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Right Ex Situ Split Grafts for Adult Liver Transplantation
A Multicenter Benchmarking Analysis

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Objective: To analyze outcomes after adult right ex situ split graft liver transplantations and compare with available outcome benchmarks from whole liver transplantation (WLT).

Background: Ex-situ split liver transplantation (SLT) may be a valuable strategy to tackle the increasing graft shortage. Recently established outcome benchmarks in WLT offer a novel reference to perform a comprehensive analysis of results after ex situ right split liver transplantation.

Methods: This retrospective multicenter cohort study analyzes all consecutive adult SLT performed using right ex situ split grafts from January 1, 2014, to June 1, 2022. Study endpoints included 1-year graft and recipient survival, overall morbidity expressed by the comprehensive complication index (CCI), and specific post-LT complications. Results were compared with the published benchmark outcomes in low-risk adult WLT scenarii.

Results: In 224 adult right ex-situ SLT, the 1-year recipient and graft survival rates were 96% and 91.5%, within the WLT benchmarks. The 1-year overall morbidity was also within the WLT benchmark (41.8 CCI points vs <42.1). Detailed analysis revealed cut surface bile leaks (17%, 65.8% grade IIIa) as a specific complication without a negative impact on graft survival. There was a higher rate of early hepatic artery thrombosis after SLT, above the WLT benchmark (4.9% vs $\leq 4.1\%$), with a significant impact on early graft but not patient survival.

Conclusions: In this multicentric study of right ex situ split graft LT, we report 1-year overall morbidity and mortality rates within the published benchmarks for low-risk WLT. Cut surface bile leaks and early hepatic artery thrombosis are specific complications of SLT and should be acknowledged when expanding the use of ex situ SLT.

Keywords: liver transplantation, partial grafts, benchmarks, ex situ split, extended right graft, full right graft

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Split liver transplantation (SLT) has been shown to provide a survival benefit for both pediatric and adult recipients.[1] Despite this fact, SLT still remains a rarely performed procedure, accounting for only 3.3% of all adult liver transplantation from 2001 to 2016 in the European Liver Transplant Registry.[2] A possible but more rarely performed approach to SLT is the in situ graft splitting. On one hand, this technique allows for short static cold ischemia time and optimal hemostasis of the transection plane but on the other hand it is a more challenging procedure from a logistical point of view.[3] A valuable alternative may be ex situ graft splitting, which has the logistical advantage of being performed at the transplant center after standard procurement and graft transport. However, comprehensive outcome data on adult ex situ SLT from large multicenter studies are currently lacking.

Thus, this study will aim to provide outcomes from a recent multicenter cohort of right ex situ SLT (RSLT). To propose a comprehensive outcome assessment and identify specific areas of improvement, we will compare outcomes after ex situ right SLT to the recently published benchmark results established in an international cohort of low-risk whole liver transplantations (WLT).[4]

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METHODS

Study Design and Population

We retrospectively analyzed all consecutive adult recipients undergoing liver transplantation with right ex situ split grafts in 4 high-volume French liver transplant centers (>70 adult liver transplantations per year) over a recent 8-year study period (January 1, 2014 to June 1, 2022). All split procedures were performed ex situ using grafts from donation after brain death (DBD). Exclusion criteria were in situ split grafts, combined transplantations, living donor grafts, and full left split grafts. Of note, DCD grafts are not allowed for split procedures in France. The study was approved by the institutional ethics committee (CNIL Number 22-5124).

Study Aims

The study had 2 main aims. First, we performed an analysis of donor and recipient characteristics as well as technical features of the right split grafts. Second, we performed a benchmarking analysis of the results obtained in the RSLT cohort. A benchmarking analysis consists in comparing outcomes obtained with a novel or alternative procedure to the best achievable outcomes with the standard procedure.[5] In the present paper, we compared the 1-year outcomes from the RSLT cohort to the previously published benchmark outcomes established in a cohort of low Model of End-Stage Liver Disease (MELD) (MELD ≤ 20) recipients with a low-risk donor–recipient matching (balance of risk score ≤9) undergoing WLT in 17 international centers.[4] Specific benchmark cutoffs for individual outcome indicatorswere defined as the 75th percentile of themedian values across all centers.

Study End Points and Definitions

Study end points included graft and recipient survival as well as 1-year overall morbidity based on the *Comprehensive Complication Index* (CCI), with a specific focus on biliary and arterial complications.[6] The CCI is a scoring system, which adds up every postoperative complications graded according to the Clavien-Dindo (CD) classification for a given patient.[7] The score is expressed on a scale from 0 to 100 points and with increasing score points, there is an increase in overall patient morbidity. Thus, the CCI allows comparing overall morbidity for individual patients as well asthe entire patient cohort.

The New World Terminology was used to describe the different graft types: G45678 was used for "Extended Right Graft" and G5678 was used for "Full Right Graft".[8]

Biliary complications were defined as bile leakage and intrahepatic and extrahepatic strictures requiring antibiotic therapy, delayed T-tube ablation, or endoscopic/surgical treatment (CD grade ≥II). Of note, cut surface leaks were also included as biliary complications, given the frequent presence of bile in cut surface leaks CD grade ≥II.

