Right Extended Split Liver Transplantation Compared With Whole Liver Transplantation: Lessons Learned at a Single Center in Latin America–Results From a Match Case-Control Study

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ABSTRACT

Background. Despite the progressively increasing gap between patients waiting for liver transplant under the Model for End-stage Liver Disease MELD system and the availability of deceased donor organs, the use of right extended split liver grafts (RESLG) has not been accepted by all centers. In this study, we compared the results obtained using RESLG vs a group of matched whole liver graft (WLG) recipients at a single center in Latin America.

Methods. A single-center retrospective review performed between August 2009 and December 2015.

Results. Fifteen RESLGs were implanted to recipients between 13 and 70 years of age; 80% were performed ex situ. The "biological MELD" score for the RESLG group was 17.5 $\pm$ 5.6, and it was 12.8 $\pm$ 4.5 for the WLG group (P = .01). Cold ischemia times were significantly longer in RESLG recipients compared with WLG recipients (528 minutes vs 420 minutes; $P < .01$). No significant differences were found in biliary (leak or strictures $P = .40$) and arterial complications (hepatic artery thrombosis, $P = .06$). RESLG patients benefited from a considerable reduction on their waiting time in list. The 1-, 3-, and 5-year patient survival rates were 93%, 93%, and 93% respectively, for RESLG recipients vs 100%, 95.7%, and 86.1%, respectively, for WLG recipients. The 1-, 3-, and 5-year graft survival rates were 79.4%, 79.4%, and 79.4% for RESLG recipients and 89.7%, 89.7%, and 89.7% for WLG recipients, respectively. No statistical differences were observed.

Conclusion. RESLG allows expeditious transplantation for low MELD recipients. Its use should be expanded in Latin America and worldwide as a valid alternative to increase the donor pool as it has been used in other regions.

SPLIT liver transplantation was developed in 1988 by Pichlmayr et al [1] based on the technique described by Bismuth and Houssin [2] to obtain a reduced liver graft from an adult liver for a pediatric recipient, but optimizing the use of the right segment that otherwise would be discarded.

The concept of performing 2 transplants with 1 liver has made split liver transplantation an attractive alternative to increase the pool of organs. Over the years, this technique has been improved, from performing the liver "partition" ex situ to the option of being in situ [3,4]; later it expanded from the initial indication to use it for 1 pediatric and 1 adult recipient, to considering its use in 2 adult recipients by obtaining a right lobe graft (segments V-VIII) and full left lobe graft (segments I-IV) [5–8].

The split technique proved to be an effective alternative to reduce the mortality of children in the waiting list, avoiding

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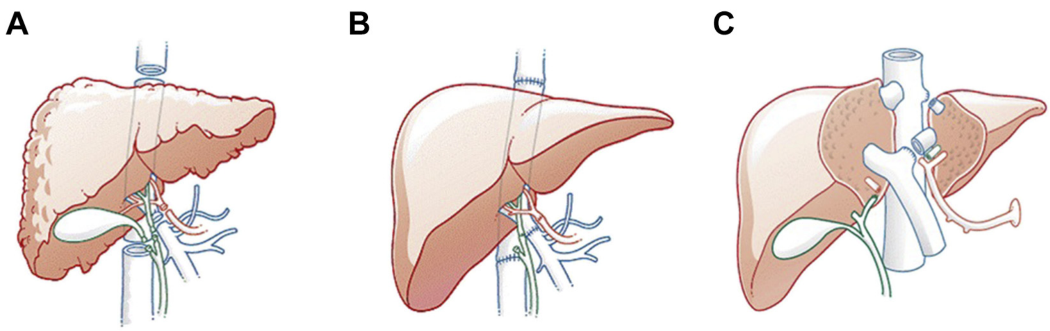

Fig 1. Illustration of (**A**) cirrhotic liver; (**B**) whole liver transplantation; (**C**) split liver transplantation.

the need for a living donor graft [9–11], but still there is a need to prove that similar results can be obtained in the adolescent and adult population using the of the right extended split liver grafts (RESLGs) worldwide. Many studies have compared outcomes using RESLGs vs whole liver grafts (WLGs), but there is still lack of consensus regarding its use and the real impact of splitting livers for adult recipients [7]. The concept that the RESLG becomes a marginal graft [12] has been associated with the prolonged cold ischemia time and the potential risk for complications after transplantation. Although no follow-up publication has been written sustaining or denying that concept, the concern for an increased risk of graft loss in adult recipients has discouraged the adoption of liver transplantation using RESLGs.

