



Short- and Long-Term Outcomes After Live-Donor Transplantation with Hyper-Reduced Liver Grafts in Low-Weight Pediatric Recipients

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Abstract

Objective To evaluate short- and long-term outcomes after live-donor liver transplantation (LT) with hyper-reduced grafts in low-weight pediatric recipients.

Summary Background Data LT is an established curative therapy for children with end-stage chronic liver disease or acute liver failure. A major problem in pediatric LT has been the lack of size-matched donor organs. The disadvantage of the use of large-for-size grafts is the insufficient tissue oxygenation and graft compression, which result in poor outcomes. The shortage of suitable donors is most notable in children under 10 kg. To overcome such obstacle, in situ hyper-reduced live-donor liver grafts have been introduced. Available articles in the literature are based on small samples and are deficient in long-term follow-up.

Methods A single-cohort, retrospective analysis was conducted including 59 pediatric patients under 10 kg who underwent hyper-reduced (in situ “a la carte” left lateral segment reduction) live-donor LT (LDLT) between February 1994 and February 2018.

Results The most frequent cause of liver failure was biliary atresia (70%). Median recipient weight was 8 kg. Vascular complications were confirmed in 15% of the sample, while 45% presented biliary complications. Median follow-up time was 40.3 months. Ten-year overall survival rate was 74%. Pediatric end-stage liver disease score > 23 was associated with a higher risk of post-operative complications.

Conclusion LDLT can be undertaken in children with body weight < 10 kg achieving good results in high-volume centers by experienced surgeons.

Keywords Liver failure · PELD · Mortality · Graft failure · Biliary leak

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Introduction

Pediatric liver transplantation in low-weight recipients remains one of the most complex and challenging surgical procedures. The technical difficulties associated with unavoidable donor-recipient size discrepancy have prompted multiple approaches to overcome the challenges of graft reduction, complex vascular reconstructions, and intricate abdominal closures.^{1–3} Several techniques such as split liver, living-donor, and monosegment transplantation have been developed over the recent years. Unfortunately, most reductions remain unable to fashion grafts suitable for recipients with very low body weights.

We had previously described the procedure of monosegmental transplantation using segment II, after having resected segment III, in situ from a living-related donor.⁴ Later, we implemented a technique capable of minimizing left

lateral segment (LLS) grafts while maintaining their vascular and biliary pedicles intact. This technique consists of an ultrasound-guided “in situ” peripheral resection of LLS parenchyma that eliminates the need for anatomic resection.⁵ Such hyper-reduction allows for the tailoring of grafts according to the recipient abdominal volume (in particular the anteroposterior diameter) and the donor liver size. We propose this hyper-reduction technique as an effective alternative to address the complex problem of liver transplantation in children under 10 kg of weight. However, scientific evidence about short- and long-term outcomes of hyper-reduced liver transplantation is limited.

The aim of the present study was to evaluate short- and long-term outcomes after live-donor transplantation with hyper-reduced liver grafts in low-weight pediatric recipients and to identify risk factors for post-operative morbidity and mortality.

Material and Methods

Design and Ethics

This is a single-cohort, retrospective analysis of a prospectively maintained database. Data for all pediatric patients undergoing living-donor liver transplantation with hyper-reduced liver grafts (HRLG) at the Liver Transplantation Unit of the Hospital Italiano de Buenos Aires between February 1994 and February 2018 were reviewed. HRLG was considered as the only option for small infants when the estimated graft-to-recipient weight ratio exceeded 4.0% according to pre-operative donor and recipient liver volumetry.⁶ Moreover, if the anteroposterior diameter of the LLS graft was larger than the anteroposterior diameter in the recipient’s abdominal cavity—defined as the distance between the abdominal wall and the vertebra on axial computed tomography images—the need for graft reduction was emphasized. All of the procedures were performed by one of the five surgeons of the Liver Transplant Unit. The back-table hyper-reduction technique has not changed since its original description.⁷

According to the Argentinean law, living donors should be genetically related until second-line blood (grandparents, father, mother, brother, or uncles). Informed consent was obtained from all patients before surgery and the Hospital Italiano Ethics Committee gave ethical approval to perform this study (Protocol No. 3699). The study protocol has been registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) database (identifier NCT03594864).

Study Aims

Primary endpoint was to assess short- and long-term overall survival. Secondary endpoint was to identify risk factors for post-operative morbidity and mortality.

Procurement Technique

A J-shaped or midline supraumbilical incision is performed based on individual donor anatomical findings. The liver is subsequently mobilized by taking down the falciform, left triangular, and left coronary ligaments. Intraoperative ultrasound is used to identify vascular and biliary structures. The left hepatic artery is dissected along its course from the common hepatic artery. Left portal vein is dissected and segment 1 branches are ligated. Left bile duct is dissected and cut at the right side of the umbilicus fissure. The ligament of Arantius is subsequently transected, and the confluence of the middle and left hepatic veins dissected. The left hepatic vein is purposefully not mobilized and kept as short as possible in order to avoid post-implantation torsions. The liver parenchyma is transected 1 cm to the right of the falciform ligament, isolating segments 2 and 3 from segment 4. Segments 2 and 3 are then hyper-reduced, tailoring the volume and shape of the graft to the specific intraoperative dimensions of the recipient abdominal cavity (reduction on demand *à la carte*, Fig. 1a). Before the hepatectomy, hepatic volumetry, abdominal angiotomography, and hepatic artery angiography are performed. Nevertheless, the section line of the peripheral hepatic parenchyma is performed in situ under ultrasound guidance prior to procurement of the graft allowing us to preserve the vascular and biliary pedicles intact and to identify areas of ischemia prior to procurement. Transecting along vertical and horizontal planes provides a cubical graft shaped like a “chocolate brownie” (Fig. 1b and c). The left portal vein, left hepatic artery, and left hepatic vein are clamped and transected. The specimen is perfused with preservation fluid (UW[®]) in the back table and prepared for implantation.