Vascular complications were defined as complications of the hepatic vein, portal vein, or hepatic artery requiring anticoagulation therapy, invasive treatment such as endovascular stenting, or surgical repair (CD grade ≥III). Hepatic artery thrombosis (HAT) was defined as either early HAT occurring during the first 30 post-LT days or late HAT occurring after the first 30 post-LT days.

We also performed a detailed analysis of anatomic and technical features of the right split grafts, including hepatic vein anatomy and arterial anastomotic site. We defined 2 distinct arterial anastomotic sites of the split graft. First, the presence of a single arterial branch for anastomosis in the case of a right branch of the hepatic artery (RBHA) or an anterior/posterior sectoral branch. Second, the presence of the entire arterial axis for anastomosis in case of a proper hepatic artery (PHA), common hepatic artery (CHA), gastroduodenal artery (GDA), celia trunk (CT), superior mesenteric artery (SMA), right hepatic artery, middle hepatic artery, or splenic artery. A detailed description of all the different types of arterial anastomosis can be found in Supplementary Material (Table S1, Supplemental Digital Content 1, http://links.lww.com/SLA/F163).

Small-for-size syndrome was defined according to Dahm et al[9] Briefly, this definition includes the presence of ≥2 of the following criteria:

- Graft-recipient weight ratio (GRWR) <0.8%
- Total serum bilirubin >100 μmol/L for at least 3 days within the first 7 post-LT days
- Encephalopathy grade III or IV for at least 3 days within the first 7 post-LT days, and international normalized ratio (INR) >2 for at least 3 days within the first 7 post-LT days

Primary nonfunction (PNF) was defined as an irreversible graft failure within the first 7 post-LT daysin the abscence of technical or immunologic causes.[10]

National Split Liver Graft Allocation Policy

In France, deceased donor matching and graft allocation are performed with a priority for pediatric recipients. Consequently, donor selection for SLT is performed by the pediatric team with a national prioritization of the left partial graft for a pediatric recipient. The contralateral right partial graft is allocated to a local adult LT in close proximity to the pediatric LT center. The adult LT center may freely choose the adult recipient based on morphologic characteristics and local priority with the aim of achieving the best possible donor–recipient matching and short static cold storage (SCS) duration.[11] The ex situ split procedure is performed by either the adult or pediatric LT surgical team depending on logistical requirements. Of note, in France the vast majority of split procedures are performed ex situ in contrast to other European countries, for example, Italy.[12] The ex situ splitting technique used was at the discretion of the surgeon and none of the centers used the CUSA for parenchymal transection.

Statistical Analysis

Categorical variables are expressed in quantities and percentages and continuous variables are expressed as median with interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test. *P* values <0.05 were considered statistically significant. Survival rates were estimated using Kaplan–Meier methods, with comparisons between groups performed using log-rank tests. Univariable analysis was performed, including relevant factors for graft loss, related to recipients and donor's baseline characteristics. Variables with *P* values <0.20 in the univariable analysis were used in the multivariable analysis. Multivariable analysis was performed using binary logistic regression for thrombosis and Cox regression for survival analysis. We performed univariate and multivariate analysis using R Studio 2023.03.0+386 and Statistical Package for the Social Sciences (SPSS version 29.0.10). Tables and figures were

designed with R studio 2023.03.0+386 and Graphpad Software 9.5.1.

RESULTS

A total of 224 adult right ex situ SLT consisting of 169 (75.4%) G45678 and 55 (24.5%) G5678 grafts were included in the study (Table 1). The median follow-up was 3.3 years (IQR: 1.9–5.4) (Table 3).

Donor–Recipient Matching

Donor and Graft Characteristics

The median donor age was 26 years, and donors had a median body mass index of 22.7 kg/m^2. The most common cause of donor death was trauma (n = 115, 52%). Overall, the majority of donors were within the official European and international selection criteria for split grafts, as listed in Supplementary Material (Table S2, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). Detailed donor characteristics are shown in Table 1. Anatomic analysis of the right split grafts showed that 63 grafts (28.1%) were procured with the entire arterial axis (Table 2). In the case of G5678, 47 grafts (85%) were procured with the inferior vena cava (IVC) and 41 (74.5%) with the middle hepatic vein. Of note, a total of 8 G5678 split grafts were transplanted without an IVC and represent a specific type of right-side grafts in terms of outflow. A detailed analysis of this subgroup can be found in Supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/SLA/F163.

Recipient Characteristics and Matching

Recipients had a median MELD score of 13, with a majority of recipients transplanted for malignancy (n = 98, 44%). Recipient risk factors such as retransplantation, intubation, or dialysis were present in < 2%, and portal vein thrombosis was seen in 25 recipients (11%). Detailed recipient characteristics are shown in Table 1.

Donor–recipient matching resulted in a median GRWR of 1.6 (IQR: 1.3–1.88) and a median balance of risk score (BAR) of 4 (IQR: 2–7). Of note, there were no statistically significant differences in graft or recipient characteristics between G5678 and G45678 SLT. Median cold ischemia time was 10 hours (IQR: 9–11.4), with no statistically significant differences between G5678 and G45678 (Table 1).