The lack of reported experience by individual centers, associated in part with the low frequency of the procedure, did not allow the experience to evolve. In Argentina the split liver transplantation experience started in 1990, and it has become a significant source of organs for pediatric transplantation [13], but it has not been accepted in the same proportion for adult recipients. Therefore, in many cases the initial splitting finally ends in a reduced size technique, because the right side graft turns to be discarded.

The question that we aim to answer with this study was whether the impact of using an RESLG in an appropriate recipient reduces mortality on the waiting list, with a low complication rate and an acceptable post-transplant survival, in our country, to stimulate its use in the whole region.

MATERIALS AND METHODS

A matched case-control retrospective single-center analysis was performed using the transplant database from the Liver Transplant Unit at Hospital Universitario Fundación Favaloro.

Patients

Recipients of RESLGs from August 2009 to December 2015 were analyzed and compared with a matched control group of WLG recipients (1 study case and 2 control cases) transplanted during the same period. Matching was performed taking age, gender, and etiology as main variables. Recipients of left liver grafts, multiorgan transplants, retransplants, and living related organ donors were excluded. Recipient and donor demographics, surgical details, early and long-term outcomes including complications and patient and graft survivals were reported and compared between groups.

Deceased Donor Allocation Policy for Split Transplantation in Argentina and Vessel Sharing

In Argentina there is no mandatory splitting policy. In general, when a liver is assigned to a pediatric or a small adult candidate, the recipient team declares the intention of proceed with split transplantation, with the main interest to use the left lateral segment. The RESLG is offered

Table 1. Demographic Analysis

	WLG (n = 30)	RESLG (n = 15)	*P* Value
Donor-related factors			
Age	42.4 ± 15.1	21.9 ± 8.1	<.01
ICU (d)	2.5 ± 1.9	3.4 ± 3.3	.58
DRI	1.34 ± 0.24	1.8 ± 0.29	<.01
Recipient-related factors			
Age	48 ± 16.1	43.1 ±16.6	.31
Sex (male; percentage)	17 (56.7%)	9 (60%)	>.99
BMI (kg/m^2)	27.9 ± 5.5	24.1 ± 4.1	.01
Real MELD	17.5 ± 5.6	12.8 ± 4.5	.01
MELD	19.2 ± 5.6	19.1 ± 4.1	>.99
ABO blood group, n (%)			.68
A	17 (56.7%)	7 (46.7%)	
B	3 (10%)	1 (6.7%)	
O	10 (33.3%)	7 (46.7%)	
AB	0 (0%)	0 (0%)	
Primary transplant	30 (100%)	15 (100%)	
Operative features			
Split technique	NA		
In situ		3 (20%)	
Ex vivo		12 (80%)	
Wait time in list (d)	221 ± 288	250 ± 189	.23
Cold ischemia time (min)	420 ± 108	528 ± 72	<.01
Warm ischemia time (min)	42 ± 9	52 ± 27	.37
Transfusions, unites (range)*			
RBC	2 (0–6)	2 (0–11)	.52
Platelets	0 (0–10)	0 (0–6)	.97
PFC	0 (0–12)	0 (0–12)	.49
Cryoprecipitates	0 (0–6)	0 (0–12)	.18

P < .05 was considered significant. Data are presented as mean ± standard deviation.