Implantation Technique

The recipient surgery entails a total hepatectomy with preservation of the inferior vena cava (IVC). The graft’s left hepatic vein is implanted onto the recipient IVC. The graft requires a rotation to be implanted. This rotation places the main section line on the anterior face of the IVC. The site of implantation on the IVC of the recipient is prepared by unifying the ostiums of the three hepatic veins in the shape of a triangle: a wide orifice is created at the confluence of all the hepatic veins by dividing the bridges of tissues between the hepatic veins and performing a longitudinal incision in the inferior angle of the orifice, in the anterior wall of the inferior vena cava, to enlarge the triangle. A broad triangular anastomosis is performed using three lines of running 6–0 polypropylene sutures (Fig. 2a and b). In order to avoid post-operative mass effect compression of the vascular structures, we perform a complete lymphadenectomy of the porta hepatis. The portal vein anastomosis is fashioned

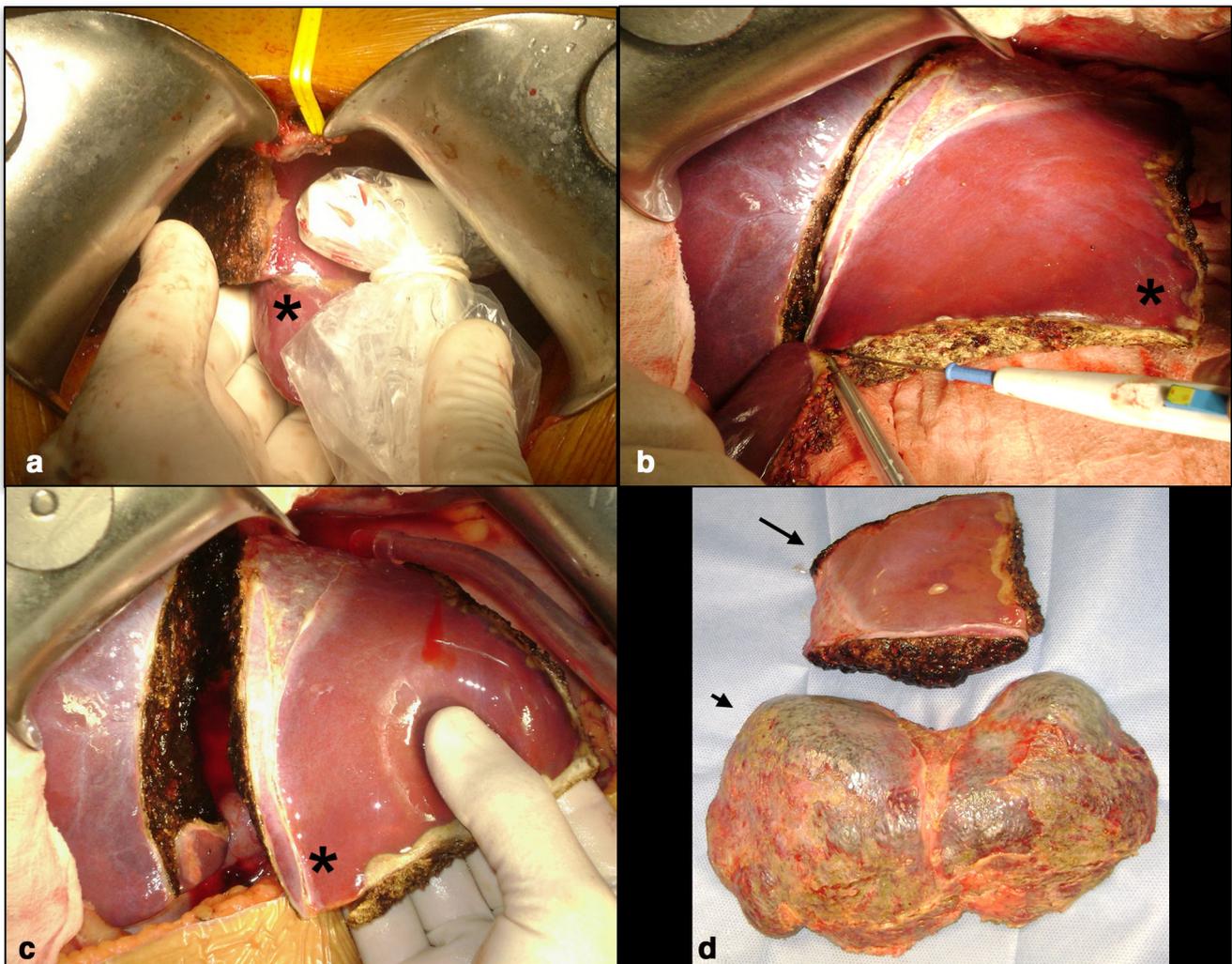


Fig. 1 A 13-month-old male patient with end-stage liver disease due to biliary atresia and a pre-transplantation weight of 8 kg, who underwent liver transplantation with a live-donor hyper-reduced left lateral segment graft from his 30-year-old father. Pictures depicting the procurement technique during donor surgery. **a** Intraoperative ultrasound used to identify vascular and biliary structures. Left lateral segment (asterisk). **b**