Benchmarking Analysis

Overall Morbi-Mortality

The overall 1- and 3-year recipient and graft survival rates were 96%, 92.9%, 91.5%, and 88%, respectively (Fig. 1), which are within the benchmark survival cutoffs observed in low-risk WLT scenarios. There were no statistically significant differences in 1-year graft and recipient survival rates between G45678 and G5678 (90.5% vs 94.5%, $P = 0.37$ and 94.7% vs 100%, $P = 0.41$) (Fig. 1). As a comparison, 1-year recipient and graft survival rates of primary whole DBD LTs (n = 3037) in the 4 centers during the study period were 88,1% and 85,7%, respectively (Supplementary Figure S1, Supplemental Digital Content 1, http://links.lww.com/SLA/F163, S2, Supplemental Digital Content 1, http://links.lww.com/SLA/F163)

The overall median 1-year post-SLT CCI was 41.8 points, which was within the WLT benchmark cutoff set at ≤ 42.1 points. There were no statistically significant differences in CCI scores between G45678 and G5678 (40 vs 42 points, $P = 0.60$, Table 3). Of note, only 1 patient (0.4%) developed a small-for-size syndrome with a favorable outcome after medical treatment.

Biliary Complications

Biliary complications occurred in 68 recipients (30%), which was above the established WLT Benchmark cutoff (≤ 28%). A total of 32 recipients (14%) presented with biliary anastomotic stenosis, and 3 recipients (1.3%) developed a nonanastomotic stricture for which 1 required a retransplantation on post-LT day 112. Thirty-eight recipients (17%) had a cut surface leak graded as CD IIIa in 65.8% (n = 25) and CD IIIb in 23.7% (n = 9), and no graft loss occurred (Table 3). Detailed treatment modalities of biliary complications are presented in Supplementary Table S4, Supplemental Digital Content 1, http://links.lww.com/SLA/F163.

Arterial Complications

Overall, 36 recipients (16%) presented at least 1 arterial complication (Table 3). The only technical risk factor for an arterial complication on multivariable analysis was an anastomosis on the entire arterial axis of the liver graft (Table S5, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). In detail, 22 (9.8%) recipients had hepatic artery stenosis, and 15 (6.7%) recipients had an HAT. The overall HAT rate of6.7% was above the WLT benchmark cutoff of 4.4%. (Table 3). In detail, early HAT occurred in 11 recipients (4.9%) andlate HAT occurred in 4 (1.8%) recipients and was secondary to a radiologic stenting of a hepatic artery stenosis in 3 out of 4 cases. No graft loss occurred in recipients with a late HAT. Arterial stenosis occurred in 22 (9.8%) recipients, who all underwent treatment using radiologic stenting, and no graft loss occurred. Of note, there was no significant difference in overall arterial complications and early HAT between G5678 and G45678. (Table 3)

Risk Factors for Graft Loss

One-year graft loss occurred in 19 recipients (8.5%) (Table S6, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). In multivariable analysis, the only risk factor for graft loss was early HAT (HR: 11.06, CI: 3.803–32.195 $P < 0{,}001$, Table 4). Eight out of 11 patients with an early HAT needed an early retransplantation (73% retransplantation rate). Among those 8 re-LT recipients, 75% (6/8 recipients) are alive to date with a functioning graft. Furthermore, there were no other significant donor or anatomic risk factors associated with early HAT in univariable analysis (Table 4 and Table S7, Supplemental Digital Content 1, http://links.lww.com/SLA/F163)

DISCUSSION

In this large multicenter study on ex situ RSLT for adult recipients, we show 1-year recipient and graft survival rates > 90%, within the established benchmarks for low-risk WLT cases. Overall post-SLT morbidity was within the published benchmark cutoffs (CCI 41.8 vs < 42.1), but we observed a higher rate of biliary (30%) and arterial (16%) complications. We identified cut-surface leaks and early HAT as the main additional morbidity burden in ex situ SLT in comparison to low-risk WLT cases. While cut-surface leaks were mainly graded CD IIIa, early HAT was the only risk factor for early graft loss and was associated