Abbreviations: BMI, body mass index; DRI, donor risk index; ICU, intensive care unit; MELD, Model for End-stage Liver Disease; NA, not applicable; PFC, platelet-derived factor concentrate; RBC, red blood cells; RESLG, right extended split liver graft; WLG, whole liver graft.

*Median used.

Table 2. Etiology of End-Stage Liver Disease in RSELG and WLG Recipients

Etiology	WLG (n = 30)		RESLG (n = 15)	
	n	%	n	%
Associated HCC	6	20	5	33.3
HCV cirrhosis	16	53.3	9	60
Autoimmune hepatitis	4	13.3	2	13.3
Amyloidosis	–	–	1	6.7
Alcoholic cirrhosis	4	13.3	1	6.7
Primary biliary cirrhosis	2	6.9	–	–
Secondary biliary cirrhosis	1	3.3	–	–
Nodular regenerative hyperplasia	1	3.3	–	–
Cystic fibrosis	–	–	1	6.7
Cryptogenic cirrhosis	2	6.7	1	6.7

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RSELG, right extended split liver graft; WLG, whole liver graft.

to the recipients on the national waiting list. Then, both teams agree on logistics, technique, and vessel sharing before the procurement occurs, as has been detailed in a recent publication [14].

Usually, the left lateral segment graft retains the left suprahepatic vein, the left portal vein, and the left bile ducts, with the hepatic artery in continuity with the celiac trunk. Therefore, the RESLG keeps the right and middle suprahepatic veins, the right and main portal vein, and the right hepatic artery (Fig 1).

In our institution, split liver candidates fulfill the following criteria: (1) a Model for End-stage Liver Disease (MELD) score between 15 and 25. We called "biological MELD" the calculated MELD without the additional "priority" points given due to specific disease conditions (eg, hepatocellular carcinoma recipients) and the time waiting on list; (2) absence of portal hypertension or portal thrombosis; (3) no acute associated disease; and (4) the ratio between liver weight and body higher than 0.8 to 1.

The donor selection criteria are (1) younger than 55 years old; (2) body mass index less than 30 kg/m^2; (3) <10 days in the intensive care unit; (4) hemodynamically stable, with low doses or none vasopressor support; and (5) steatosis assess by biopsy: less than 30% of macrosteatosis.

Statistical Analysis

Categorical variables were compared using Fisher exact test or χ^2 test, as applicable. Student *t* test (Mann-Whitney *U* test) was used to compare continuous variables. Unless otherwise specified, quantitative data are expressed as mean and standard deviation. Survival rates were estimated with the Kaplan-Meier method and compared with the log-rank test. A *P* value less than .05 was considered significant. All statistical analyses were done using GraphPad Prism v5.0 (GraphPad Software Inc., San Diego, CA, USA) and IBM SPSS 22 (IBM SPSS statistics 22, IBM Corp., New York, NY, USA).

RESULTS

Donor Demographics

Table 1 shows donor demographic information. RESLGs were procured from younger donors (21.9 ± 8.1 years) compared with WLG donors (42.4 ± 15.1 years, $P < .01$).

Donor risk index was statistically higher in the RESLG group compared with the WLG group (1.8 ± 0.29 vs 1.34 ± 0.24, respectively; $P < .01$; Table 1). Procedures were performed at regional or national centers (in situ: regional: 1; national: 2; ex vivo: regional: 6, national: 6). Three of 15 (20%) splits were done in situ, and the remaining were done ex vivo. The in situ procedure presented shorter cold ischemia time (489.6 minutes) vs the ex vivo (537 minutes), although the difference did not reach significance ($P = .51$).

Recipient Demographics

Fifteen transplants using RESLGs from deceased donors were performed during the analyzed period. RESLGs were implanted in 13 adult patients (25-68 years) and in 2 adolescent recipients (13 and 15 years). The control group consisted of 30 recipients that received WLG transplants from brain-dead donors in the same period (Table 1).