In situ left lateral segment (asterisk) hyper-reduction using monopolar electrocautery and Cavitron ultrasonic surgical aspirator. **c** Hyper-reduced left lateral segment (asterisk). **d**¹⁰ Contrast between the size of the hyper-reduced left lateral segment graft (arrow) and explanted recipient's liver (arrowhead)

with running 7–0 polypropylene sutures, as close as possible to the confluence of the recipient's splenic and mesenteric veins (Fig. 2c). The arterial reconstruction is performed in all instances with 9–0, 10–0, or 11–0 polypropylene sutures under microscopic magnification (surgical microscope OPMI ORL, Carl Zeiss, Germany) (Fig. 2d). The bile duct is anastomosed onto a Roux-en-Y jejunal limb with two lines of simple interrupted 7–0 or 8–0 polypropylene or polydioxanone sutures, one for each wall of the anastomosis. We do not use any biliary stents or drains. Doppler ultrasound before and after closing the abdominal wall is routinely performed in order to check permeability of vascular anastomoses. The criteria to assess the patency of vascular structures using Doppler ultrasound are as follows: hepatic artery—peak systolic

velocity >30 cm/s and end diastolic velocity >5 cm/s; portal vein—flow velocity >5 cm/s, hepatopetal flow with respiratory wave oscillations and absence of echogenic material inside the vein; hepatic vein—visualization of the vein with hepatofugal non-filiform flow, respiratory wave oscillations, and absence of echogenic material inside the vein. In case of diagnostic doubt, a digital splanchnic angiography is performed. A prosthetic mesh (Gore® Dualmesh® W. L. Gore & Associates, Inc., DE, USA) is sometimes needed for abdominal closure, despite hyper-reduction and whenever primary abdominal wall closure is not possible due to the small recipient cavity size and the consequently increased risk of graft compression and compartment syndrome. During post-operative course, daily laboratory