TABLE 1. Donor and Recipient Characteristics

	Overall n = 224	G45678 n = 169	G5678 n = 55	*P*
Donor characteristics				
Sex				0.20
Female	94 (42)	76 (45)	18 (33)	
Age (y)	26 (20–41)	25 (20–41)	27 (21–44)	0.11
BMI (kg/m^2)	22.7 (20.2–24.8)	22.9 (20.4–24.7)	21.6 (20.1–25.4)	0.90
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
ICU stay (d)	2 (1–4)	2 (1–4)	2 (1–3.5)	0.70
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Cause of death				0.20
Trauma	115 (51.4)	83 (49.1)	32 (58.2)	
Cerebrovascular accident	80 (35.7)	66 (39)	14 (25.4)	
Hypoxic brain injury	25 (11.2)	16 (9.5)	9 (16.4)	
Other	3 (1.3)	3 (1.8)	0 (0)	
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Cardiac arrest	58 (26%)	44 (26%)	14 (25%)	> 0.90
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
AST max (IU/L)	67 (44–112)	64 (40–100)	73 (53–120)	0.04
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
ALT max (IU/L)	38 (23–67)	36 (23–61)	48 (29–99)	0.03
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
GGT max (IU/L)	25 (17–42)	24 (16–40)	29 (20, 57)	0.08
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Norepinephrine > 1µg/kg/min	20 (8.9)	10 (5.9)	10 (18.2)	0.01
Missing data	*6 (2.7)*	*4 (2.4)*	*2 (3.6)*	
Recipient characteristics				
Sex				> 0.90
Female	109 (49)	82 (49)	27 (49)	
Age (y)	58 (48, 63)	57 (50–63)	58 (45–64)	> 0.90
BMI (kg/m^2)	23 (20.8, 26.2)	23 (21.1-25.9)	23.2 (20.2-27.2)	0.60
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Prior major abdominal surgery	44 (20)	34 (20)	10 (19)	0.80
Missing data	*1 (0.4)*	*0 (0)*	*1 (1.8)*	
Indication for LT				0.40
Malignancy	98 (43.8)	79 (46.6)	19 (34.5)	
Alcohol	32 (14.3)	26 (15.4)	6 (11)	
Viral	26 (11.6)	18 (10.7)	8 (14.5)	
Primary sclerosing cirrhosis	18 (8)	14 (8.3)	4 (7.3)	
Autoimmune hepatitis	17 (7.6)	12 (7.1)	5 (9)	
NAFLD	7 (3.1)	5 (3)	2 (3.6)	
Secondary biliary sclerosis	7 (3.1)	3 (1.8)	4 (7.3)	
Acute liver failure	2 (0.9)	1 (0.6)	1 (1.8)	
Other	17 (7.6)	11 (6.5)	6 (11)	
Redo-LT	2 (0.9)	2 (1.2)	0 (0)	> 0.90
Lab MELD preop	13 (8-18)	13 (8-17)	15 (9-20)	0.30
Lab MELD > 25	22 (9.8)	19 (11)	3 (5.5)	0.20
Lab MELD > 35	5 (2.2)	4 (2.4)	1 (1.8)	> 0.90
Portal thrombosis	25 (11)	16 (9.5)	9 (16)	0.20
Pre LT intubation	2 (0.9)	1 (0.6)	1 (1.8)	0.40
Pre LT dialysis	3 (1.3)	2 (1.2)	1 (1.8)	0.60
Donor–recipient matching				
Recipient height (cm)	168 (162-174)	168 (162-174)	165 (160-173)	0.30
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Recipient weight (Kg)	65 (58–73)	65 (58–73)	65 (60–75)	> 0.90
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Donor height (cm)	173 (165–178)	172 (165–177)	175 (168–180)	0.09
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Donor weight (Kg)	68 (59-75)	66 (59-75)	69 (58-80)	0.40
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
GRWR	1.6 (1.3–1.88)	1.61 (1.33–1.86)	1.49 (1.18–1.93)	0.40
Missing data	*2 (0.9)*	*2 (1.2)*	*0 (0)*	
BAR score	4 (2–7)	4 (2–7)	4 (3–8.5)	0.20
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	
Cold ischemia time (h)	10.37 (9-11.4)	10.38 (9-11.4)	10.2 (8.9-11.4)	0.90
Missing data	*1 (0.4%)*	*1 (0.6%)*	*0 (0%)*	

Data are expressed as n (%) or median (IQR).

ALT indicates alanine transaminase; AST, aspartate transaminase; BAR, balance of risk; BMI, body mass index; GGT, gamma-glutamyl transpeptidase; ICU, intensive care unit; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease.

TABLE 2. Graft Characteristics and Perioperative Data

	Overall n = 224	G45678 n = 169	G5678 n = 55	*P*
Ex situ right graft				
Graft weight (g)	1040 (875–1216)	1040 (877–1202)	1000 (810–1236)	0.60
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	—
IVC				—
Graft with IVC	216 (96.4)	169 (100)	47 (85)	—
Graft without IVC	8 (3.6)	0 (0)	8 (15)	—
MHV	—	—	—	—
Graft with MHV	210 (93.8)	169 (100)	41 (74.5)	—
Graft with reconstructed MHV	11 (4.9)	—	11 (20)	—
Graft without MHV	3 (1.3)	—	3 (5.5)	—
Spiegel lobe	209 (93)	166 (98)	43 (78)	**< 0.001**
Artery	—	—	—	0.20
Main arterial axis available	63 (28.1)	51 (30.2)	12 (22)	—
RBHA	138 (61.6)	100 (59.2)	38 (69)	—
Missing data	*23 (10.3)*	*18 (10.6)*	*5 (9)*	—
RHA	29 (12.9)	20 (11.8)	9 (16.4)	0.40
Missing data	*15 (6.7)*	*12 (7.1)*	*3 (5.5)*	
PV	—	—	—	0.30
Main portal vein	220 (98.2)	167 (98.8)	53 (96.4)	—
Right branch of the portal vein	4 (1.8)	2 (1.2)	2 (3.6)	—
CBD	224 (100)	168 (100)	56 (100)	—
Per operative data				
Operation duration (min)	393 (340–480)	385 (335–469)	443 (372–509)	**0.003**
Missing data	*8 (3.6%)*	*5 (2.9%)*	*3 (5.5%)*	
Intraoperative blood transfusion (unit of RBC)	2 (0-4)	2 (0-4)	3 (0.3–5)	0.03
Missing data	*23 (10.3)*	*22 (13)*	*1 (1.8)*	—
Cold ischemia time (h)	10.37 (9–11.39)	10.38 (9–11.42)	10.17 (8.89–11.37)	0.90
Missing data	*1 (0.4)*	*1 (0.6)*	*0 (0)*	—
Graft arterial anastomosic site	—	—	—	0.20
Main arterial axis	63 (28.1)	51 (30.2)	12 (22)	—
RBHA	138 (61.6)	100 (59.2)	38 (69)	—
Missing data	*23 (10.3)*	*18 (10.6)*	*5 (9)*	—
PV anastomosis	—	—	—	0.30
Direct anastomosis	220 (98.2)	167 (98.8)	53 (96.4)	—
Iliac vein graft interposition	4 (1.8)	2 (1.2)	2 (3.6)	—
Biliary anastomosis	—	—	—	0.70
Duct to duct	214 (95.5)	162 (95.8)	52 (94.5)	—
Choledocojejunostomy	10 (4.5)	7 (4.2)	3 (5.5)	—
Anastomosis on a single duct	223 (99.5)	169 (100)	54 (98.2)	0.20

