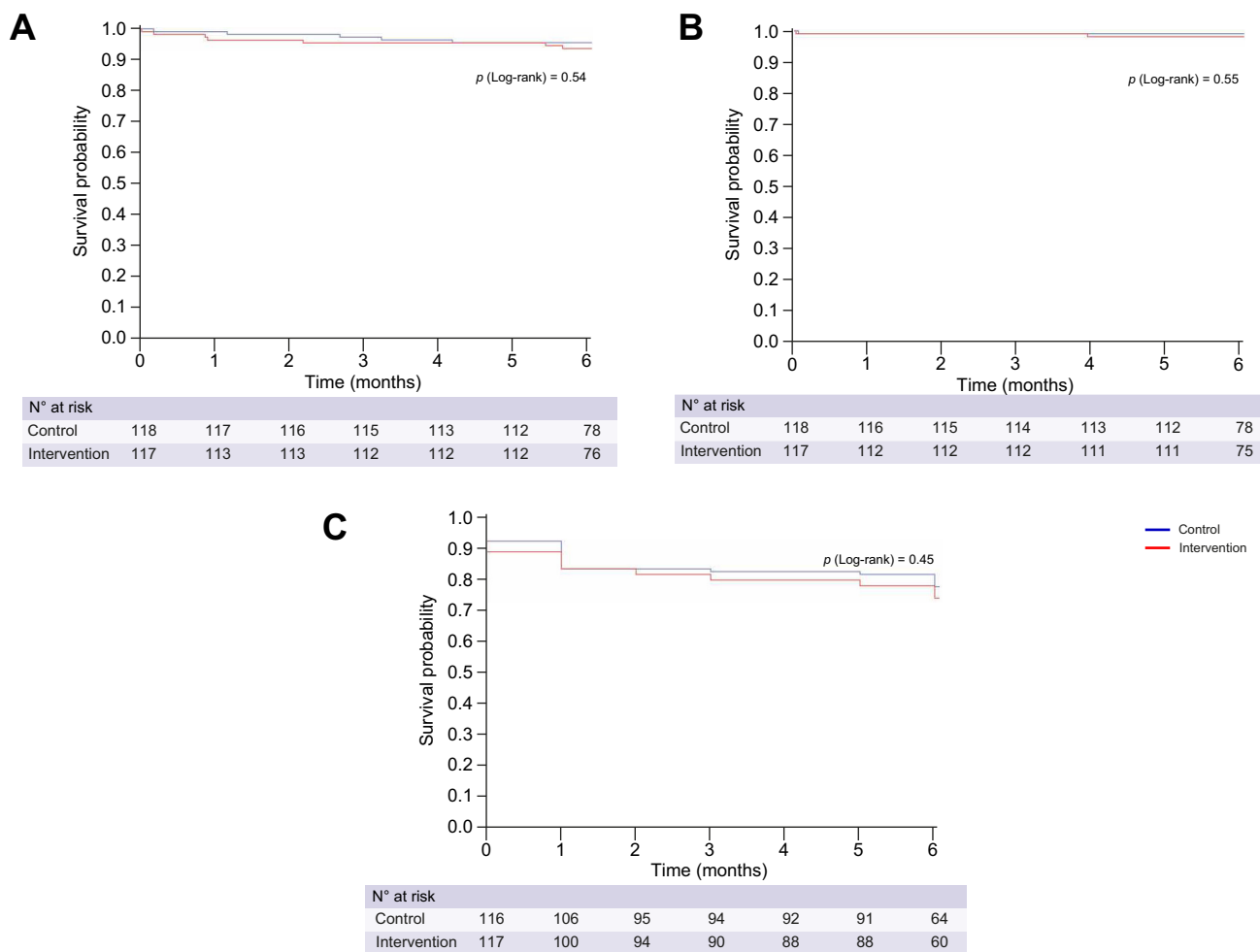

Fig. 3. Overall, graft and ABC-free survival in patients in the IRS *vs.* control groups. (A) Overall survival at 6 months post LT in the IRS and control groups. (B) Graft survival at 6 months post LT in the IRS and control groups. (C) ABC-free survival at 6 months post LT in the IRS and control groups. ABC, arterial and biliary complications; IRS, intraductal removable stent; LT, liver transplantation.

Table 4. Cox proportional hazards model on ABC-free survival.

Variable	Unadjusted analysis HR [95% CI]	p value
IRS	1.75 [0.91–3.36]	0.09
Warm ischaemia time ≥30 min	0.80 [0.24–2.69]	0.72
Reconstruction technique		0.35
Separate stiches	1.12 [0.44–2.86]	
Mixed	1.87 [0.73–4.80]	
Running suture	1	
Thread size (≥6/0)	0.62 [0.27–1.47]	0.28

Because there is no variable with a p value <0.2 in the univariate analysis, no adjusted analysis was performed.
ABC, arterial and biliary complications; HR, hazard ratio; IRS, intraductal removable stent.

endoscopist who had extensive experience in biliary manoeuvres in patients undergoing LT and who developed the technique with the surgical team. This multicentric trial included 7 centres, and therefore, the experience of the endoscopist could not be controlled. Moreover, the majority of ERCP-described difficulties were in fact related to catheterism (79%) and not IRS extraction in itself. Nevertheless, severe adverse events related to IRS extraction, such as severe acute pancreatitis, haemorrhage, or perforation, were rarely encountered (n = 2 [1.8%], n = 5 [4.8%], and n = 1 [0.9%], respectively), and their proportion was comparable with the one seen in the literature.

There are several limitations to this study. Despite the prospective randomised design, surgical practice, and intraoperative choices such as IRS placement or tube diameter remain up to the surgeon at the moment of LT, even though a movie was broadcasted to homogenise the technique. Moreover, the size discrepancy between graft and donor's bile duct was not specifically evaluated and may play a role in the development of a biliary stenosis or in the migration of the IRS. Last, the quite rare number of events limited the number of variables included into the predictive model.

One way to overcome extraction-related complications would be to use biodegradable stents, which are currently under investigation with potentially promising *in vitro* results.[30,31] However, some uncertainties remain regarding potential residual material derived from the degradation process within the bile duct and the optimal duration of stenting. In addition, the possibility of 'salvage' extraction in case of complication would have to be anticipated.

In conclusion, the use of an IRS in case of a small bile duct diameter (≤7 mm) was not associated with a reduction of BC at 6 months post LT, and technical ways to overcome the so-called 'Achille's heel of LT' remain to be found.

Abbreviations
ABC, arterial and biliary complications; BC, biliary complications; CMV, cytomegalovirus; DMC, data monitoring committee; ERCP, endoscopic retrograde cholangio-pancreatography; HCC, hepatocellular carcinoma; HR, hazard ratio; IRS, intraductal removable stent; LT, liver transplantation; MRC, magnetic resonance cholangiography; OR, odds ratio.

Conflicts of interest
The authors have declared no conflicts of interest in relation to this study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Scientific coordinator of the trial, conducted data analysis, and wrote the manuscript: CG. Co-investigators and substantially contributed to data acquisition and analysis: EB, RB, FD, AH, ML, LB, KL, OSo, HB, JYM, ES. Performed statistical analysis: MC.
Contributed substantially to the trial methodology: TS. Principal investigator of the trial: OSc. Critically reviewed the manuscript: MC, TS, OSc.

Data availability statement
The data associated with this paper are available upon request to the corresponding author.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2022.100530 and https://youtu.be/BY29ybb-01M.

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