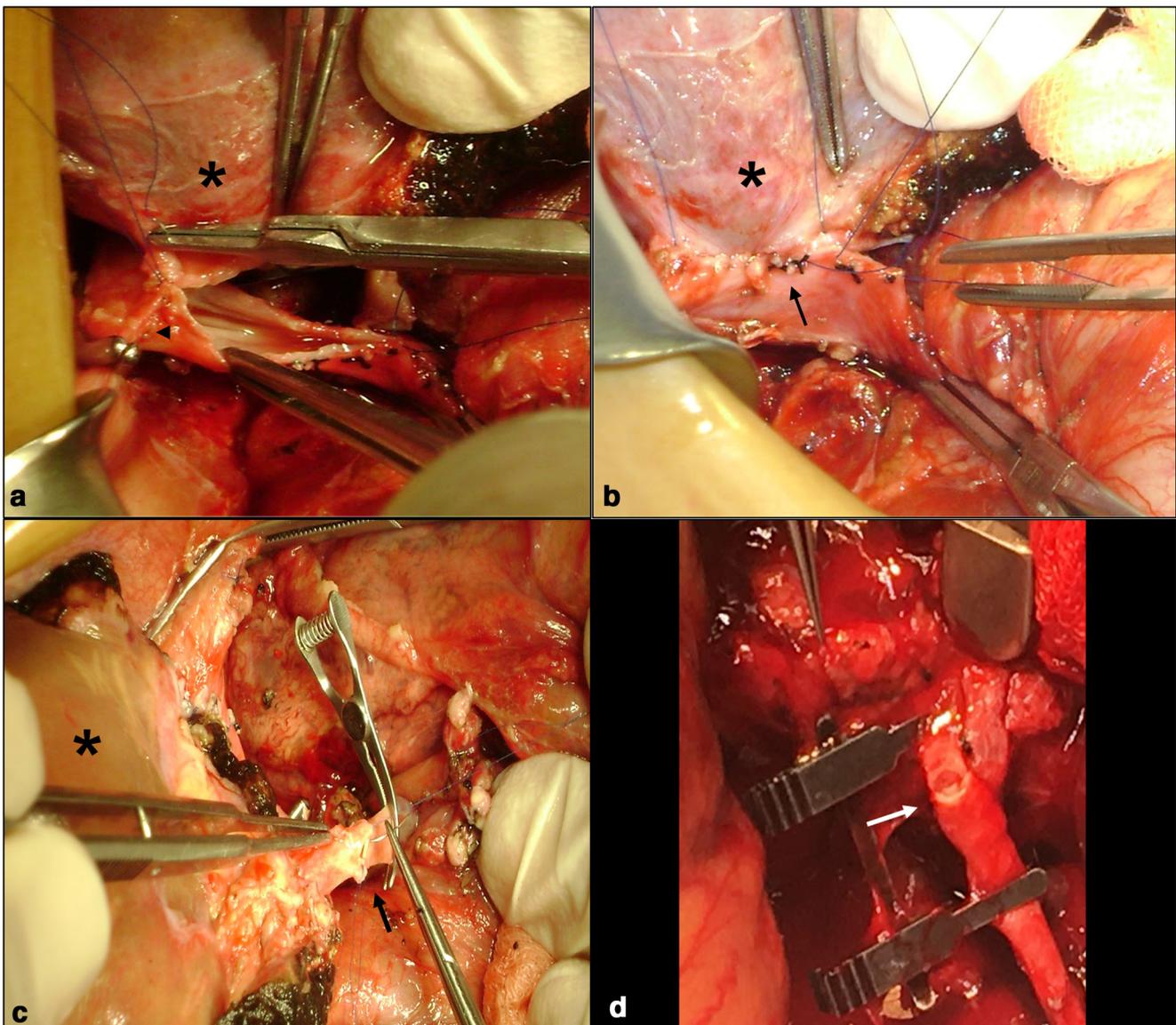


Fig. 2 A 17-month-old male patient with end-stage liver disease due to Alagille syndrome and a pre-transplantation weight of 7.7 kg, who underwent liver transplantation with a live-donor hyper-reduced left lateral segment graft from his 38-year-old mother. Pictures depicting vascular anastomosis during implantation surgery. **a** Anastomosis between hyper-reduced left lateral segment (asterisk) graft's left hepatic

vein and the recipient's inferior vena cava (arrowhead). **b** Complete anastomosis between hyper-reduced left lateral segment (asterisk) graft's left hepatic vein and the recipient's inferior vena cava (arrow). **c** Portal vein anastomosis (arrow) with Bulldog clamp placed directly adjacent to the portosplenic confluence. Hyper-reduced left lateral segment (asterisk). **d** Arterial anastomosis (arrow)

monitoring of liver function (serum bilirubin concentration, liver enzymes levels, prothrombin time, factor V, and lactic acid) and Doppler ultrasound is performed.

Pre- and Post-Transplant Management

Details related to donor evaluation, infectious considerations, chemoprophylaxis, post-operative immunosuppressive management, and post-operative thromboprophylaxis are addressed in the Annex 1.1 through 1.4 ([Supplemental Digital Content](#)).

Variables Analyzed

Variables collected included recipient demographics (age, body mass index, diagnosis, sex, height, transplant era, transplant number, weight, pre-transplant acuity), biochemical tests on the day of liver transplantation (albumin, total and direct bilirubin, creatinine, calculated creatinine clearance, pediatric end-stage liver disease (PELD) score),⁸ operative parameters (warm ischemia time, operative time), donor variables (age, donor-recipient weight ratio, height, weight), post-operative liver function, post-operative complications, length of hospital stay, and overall survival and re-listing for liver

transplantation. Primary allograft non-function was defined as early graft failure in the absence of vascular or immunologic complications. Biliary anastomotic stenosis was defined by X-ray cholangiography or endoscopic retrograde cholangiopancreatography as a focal or segmental narrowing at the site of biliary anastomosis. Bile anastomotic leaks (fistula) were defined by emission of contrast medium seen in the X-ray cholangiography or by bile secretion seen in the abdominal drains.

Post-operative Complications and Follow-Up

Post-operative adverse events were evaluated according to the Dindo–Clavien classification of surgical complications.⁹ Major complication was defined as a complication grade \geq IIIa. Complications were classified as early or late with a cut-off time of 90 days.¹⁰ Vascular complications, including hepatic artery thrombosis and portal venous thrombosis, required radiographic or operative confirmation. Mortality was recorded when death occurred during hospital stay or up to 90 days of the follow-up period if the patient was discharged before this time point. Follow-up consisted of outpatient clinical evaluation, routine laboratory tests, tumor markers, and imaging evaluation (multislice computed tomography or magnetic resonance imaging) 1 month after surgery and every 3 months thereafter. Median follow-up time was 40.3 months.

Statistical Analysis

Categorical variables are described using percentages. Continuous variables are expressed as means and standard deviation (SD) for symmetrically distributed, and median and interquartile interval (IQI) for non-symmetrically distributed data. The primary endpoints of the study were overall survival (OS) and re-listing for liver transplantation following live-donor liver transplantation (LDLT). OS was defined as the time from surgery to death (all causes) or date of last follow-up. Kaplan–Meier method was used to estimate overall survival. Variables potentially associated to early and late complications were compared using chi-squared test or Fisher's exact test. The variables were as follows: era at transplantation (era 1: consisted of the first 30 transplanted patients, from February 1994 to November 2009; era 2: consisted of the last 29 transplanted patients, from December 2009 to February 2018), age (\leq 12 months, and $>$ 12 months), recipient's weight ($<$ 6 kg or $>$ 6 kg),¹¹ PELD score (\leq 23, and $>$ 23),¹² donor weight to recipient weight ratio (DRWR) ($>$ 8 and $<$ 8),¹³ and pre-transplantation acuity (ICU-bound).¹² Cut-off values for these variables were selected according to published literature on the subject in question. The assessment of factors associated with overall survival was calculated using Cox's proportional hazard models. Statistical analyses were performed

using STATA version 13 (StataCorp LP, TX). A *p* value $<$ 0.05 was regarded as significant.