Data are expressed as n (%) or median (IQR).
CBD indicates common bile duct; PV, portal vein; RBC, red blood cells; RHA, right hepatic artery.

with a 73% retransplantation rate. We could not identify any significant donor, recipient, anatomic, or technical-related risk factors for early HAT in the presented cohort. Altogether, this study highlights that ex situ RSLT with an optimal graft-recipient matching and a median SCS duration of 10 hours allows for benchmark 1-year survival and morbidity rates.

Comparing outcomes in LT is challenging due to numerous confounding factors such as allocation policies, donor types, and transplant techniques. In this context the benchmark methodology, which aims at defining best achievable outcomes in optimal low-risk cases from multiple centers, has been proposed as a more comprehensive approach to outcome analysis.[13] The main strength of the benchmark methodology applied to LT is that it allows to take into account the complex donor–recipient matching to establish meaningful reference values for cumulative morbidity as well as for specific complications.[5,14] The present study uses the previously established benchmarks in WLT to perform a benchmarking analysis of the outcomes of the French national ex situ RSLT program.[4] In contrast to providing a matched case series with whole LT from the same centers, the benchmarking methodology allowed us to go beyond comparisons with the national average and present meaningful comparisons with a large data set of optimal LT cases from multiple international centers.[13]

First, we want to highlight that the French split policy allows for optimal donor–recipient matching with grafts from young donors (median 26 y) allocated to low MELD recipients with an optimal GRWR > 1% resulting in a median BAR score of 4 (low-risk). Consequently, 1-year graft and recipient survival were both > 90% and within the published benchmarks for whole LT. These survival rates are superior to the published figures from cohorts with a majority of ex situ SLT, ranging from 63.4% to 82% for graft survival and 76.3% to 87% for recipient survival[15–18] (Table S9, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). One potential explanation beyond the optimal matching is that right partial grafts in our study were always allocated to a local recipient close to or within the center performing the split procedure. This strategy allowed to keep SCS duration short and close to the recommended cutoff for split grafts.[3,19] This strategy is in stark contrast to Germany for example, where ex situ split