The most frequent etiology of liver disease was hepatitis C, followed by autoimmune hepatitis, amyloidosis, alcoholic cirrhosis, cystic fibrosis, and cryptogenic hepatitis. Associated hepatocellular carcinoma was observed in 5 RESLG (33.3%) and in 6 WLG recipients (20%; $P = .46$; Table 2).

As expected, when the biological MELD was compared between groups, it was significantly lower in the RESLG group (12.8 ± 4.5 vs 17.5 ± 5.6 in WLG recipients; $P = .01$). On the other hand, when comparing MELDs with the additional points given due to specific disease conditions and the time waiting on list, no statistical differences were seen (19.1 ± 0 4.1 for RESG and 19.2 ± 5.6 for WLG; $P > .99$; Table 1). RESLG recipients had significantly lower body mass index compared with WLG recipients (24.1 kg/m^2 vs 27.7 kg/m^2, $P = .01$).

Transplant Variables and Complications

Generally, the recipient operation is started immediately after the split procedure is completed in the donor hospital. Warm ischemia times were comparable between the 2 groups, 52 ± 27 minutes for RESLG vs 42 ± 9 minutes in WLG ($P = .37$; Table 1).

All the engraftments of RESLGs and 29 of 30 of WLGs were performed using vena cava preserving technique; the main

Table 3. Operative Course and Relevant Anatomy in Recipients of RESLG and WLG Transplants

	WLG (n = 30)	RESLG (n = 15)	*P* Value
Cava drainage			.67
Piggyback	29 (96.3%)	15 (100%)	
Conventional cava interposition	1 (3.3%)	0 (0%)	
Portal anatomy			.54
Main porta	27 (90%)	15 (100%)	
Cadaveric graft	3 (10%)	0 (0%)	
Arterial anatomy			.10
Right hepatic artery reconstruction	29 (96.7%)	12 (80%)	
Cadaveric graft	1 (3.3%)	3 (20%)	
Biliary drainage			.67
Duct to duct	28 (93.3%)	15 (100%)	
Choledochojejunostomy	2 (6.7%)	0 (0%)	
With T-tube	0 (0%)	14 (93.3%)	<.01

$P < .05$ was considered significant.
Abbreviations: RSELG, right extended split liver graft; WLG, whole liver graft.

Table 4. Surgical Complications

Complications	WLG (n = 30)	RESLG (n = 15)	*P* Value
ICU stay (d)	5 ± 2.7	5.7 ± 5	.64
Hospital room stay (d)	6.8 ± 5.1	6.7 ± 5.3	.58
Bleeding	6 (20%)	2 (13.3%)	.70
Reoperation (%)	2 (6.7%)	1 (6.7%)	>.99
Bile complications			.40
Leak (%)	2 (6.7%)	3 (20%)	
Strictures (%)	2 (6.7%)	1 (6.7%)	
Treatment			
Percutaneous	2 (6.7%)	1 (6.7%)	
Endoscopic	2 (6.7%)	2 (13.3%)	
Surgical	1 (3.3%)	1 (6.7%)	
Thrombosis			.06
HAT (%)	1 (3.3%)	3 (13%)*	
SHV (%)	0 (0%)	1 (6.7%)	
PVT (%)	0 (0%)	0 (0%)	
Reoperation	1 (3.3%)	3 (20%)	
SFSS	0	0	
Retransplant (%)	3 (10%)	3 (20%)	.38
Early	2	2	>.99
Late	1	1	>.99

Abbreviations: HAT, hepatic artery thrombosis; ICU, intensive care unit; PVT, portal vein thrombosis; RSELG, right extended split liver graft; SFSS, small-for-size syndrome; SHV, suprahepatic vein; WLG, whole liver graft.

*Two cases (13.3%) could have been related to technical factors; 1 case (6.6%) was secondary to a postoperative hypovolemic shock (total 20%).

portal veins of donors and recipients were used to perform the anastomosis in all the RESLG grafts and in 27 of 30 of WLG grafts. In most RESLG cases the right hepatic artery was reconstructed, with the exception of 3 cases that required using infrarenal aortic grafts; the proper hepatic artery reconstruction was most commonly used in the transplants performed using WLG (29 of 30). The duct-duct anastomosis was the standard technique for biliary reconstruction in both groups (28 of 30 WLGs and 15 of 15 RESLGs), and it was done over T-tubes in 14 of 15 RESLGs (Table 3).