Results

Study Population

Between February 1994 and February 2018, 1237 consecutive liver transplants were performed at the Hospital Italiano de Buenos Aires. Three hundred and sixty-three involved pediatric recipients, of which 145 (40%) were from living donors. Among the latter, 59 (41%) patients weighted $<$ 10 kg and underwent hyper-reduced LDLT.

Pre-operative Recipient and Donor Characteristics

The following data are detailed in Table 1. The hyper-reduced living-donor recipients were 32 females (53%) and 27 males (47%), with a median age of 14 months (IQI 10–19) and a median weight of 8 kg (IQI 7.1–8.9). The underlying cause of liver failure was biliary atresia in 46 cases (78%), Alagille syndrome 6, familial intrahepatic cholestasis 3, autoimmune hepatitis, secondary biliary cirrhosis, hepatitis caused by cytomegalovirus, and ornithine transcarbamylase deficiency in 1 case each. All transplants were performed electively. Regarding pre-liver transplantation acuity, 10% of the patients required admission to the Intensive Care Unit (ICU) and 14% had been admitted to the general ward before the procedure, mainly due to clinical manifestations of their underlying disease. Median PELD score was 17 (IQI 12–21), with 22% of the recipients with a PELD score higher than 23. Forty-six (78%) had undergone previous Kasai surgery. Donor median age was 31 years (IQI 31–38) and median weight was 69 kg (IQI 63–78). Median DRWR was 8.5 (IQI 7.46–9.87).

Technical and Intraoperative Variables

Median recipient operative time was 330 min (IQI 248–375), with a warm ischemia time of 120 min (IQI 70–205). Since graft procurement and receptor hepatectomy were performed simultaneously, cold ischemia time was $<$ 30 min in all patients. Donor portal vein had to be lengthened with cadaveric vein grafts in eight recipients. There were eight intraoperative portal vein thrombosis which required thrombectomy with a Fogarty catheter, reanastomosis, and/or portal vein stenting using the inferior mesenteric vein approach (3 cases). Despite hyper-reduction and due to the small recipient cavity size, a prosthetic mesh was needed for abdominal closure in seven recipients. The previous data are presented in Table 2.

Table 1 Pre-transplantation patient and donor characteristics (*n* = 59)

| | |
|---|------------------|
| Recipient | |
| Age (months) ^a | 14 (10–19) |
| Gender—female ^b | 32 (53) |
| Etiology ^b | |
| Biliary atresia | 46 (78) |
| Alagille syndrome | 6 (10) |
| Familial intrahepatic cholestasis | 3 (5) |
| Autoimmune hepatitis | 1 (1.7) |
| Secondary biliary cirrhosis | 1 (1.7) |
| Cytomegalovirus hepatitis | 1 (1.7) |
| Omithine transcarbamylase deficiency | 1 (1.7) |
| Weight (kg) ^a | 8 (7.1–8.9) |
| Height (cm) ^a | 71 (68–73) |
| Pre-transplantation acuity ^b | |
| Home | 39 (66) |
| General ward | 14 (24) |
| Intensive care unit | 6 (10) |
| Albumin (g/dL) ^a | 3.4 (2.4–3.8) |
| Bilirubin (mg/dL) ^a | 15.2 (9.1–19) |
| Creatinine (mg/dL) ^a | 0.20 (0.15–0.26) |
| International normalized (ratio) ^a | 1.22 (1.04–1.68) |
| PELD score ^a | 17 (12–21) |
| PELD score > 23 ^b | 13 (22) |
| Previous Kasai surgery ^b | 46 (78) |
| Donor | |
| Age (years) ^a | 31 (31–38) |
| Weight (kg) ^a | 69 (63–78) |
| DRWR ^a | 8.5 (7.46–9.87) |

^aMedian (interquartile interval 25–75%); ^b*n* (%)

DRWR, donor-to-recipient weight ratio; PELD, pediatric end-stage liver disease

Post-operative Variables

As stated in Table 3, median length of ICU stay was 12 days (IQR 8–17) and 16% of the patients required post-operative

Table 2 Technical and intraoperative variables in hyper-reduced LDLT (*n* = 59)

| | |
|--|---------------|
| Surgery time, minutes ^a | 330 (248–375) |
| Warm ischemia time, minutes ^a | 120 (70–205) |
| Portal Venous conduit ^b | 8 (14) |
| Biliary anastomosis ^b | |
| Hepaticojejunostomy | 55 (93) |
| Hepaticocholedochostomy | 4 (7) |
| Abdominal wall closure with mesh ^b | 7 (12) |
| Intraoperative portal vein thrombosis ^b | 8 (13.5) |

^aMedian (interquartile interval 25–75%); ^b*n* (%)