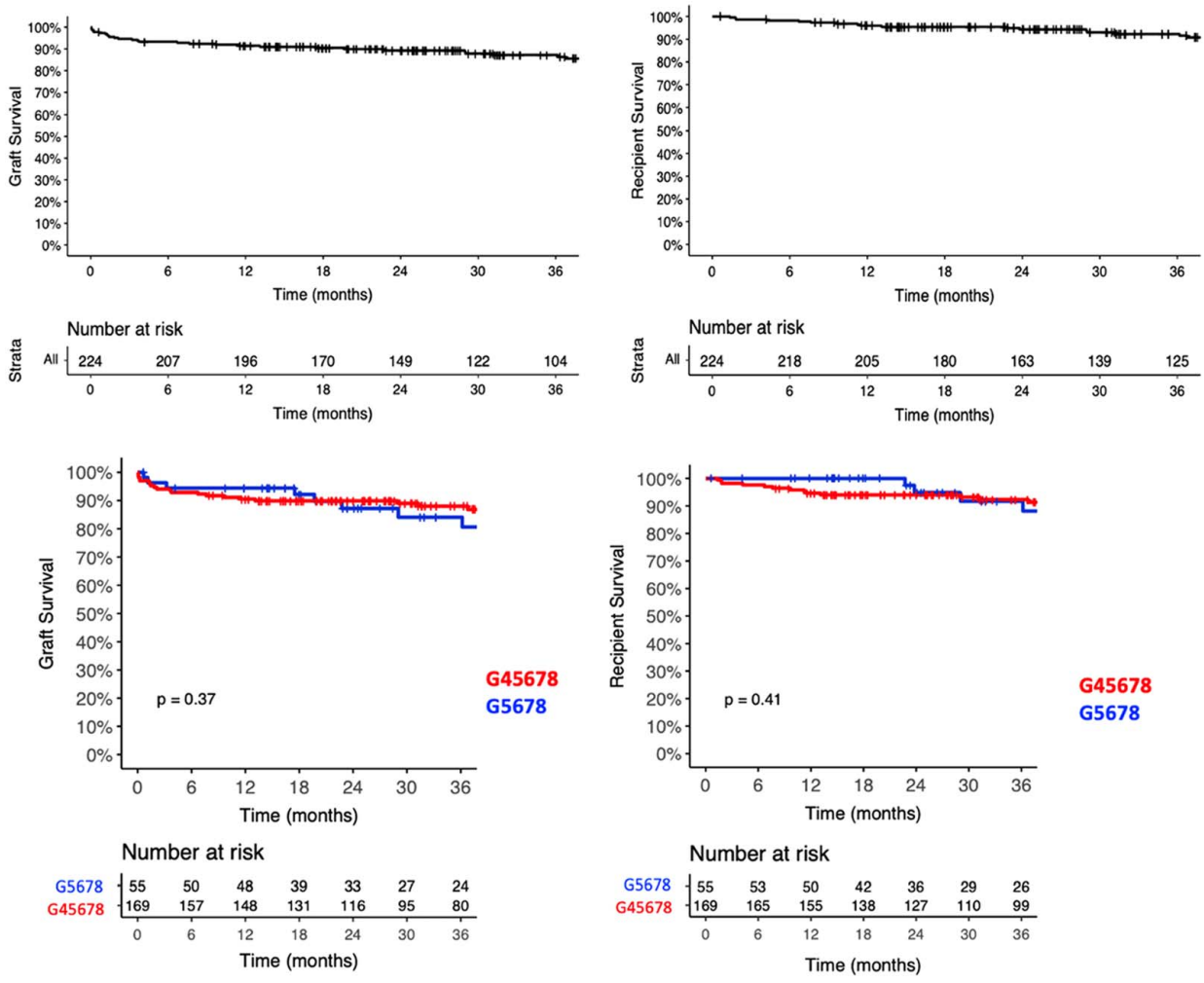

FIGURE 1. Overall and graft type specific recipient and graft survival rates.

grafts are now allocated nationwide based on the MELD score, which led to a significant increase in SCS duration.[20] In this context, the group from Hamburg has shown that SLT grafts with prolonged SCS (14 ± 2 h) had significantly impaired survival outcomes compared with grafts with shorter SCS (median 12 ± 2 h).[21]

Second, we found an overall post-SLT morbidity within the published WLT benchmarks. However, when looking at individual complications, we found a higher biliary and arterial complication rate compared with the benchmark cohort.

The higher rate of biliary complications was due to a specific complication of split grafts: cut surface leaks. In our cohort, 17% of the recipients presented a cut surface leak. This figure is in line with the reported datafrom otherex situ SLT cohorts (13.6%–18%)[18,22–24] (Table S9, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). Importantly, in our cohort no graft loss or recipient death occurred following a cut surface leak. Furthermore, a treatment-based analysis revealed that the majority of these leaks were treated with a single radiologic drainage under local anesthesia (CD grade IIIa), which is in stark contrast to anastomotic or nonanastomotic strictures, which often require multiple interventions.[25] Interestingly, we found a low rate (1.3%) of nonanastomotic strictures in our SLT cohort, despite longer SCS durations than in WLT. We conclude that although cut surface bile leaks are an additional morbidity burden in SLT, their severity is low. To allow for a quick diagnosis and treatment of these leaks, we advise a routine abdominal CT scan on postoperative day 7.

As for arterial complications, early HAT was the only significant factor associated with graft loss. To investigate potential modifiable risk factors for early HAT, we first focused on the arterial anastomotic site of the partial graft. We did not find any single or combined donor risk factors for early HAT in univariable analysis. In addition, the presence of a RBHA as graft anastomotic site (61.6% of the cases) was also not significantly associated with a higher rate of early HAT compared with the presence of the entire arterial axis. Another important anatomic feature that has been shown to be associated with early HAT is hepatic venous drainage. Indeed, it is well known from living donor liver transplantation that an optimal graft outflow is paramount to assure early graft function and reduce the rate of early HAT.[26] In line with these observations, we found that in the G5678 grafts with a preserved or reconstructed middle hepatic vein (MHV), the early HAT