When analyzing the perioperative bleeding, 2 RESLG recipients and 6 WLG recipients suffered from bleeding ($P = .70$).

Biliary complications occurred with a higher frequency in the RESLG group (26.7%) compared with the WLG group (13.4%), but the difference lacks statistical significance ($P = .4$). RESLG recipients had 3 leaks from the liver cut surface (1 leak in situ and 2 leaks ex situ) and 1 late biliary stricture (18 months after transplantation; 1 stricture ex situ). In the WLG group, 2 early leaks and 2 strictures (diagnosed at an average of 34 days after transplantation) were detected. The resolution of the biliary complications was achieved by endoscopic or percutaneous procedures in the majority of the cases; only 1 case required a surgical resolution (Table 4).

Hepatic artery thrombosis (HAT) occurred in 2 patients as consequence of technical factors (13.3%), which were diagnosed at a mean of 5.5 days post-transplant; one was managed with surgical thrombectomy, and the other needed retransplantation. A third case of HAT was an acute event secondary to a hypovolemic shock due to rupture of a splenic artery aneurysm, leading to retransplantation; all those belong to the RESLG group. In the WLG group, 1 of 30 recipients had HAT (3.4%), which was successfully managed with thrombectomy. The statistical analysis showed that the thrombosis was higher in split transplantation but was not statistically different ($P = .06$; Table 4).

The mean length of intensive care unit (ICU) stay and the hospital room stay was comparable between RESLG recipients (ICU: 5.7 ± 5 days; ward: 6.7 ± 5.3 days) and WLG recipients (ICU: 5 ± 2.7 days; ward: 6.8 ± 5.1 days; $P = .64$ and $P = .58$, respectively).