LDLT, live-donor liver transplantation

Table 3 Post-operative variables in hyper-reduced LDLT (*n* = 59)

| | |
|--|-----------|
| ICU stay (days) ^a | 12 (8–17) |
| Mechanical ventilation > 7 days ^b | 9 (16) |
| Major complications ^b | |
| Dindo–Clavien 3 | 13 (22) |
| Dindo–Clavien 4 | 28 (48) |
| Dindo–Clavien 5 | 12 (21) |
| Early complications (< 90 days) ^b | |
| Early vascular complications | 6 (10) |
| Early biliary complications | 6 (10) |
| Late complications (> 90 days) ^b | |
| Late vascular complications | 3 (5) |
| Late biliary complications | 18 (35) |
| Re-operation ^b | |
| Percutaneous/endoscopic procedure | 10 (17) |
| Open surgery | 17 (29) |
| Re-transplantation | 2 (3) |

^aMedian (interquartile interval 25–75%); ^b*n* (%)

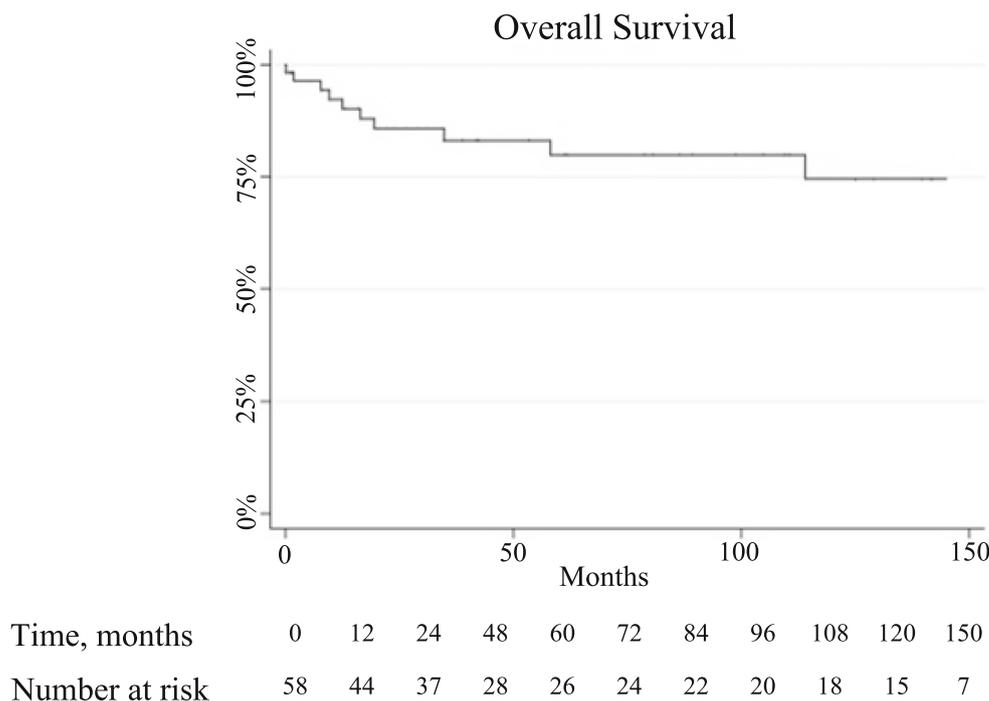
LDLT, live-donor liver transplantation; ICU, intensive care unit

mechanical ventilation for more than 7 days. There were 53 major post-operative complications distributed as follows: 13 grade III, 28 grade IV, and 12 grade V. Early complications consisted of three portal vein stenosis, three portal vein thrombosis, four biliary fistulas, and one biliary stenosis. Late complications comprised three portal vein thrombosis, three biliary fistulas, and 15 biliary stenosis. Twenty-seven patients required one or more re-interventions. After liver transplantation, percutaneous and other minimally invasive procedures were performed in 10 patients (17%) and 17 (29%) required open surgery. More specifically, anastomotic strictures and leaks were treated with a combination of percutaneous and endoscopic drainage catheters and stent placements. Only 1 patient died within the same hospital stay on post-operative day three due to multiple organ dysfunction.

Re-Listing for Liver Transplantation, Overall Survival, and Associated Variables

Median follow-up time was 40.3 months (IQR 12–114). One-, 3-, 5-, and 10-year overall survival rates were 92, 83, 79, and 74%, respectively (Fig. 3). We documented 5 patients who had to be re-listed for liver transplantation after graft failure. Two of them underwent successful liver re-transplantation 1 and 2 years after index surgery. One of them was a male patient who had undergone liver transplantation at the age of 3 years due to Alagille syndrome. He had to be re-listed 20 years after the primary procedure owing to progressive graft cirrhosis as a consequence of Budd-Chiari syndrome. The second case was a female patient had been transplanted at 2 years old secondary to autoimmune hepatitis. She was re-listed 7 months after transplantation due to

Fig. 3 Overall survival in low-weight pediatric patients who underwent live-donor transplantation with in situ hyper-reduced left lateral segment grafts. Kaplan–Meier curve



chronic graft rejection and autoimmune hepatitis relapse. These 2 patients died before re-transplantation due to refractory septic shock and multiple organ failure, respectively. The third patient had undergone liver transplantation at 12 months old due to Alagille syndrome. He re-entered the waiting list due to acute severe rejection 2 years after the initial surgery. To date, patient is alive awaiting re-transplantation.