TABLE 3. Post-transplant Outcomes

	Overall n = 224	G45678 n = 169	G5678 n = 55	*P*
Postoperative results				
Median follow-up (y)	3.3 (1.9–5.4)	3.6 (2–5.6)	2.6 (1.6–4.6)	0.12
ICU stay (d)	7 (4–10)	7 (4–10)	5 (4–10)	0.20
Missing data	*12* (*5.3*)	*12* (*7.1*)	*0* (*0*)	
Hospital stay (d)	21 (15–32)	21 (16–32)	19 (14–29)	0.15
Missing data	*8* (*3.6*)	*8* (*4.7*)	*0* (*0*)	
Overall morbidity (CCI score)				
3 mo	34 (21–50)	34 (21-52)	37 (21-49)	0.70
6 mo	40 (21–54)	34 (21–54)	42 (30–52)	0.40
1 y	41.8 (29.6–56.1)	40 (26–58)	42 (34–52)	0.60
Portal vein complication	7 (3.1)	6 (3.6)	1 (1.8)	> 0.90
Thrombosis	3 (1.3)	2 (1.2)	1 (1.8)	—
Stenosis	4 (1.8)	4 (2.4)	0 (0)	—
Arterial complication	36 (16)	24 (14)	12 (22)	0.20
Hepatic artery stenosis	22 (9.8)	14 (8.3)	8 (15)	0.20
Hepatic artery thrombosis	15 (6.7)	10 (5.9)	5 (9.1)	0.50
Early (≤ 30 d)	11 (4.9)	8 (4.7)	3 (5.5)	0.70
Late (> 30 d)	4 (1.8)	2 (1.2)	2 (3.6)	0.30
Hepatic artery false aneurysm	4 (1.8)	3 (1.8)	1 (1.8)	> 0.90
Outflow complication				> 0.90
IVC stenosis	3 (1.3)	3 (1.8)	0 (0)	
Biliary complications	68 (30)	52 (31)	16 (29)	0.80
Anastomotic leak	14 (6.3)	14 (8.3)	0 (0)	**0.02**
Anastomotic stenosis	32 (14)	24 (14)	8 (15)	> 0.90
Cut surface leak	38 (17)	30 (18)	8 (15)	0.80
Nonanastomotic stenosis	3 (1.3)	1 (0.6)	2 (3.6)	0.15
Small-for-size syndrome	1 (0.44)	0 (0)	1 (1.8)	0.20
PNF	1 (0.44)	1 (0.6)	0 (0)	> 0.90
Retransplantation	16 (7.1)	11 (6.5)	5 (9.1)	0.50
1-year graft loss	19 (8.5)	16 (9.5)	3 (5.5)	0.60
Hepatic artery thrombosis	8 (3.6)	5 (3)	3 (5.5)	
Rejection	1 (0.44)	1 (0.6)	0 (0)	
Nonanastomotic stenosis	1 (0.44)	1 (0.6)	0 (0)	
Hepatic aneurysm rupture	1 (0.44)	1 (0.6)	0 (0)	
PNF	1 (0.44)	1 (0.6)	0 (0)	
Outflow block	1 (0.44)	1 (0.6)	0 (0)	
Infection	1 (0.44)	1 (0.6)	0 (0)	
Cardiac/vascular	1 (0.44)	1 (0.6)	0 (0)	
Other	4 (1.8)	4 (2.3)	0 (0)	
Mortality				
90 d	3 (1.3)	3 (1.8)	0 (0)	0.60
1 y	9 (4)	9 (5.4)	0 (0)	0.12

Data are expressed as n (%) or median (IQR).
ICU indicates intensive care unit; IVC, inferior vena cava.

rate was 3.8% compared to33% in G5678 grafts without an MHV (data not shown). Accordingly, the absence of a MHV in the split graft was the only factor presenting a $P < 0.2$ in the multivariable risk analysis for early HAT. However, > 95% of G5678 in our study were transplanted with a MHV as it is common practice in the study centers to reconstruct the MHV if necessary.[27] Indeed, we observed a 20% MHV reconstruction rate in our study. The small overall number of G5678 without a MHV explains that we could not identify the absence of a MHV as a significant risk factor for HAT. Another technical aspect for graft drainage is the absence of the IVC, which was observed in only 8 (3.6%) G5678 grafts in this study. No early graft loss occurred in this subgroup (Table S3, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). Finally, another potential risk factor for early HAT is the arterial buffer effect due to a small-for-flow syndrome.[28] Indeed, high portal pressure and portal flow have been identified as significant risk factors for HAT.[29] This effect has, however, not been investigated systematically in this study, given the absence of routine intraoperative flow and pressure measurements. Of note, due to the optimal GRWR, we observed a very low rate of clinically relevant SFSS syndrome (0.4%). In conclusion, we found an increased risk of early HAT in ex situ RSLT which is important to consider when selecting recipients for SLT, especially in case of higher acuity candidates. The presented data suggest that the arterial anastomotic site (RBHA vs arterial axis) of the split graft is not per se a contraindication to perform a RSLT. In addition, as forliving donor liver transplantation, outflow optimization by reconstructing the MHV if necessary is key.[30]

As for arterial stenosis, we observed a rate of 9,8% which is partly due to a very frequent ultrasound screening during the first 3 months after LT by all the participating centers, even in the absence of anomalies in the blood tests. The main technical risk factor for occurrence of an arterial stenosis was an anastomosis on the arterial axis of the liver

TABLE 4. Univariable and Multivariable Analysis of Risk Factors for Graft Loss and Early Hepatic Artery Thrombosis