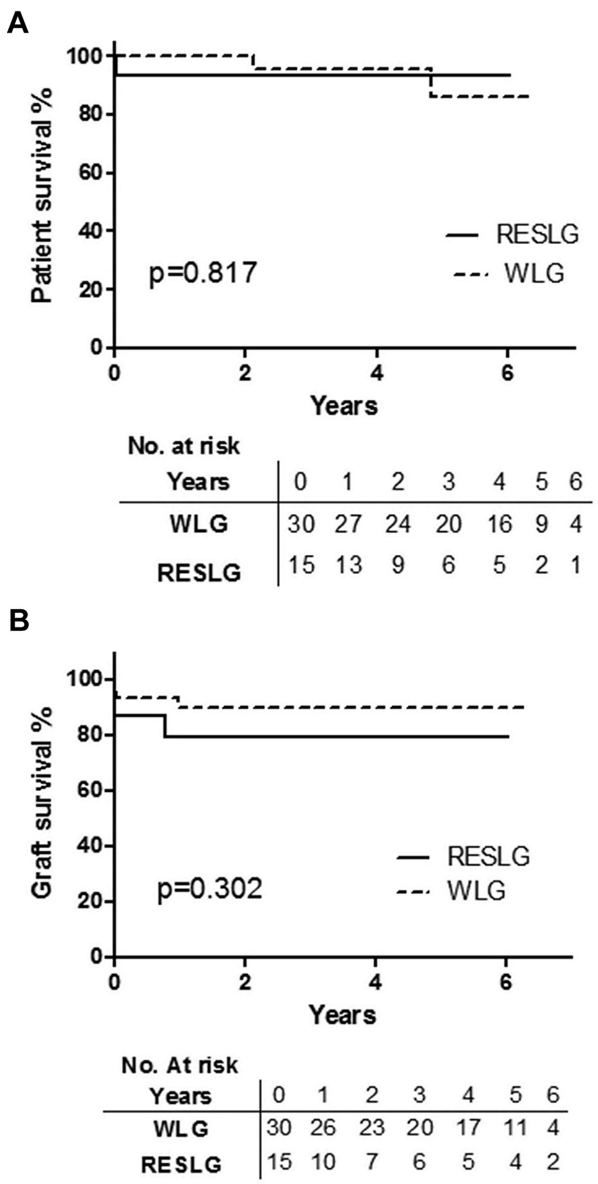

Fig 2. Kaplan-Meier curves from (**A**) patients and (**B**) grafts survival after liver transplantation using right extended split liver grafts (RESLG) and whole liver grafts (WLG). *P* value obtained using log-rank test.

Table 5. Results of RESLG Transplantation in Adults Recent Series (2006-2016)*

Author	Center	Years of Analysis	Number of Patients	Complications				% Graft Survival	
				% HAT		% Bile Leak	% Strictures		
				Early	Late			1 y	5 y
Wilms et al (2006) [30]	University Hospital Hamburg Eppendorf, Germany	1993–2005	70 in situ and ex vivo	2.9	–	14.3	not specified	70.3	70.3
Hong et al (2009) [17]	David Geffen School of Medicine at the University of California, United States	1993–2006	72 in situ	4.2	not specified	4.2	not specified	75	68
Vagefi et al (2011) [33]	University of California, United States	1993–2010	63 in situ and ex vivo	4.8	3.2	11.1	3.2	89	76
Boillot et al (2013) [34]	Edouard Herriot Hospital, France	1996–2010	16 ex vivo	6.6	not specified	3.3	not specified	75	53
Doyle et al (2013) [21]	University of Mississippi Medical Center, United States	1995–2012	23 in situ and ex vivo	0		8.7		86	72.3
Hashimoto et al (2014) [27]	Institute Cleveland Clinic, United States	2004–2012	25 in situ and ex vivo	4	not specified	12	20	88	80
Mabrouk Mourad et al (2015) [19]	Queen Elizabeth Hospital, United Kingdom	2000–2012	171 ex vivo	4	6	20	5	79	72
Maggi et al (2015) [32]	Multicenter	1997–2004	198 in situ	6.1	not specified	19.3	not specified	73.5	60.7
		2005–2011	184 in situ	3.3	not specified	15.8	not specified	83.5	68.9
Memeo et al (2015) [28]	Henri-Mondor Hospital, France	2001–2011	71 ex vivo	3	not specified	17	7	84	68
Halac et al (2016) [14]	Multicenter	2009–2013	54 in situ and ex vivo	9.3	not specified	29.7	5.6	78	–
Battulla et al (2016) [28]	Queen Elizabeth University Hospital	1992–2000	38 in situ and ex vivo	21	not specified	21	18	82	81
		2001–2014	188 in situ and ex vivo	6	not specified	13	3		
Current Report	Hospital Universitario Fundacion Favaloro	2009–2015	15 in situ and ex vivo	13*	–	20	6.7	89.7	89.7

Abbreviations: HAT, hepatic artery thrombosis; RSELG, right extended split liver graft; WLG, whole liver graft.
*RESLG: 2 cases (13.3%) could have been related to technical factors; 1 case (6.6%) was secondary to postoperative hypovolemic shock (total 20%).

Patient and Graft Survivals

Retransplantations were registered in both groups of transplantation, 2 early events and 1 late event in each group, showing no significant difference among them (P = .38). The causes for early graft loss in RESLG recipients were HAT and rupture of splenic artery aneurysm, and the late graft loss was due to chronic rejection. For WLG group, the 2 early graft losses were due to primary graft dysfunction and early viral recurrence, and the late graft loss was due to a diffuse ischemic cholangiopathy. Early graft loss requires immediate retransplantation. And for that reason in our country patients are immediately relisted as emergency to obtain a new organ expeditiously. In chronic cases, patients are relisted for transplantation with exception to MELD scores to give some priority.