The multivariate analysis revealed no statistically significant association between overall survival and era at transplantation, age, recipient’s weight, PELD score, DRWR, or pre-transplantation acuity. Recipient weight < 6 kg was associated with graft survival (HR 19; 95% CI 1.18–306, *p* 0.038).

A higher risk for early complications was associated with PELD score > 23 (*p* = 0.028). Early biliary fistula was associated with PELD > 23 (*p* = 0.005) and DRWR > 6 (*p* = 0.013). Early infectious complications were associated with era 1 (*p* = 0.014), age > 12 months (*p* = 0.046), recipient weight > 8 kg (*p* = 0.039), and PELD score > 23 (*p* = 0.03).

Concerning late events, PELD score > 23 was associated with late overall complications (*p* = 0.018), late overall biliary complications (*p* = 0.011), and late biliary stenosis (*p* = 0.028). The latter was also associated with early biliary fistula (*p* = 0.018). There were no variables with a statistically significant association with vascular complications.

Discussion

One of the main barriers to transplantation in the pediatric population with end-stage liver disease is the access to a

suitably sized organ, resulting in infants having the highest pre-transplant mortality rate of all pediatric liver transplant candidates.³ Because of the limited supply of suitable whole organs, many pediatric liver recipients must receive a reduced allograft. Both recipient size and liver allograft type have been found to have a significant impact in the outcomes of pediatric liver transplantation.^{14,15} Reduced-size, split-liver, and living-donor transplantations have effectively reduced the shortage of organs for pediatric patients. In small infants receiving LLS grafts, problems related to size mismatching between the recipient and the graft are still encountered in the form of so-called “large-for-size” grafts.⁶ The use of these grafts increases the risk of abdominal compartment syndrome, size discrepancies in vascular caliber, and insufficient portal circulation and tissue oxygenation.⁶ Further reducing the size of the LLS to that of a monosegment or hyper-reduced LLS graft is thus sometimes necessary. In 1984, Bismuth and Housin described the first liver size reduction technique.¹⁶ However, the concept of monosegment liver transplantation was not reported until 1992,¹⁷ and several graft reduction techniques were described since then. In this scenario, this group has previously reported that LDLT using “a la carte” ultrasound-guided HRLG is feasible and effective in recipients with concerns for large-for-size grafts.⁵ Several subsequent reports have supported the reliability and technical feasibility of HRLG.^{13,18,19}

Liver transplantation in very small infants with size-matched organs remains challenging, and long-term outcome data is still sparse. Armon et al. described the results of liver transplantation in children ≤ 5 kg using data from the United Network for Organ Sharing (UNOS) database. Authors

concluded that graft survival has improved over time, although it remains inferior to that of the general pediatric recipient population.²⁰ In 2015, Desai et al. published a series of 1311 pediatric liver transplants reporting donor weight as the most predictive factor to lower patient survival during the first year post-transplant, with analysis of the ROC curve showing a cut-off point at 7.8 kg. Authors concluded that DRWR > 1.5 was preferable, although their analysis did not show statistical significance in this regard.¹⁵ Contrary to this, a series published by Chung et al. in 2014 showed both best graft and patient survivals in recipients < 6 kg. Interestingly, these patients showed the highest incidence of biliary tract complications but the lowest incidence of vascular complications.²¹

It must be noted that pediatric patients with end-stage liver disease are chronically ill patients whose worsening clinical, immunological, and nutritional conditions contribute to a high mortality on the waiting list or, in many other cases, delisting for decondition.²² Lineker et al. recently gave guidance on this matter providing a definition of potentially inappropriate conditions for liver transplantation, with the objective of decreasing the mortality rate in the first 3 months after transplantation.²³ LDLT in low-weight children, although more technically challenging, offers a useful tool to electively treat these patients at an earlier stage of their disease.

In our series, the 1-, 3-, 5-, and 10-year overall survival rates were 92%, 83%, 79%, and 74%, respectively. These findings are consistent with those of the literature. A recent high-volume study reported overall graft and patient survival rates at 0.5, 1, 5, 10, and 20 years as follows: 76%, 73%, 67%, 63%, 53%, and 87%, 86%, 81%, 78%, 69%, respectively.²⁴ However, recipients included in this report were older—median age of 29 months—with a median weight of 12 kg. Another smaller series of LDLT recipients secondary to fulminant hepatic failure presented 10-year patient and graft survival rates of 92.9% and 90.3%, respectively.⁸ This cohort, however, did not include patients with biliary atresia. It should be noted that the mentioned studies included populations with some sensible differences (i.e., cadaveric-donor liver transplants or patients presenting primary liver neoplasm as the cause for transplantation) that differs a reliable comparison.