	Univariable			Multivariable		
Hazard ratio	**CI 95%**	***P***	**Hazard ratio**	**CI 95%**	***P***	
Pretransplant risk factor for graft loss						
Donor age	1.020	0.986–1.054	0.25	—	—	—
Donor age >40 y	1.218	0.463–3.204	0.69	—	—	—
Donor BMI	1.108	0.990–1.239	0.07	—	—	—
BMI >25	3.1	1.164–8.261	**0.02**	1.975	0.676–5.768	0.21
Donor Cardiac arrest	0.32	0.075–1.397	0.13	0.187	0.024–1.465	0.11
Donor norepinephrine >1 µg/kg/min	1.96	0.560–6.687	0.29	—	—	—
Recipient age	0.98	0.953–1.017	0.33	—	—	—
Recipient MELD	0.96	0.9–1.038	0.35	—	—	—
MELD >25	0.54	0.073–4.073	0.55	—	—	—
Graft type						
G5678	1.582	0.464–4.462	0.46	—		
Cold ischemia (min)	0.83	0.647–1.073	0.16	0.769	0.552–1.073	0.12
Cold ischemia >12 h	0.32	0.042–2.377	0.26	—	—	—
BAR	0.91	0.781–1.067	0.25	—	—	
BAR >8	0.71	0.205–2.418	0.57	—	—	—
GRWR	0.45	0.1381.487	0.19	0.56	0.166–1.948	0.37
Early HAT	13.5	5.441–33.629	**0.001**	11.06	3.803–32.195	**0.001**
Biliary complication	1.41	0.557–3.593	0.46	—	—	—
Cut surface leak	1.81	0.653–5.036	0.25	—	—	—
Pretransplant risk factor for early HAT						
Donor age	1.006	0.962–1.053	0.78	—	—	—
Donor age >40 y	1.002	0.257–3.908	0.99	—	—	—
Donor BMI	0.953	0.795–1.142	0.61	—	—	—
BMI >25	2.171	0.583–8.087	0.25	—	—	—
Donor cardiac arrest	1.070	0.274–4.179	0.92	—	—	—
Donor norepinephrine >1microgram/kg/min	0.989	0.120–8.154	0.99	—	—	—
Recipient age	0.984	0.941–1.028	0.46	—	—	—
Recipient MELD	0.975	0.890–1.068	0.58	—	—	—
Graft type						
G5678	1.16	0.297–4.538	0.83	—	—	—
Cold ischemia (min)	0.892	0.636–1.250	0.51	—	—	
Cold ischemia >12h	0.563	0.070–4.457	0.58	—	—	—
Middle hepatic vein	0.269	0.052–1.384	0.12	—	—	—
Arterial anastomosis on the RBHA	0.53	0.155–1.797	0.31	—	—	—
BAR	0.922	0.756-1.125	0.42	—	—	—
BAR >8	0.342	0.043-2.737	0.31	—	—	—
GRWR	0.48	0.105-2.270	0.36	—	—	—

BMI : body mass index.

graft. It should be noted that no split graft was lost due to an arterial stenosis in the present series and an effective treatment by radiologic stenting was possible in all cases. As a comparison, a recent study on 155 G45678 in situ split grafts from Australia[31] reports an arterial stenosis rate of 11%.

Third, while our study was not designed to directly compare ex situ to in situ SLT, we made some interesting observations worth highlighting (Table S8, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). First, the median cold ischemia duration in our cohort was 10 hours which is longer than those reported in large in situ SLT series from Australia (median 6.4 h)[31] and Italy (median 6–7 h).[3] Given the negative impact of prolonged SCS duration on outcomes, this is certainly an aera of improvement for ex situ SLT. A possible strategy to reduce SCS in ex situ SLT and approach the optimal 6-hour cutoff recommended for in situ SLT,[3] is to perform ex situ split during hypothermic oxygenated perfusion.[11,32] Preliminary data suggests that this allows to hamper early ischemia-reperfusion injury in both right and left split grafts.[11] A second often cited disadvantage of ex situ split is a suboptimal hemostasis and biliostasis of the cut surface. In our study, we observed a cut surface leak rate of 17%, which is only slightly higher than the 13.5% reported by a recent single-center study on155 in situ SLT.[31] Third, our HAT rate of 6.7% is also comparable to available figures from in situ SLT cohorts ranging from 4.2% in study from Hong Kong to 9% in the recent Australian series.[31] Finally, the logistics of SLT are also a matter of debate. While a recent paper from Italy has convincingly shown that a well-organized nationwide in situ SLT program is feasible,[3] ex situ SLT has several logistical advantages. For example, the latter does not require an experienced HPB surgeon to travel to the procurement center and allows for a standard multiorgan procurement. A per-procedure cholangiography is also technically easier in ex situ split which is of major importance in case of full left/full right splits. Finally, 1-year graft and recipient survival rates in our ex situ SLT cohort were comparable to the published figures from large in situ SLT cohorts (91.5% vs 60.7%–95.5%[33,34] and 96% vs 68.3%–95.9%,[3,35] respectively ,Table S8, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). We conclude that in situ and ex situ SLT should not be

mutually exclusive but are complementary strategies (Table S8, S9, Supplemental Digital Content 1, http://links.lww.com/SLA/F163, Supplemental Digital Content 1, http://links.lww.com/SLA/F163). It is our understanding that modern LT centers need to be able to perform both procedures especially in the context of rapidly expanding indications in the field of transplant oncology.[36]

The present study has several limitations. First, due to is retrospective design we cannot exclude data reporting bias. Second, we want to emphasize that the reported data reflects a specific SLT framework including national allocation rules and recipient selection policies. Due to this fact, the presented data may not be transposable to transplant centers in other countries. Third, we could not provide any data on perioperative portal, arterial and caval flow and pressure measurements in the present cohort as these were not routinely performed in the participating centers. Future studies should aim at investigating hemodynamic characteristics in SLT. Fourth, we did not provide data on outcomes of the contralateral left split graft allocated to pediatric recipients, which should be assessed in a future study.

In conclusion, we report benchmark survival rates and overall morbidity in well-matched ex situ RSLT. These results are in favor of a wider use of ex situ RSLT for adult recipients and will serve as a reference for discussing less stricter selection criteria and novel indications.

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