Patient and graft survival rates in RESLG and WLG recipients were not statistically different. The 1-, 3-, and 5-year patient survival rates were 93%, 93%, and 93%, respectively, for RESLG recipients vs 100%, 95.7%, and 86.1%, respectively, for WLG recipients (Fig 2A). The 1-, 3-, and 5-year graft survival rates were 79.4%, 79.4%, and 79.4% for RESLG recipients and 89.7%, 89.7%, and 89.7% for WLG recipients, respectively (Fig 2B). No statistical difference was observed.

DISCUSSION

The worldwide experience with the use of segmental liver grafts, including split liver grafts and living donor liver transplantation, resulted in a growing experience worldwide [14]. Nonfavorable initial results have been overcome in large-volume centers, and nowadays, there is a need to reconsider the use of the split technique for adult recipients [1–3,15].

The argument against this statement was strong when complications and outcomes for split liver transplant were marginal. The current results favor the opposite, emphasizing the fact that 2 patients can be transplanted with 1 organ with an acceptable risk for both, as it has been shown in this series.

Our work demonstrated that patients receiving RESLGs benefited by reducing their waiting time when compared with the mean time on the waiting list by primary disease during the same period of analysis (2009-2015; data provided by the Instituto Nacional Central Único Coordinador de Ablación e Implante [INCUCAI]). Therefore, to perform a split transplant in adult recipients increases the transplant applicability and reduces mortality on the waiting list.

Our team favors the in situ procedure, although it was only feasible in few cases; all of them were done when organs were primarily offered to 1 of our recipients. The ex situ technique, used in most cases, was performed when the organs were primarily allocated to different programs [14,17].

The ex vivo technique increases the cold ischemia time, and in agreement with other publications, it can become a significant independent risk factor for graft failure and patient survival [18]. To minimize cold ischemia times, we established the policy of starting the recipient's operation as soon as the retrieving team arrives to the pediatric hospital, where the ex vivo partition was taking place. Our results reinforce the concept that reduction of ischemia time in split grafts can only be possible with an adequate coordination between the splitting team and the engrafting team and by having trained teams to perform the procedure in situ; therefore allocation policies should favor the use of in situ splitting for all cases.

The main post-transplant complications seen after RESLG procedures were bile leaks and HAT, followed by the bile duct strictures [19,20]. Those results are in agreement with the manuscripts published by Doyle et al, who reported 2 of 23 RESLG recipients with bile leaks, which was comparable to WLG patients [21]. On the other hand, a bigger work by Mabrouk Mourad et al showed significant differences in biliary complications between groups but those did not affect the survival rates [19] (Table 5).

In our study, the rates of biliary and vascular complications after using RESLGs were comparable or even lower than the ones reported when adult right lobe living donor liver transplants are performed [22–25] and have the advantage of not using a living donor.

In our series, HAT was the most serious vascular complication. The reported incidence and impact are comparable to other type of segmental grafts [26]. Early diagnoses allowed salvaging the graft and avoiding the need for retransplantation.

The splitting technique has decreased the need for pediatric living donation in many pediatric transplant programs worldwide [14,16,17,27,28]. The left lateral segment and RESLGs impact both pediatric and adult liver lists, but left lobe-right lobe split for 2 adults is a practice that still requires increased use to be able to estimate the impact on mortality on the waiting list and transplant applicability.

The increasing experience in performing split transplantation has also expanded the selection criteria for splitting. A recent publication from France presents the outcomes of right lobe split from donors older than 70 years, with acceptable complication and survival rates [28]. This study and others support the concept that performing a split procedure should not longer be considered as a variable that increases the donor risk index [12,29].

In the current series, patient and graft survival rates were similar or better than WLGs and comparable to or better than other studies reporting long-term results using adult split and adult living donor liver transplantation [21,26,27,30–36] (Table 5).

These results, obtained in a single Latin-American center, are promising and should encourage national organ procurement organizations to set regulations to directly assign a liver for a split procedure when a "split-able" donor is identified and allocated to an adequate adult recipient.

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