Concerning patient and procedure characteristics relevant to the detriment of graft and patient survival, it has been reported that a PELD score > 25 is significantly associated with graft loss, whereas UNOS status 1a and 1b and chronic rejection are significant risk factors for both graft and patient overall mortality.²⁵ In 2018, Kitajima et al. stated that significant risk factors for graft loss in LDLT included fulminant hepatic failure, high PELD score, ICU-bound, hepatofugal portal vein flow prior to LDLT, use of non-anatomically reduced LLS graft, and presence of portal vein complication and reoperation.¹² Interestingly, none of the variables included were associated with higher mortality in the present study. Body weight < 6 kg showed a statistically significant

association with graft survival. However, a single cut-off point for DRWR could not be found. In addition, body weight > 6 kg was not associated with higher patient mortality nor had any correlation with post-operative morbidity. This might be explained by the fact that pediatric liver transplantations in this difficult population are mostly performed by experienced transplant surgeons in high-volume centers, resulting in a lower rate of post-operative complications. In our institution in particular, surgeons performing liver transplantation in low-weight recipients rely on a 10- to 30-year experience in pediatric liver transplantation.

PELD score > 23 was associated with a higher risk of overall early complications, early biliary fistula, early infectious complications, overall late complications, late biliary complications, and late biliary stenosis. PELD score cut-off value was extrapolated from recently published literature.¹² Interestingly, there was no association between PELD score and post-operative mortality. The literature regarding this matter has been contradictory so far. In 2005, Bourdeaux et al. published a series of 100 pediatric recipients of LT from living-related and cadaveric donors, concluding that PELD scores at listing and at liver transplantation did not impact on patient survival, graft survival, or re-transplantation rate.²⁶ However, a more recent report of 581 recipients showed a statistically significant association between pre-operative severity of liver disease, as measured by PELD, and post-operative mortality. The correlation between these two measures was weak, however.²⁷ The disparity in these findings may have an explanation in the PELD scoring system. The PELD score has been criticized for potentially miscalculating the severity of illness in pediatric patients. Shneider et al. reported that PELD score underestimated severity of illness, leading to increased patient waiting time, and increased patient morbidity (i.e., ascites, hemorrhage, infectious complications, etc.).²⁸ PELD score is a static variable and it may not account for the dynamic condition of pediatric patients' clinical status or eventual deterioration. Furthermore, the petitioned PELD score may be higher than the calculated PELD score, highlighting the current practice of petitioning for exception points.

The present study has several limitations. On one hand, graft survival was defined as the time from surgery to the date of re-entry to waiting list in order to unify diagnostic criteria. This definition does not include cases of recipient death if the patient had not been previously listed for re-transplantation. However, some patients may have died before a diagnosis of graft failure could be made, possibly due to complications related to graft dysfunction, (i.e., hemorrhagic shock due to variceal bleeding, sepsis, or multiple organ failure). Furthermore, some patients included in the series could not complete a formal long-term follow-up. This was a problem particularly in a subpopulation of foreign patients that traveled to our institution for the transplantation. However, it should be

noted that the percentage of patient that completed long-term follow-up in our series is comparable to that of most reports on pediatric transplantation.

In addition, this series only includes cases of LDLT using hyper-reduced LLS; thus, it does not compare this technique with other transplant modalities (i.e., LDLT with whole LLS and deceased-donor liver transplantation with reduced grafts). Over 90% of low-weight pediatric patients who undergo liver transplantation at this high-volume center, received hyper-reduced grafts from living, related donors. More accurate pre-operative planning, careful donor selection, shorter ischemia times, and pre-operative assessment of vascular anatomy are among the advantages that explain this preference. A comparative study should be conducted between low-weight pediatric patients undergoing LDLT with hyper-reduced LLS, LDLT with whole LLS, and deceased-donor liver transplantation with reduced grafts. However, randomized treatment allocation in such a study would be ethically challenging. In non-randomized studies, patient selection criteria to choose between live or deceased donors and whole or hyper-reduced LLS would create two fundamentally different groups of patients due to selection bias, not suitable to be compared with statistical accuracy.

This analysis includes one of the largest series of low-weight pediatric patients who underwent LDLT with non-anatomically hyper-reduced LLS grafts. To date, our institutional experience shows that liver transplantation can be undertaken in low-body weight (< 10 kg) recipients with encouraging results. It should be possible to substantially reduce the mortality of patients on the waiting list by taking advantage of new technical options, including tailored live-donor hyper-reduced LLS grafts. Nevertheless, these procedures should be performed in high-volume centers by experienced surgeons.

Author Contribution

Category 1:
Conception and design of study: MDS, MR, and MEC.
Acquisition of data: MDS, MR, MEC, VA, and GB.
Analysis and/or interpretation of data: MDS, MR, MEC, DD, JMDP, JP, JM, CB, MC, and EDS.

Category 2:
Drafting the manuscript: MDS, MR, and MEC.
Revising the manuscript critically for important intellectual content: MDS, MR, MEC, VA, GB, DD, JMDP, JP, JM, CB, MC, and EDS.

Category 3:
Approval of the version of the manuscript to be published (the names of all authors must be listed): MDS, MR, MEC, VA, GB, DD, JMDP, JP, JM, CB, MC, and EDS.

Compliance with Ethical Standards

Informed consent was obtained from all patients before surgery and the Hospital Italiano Ethics Committee gave ethical approval to perform this study (Protocol No. 3699). The study protocol has been registered on ClinicalTrials.gov database (identifier NCT03594864).

Authorship Statement All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in *Journal of Gastrointestinal Surgery*.

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