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REVIEW

AN OVERVIEW ON PEDIATRIC LIVING DONOR LIVER TRANSPLANTATION

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Summary

Living donor liver transplantation offers a crucial alternative for young patients in need. While the feasibility and safety of this procedure in pediatric recipients have been extensively established, surgeons navigating this specialized domain encounter formidable challenges. These challenges include meticulous donor selection and evaluation, comprehensive recipient pretransplant workup and management, the intricacies of both donor and recipient operations, and life-long monitoring of surgical and medical complications - particularly those stemming from chronic immunosuppression.

In alignment with the dynamic nature of medical advancements, pediatric liver transplantation continually evolves, propelled by emerging technologies that impact various facets of both surgical and non-surgical aspects. This review, acknowledging the vastness of the subject matter, refrains from exhaustive coverage, opting instead to provide a comprehensive overview of fundamental principles. Additionally, it serves as a glimpse into rapidly progressing elements, encompassing advancements in preoperative assessments, the integration of minimally invasive surgical techniques, and the integration of cutting-edge technologies such as machine learning algorithms and artificial neural networks.

In essence, this review seeks to offer a nuanced perspective on pediatric living donor liver transplantation, capturing essential principles while highlighting key areas of innovation and progress.

Key words: pediatric liver transplantation, graft volume assessment, future liver remnant, minimally invasive donor hepatectomy, advances in liver transplantation

List of abbreviations

AI: artificial intelligence
BW: body weight
FLR: future liver remnant
GRWR: graft-to-recipient weight ratio
HAT: hepatic artery thrombosis
LDLT: living donor liver transplantation

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LFS: large for size
LT: liver transplantation
SFSS: small-for-size syndrome

INTRODUCTION

Several techniques have been recently introduced to expand donor pool and improve LT outcomes. Rapidly accumulating evidence supports the use of machine perfusion for grafts from extended criteria donors [1-3] also in the setting of pediatric LT [4-6]. Implementation of split liver in deceased donors has allowed greatly expanding the number of available grafts, especially for pediatric recipients, with excellent outcomes [7]. Nevertheless, LDLT still remains a fundamental therapeutic option to be offered to pediatric recipients, especially in some geographical areas.

Prevalence of living donor liver transplantation (LDLT) is highly heterogeneous worldwide. Living donation was initially proposed in Asia in the late 80s as a life-saving procedure in patients suffering from biliary atresia awaiting LT [8]. Developed out of necessity, LDLT still remains the commonest form of LT in Asia and in the Middle East, where it represents about 90% of liver transplant procedures [9,10]. In contrast, in Europe and the US living donation represents about 5% of donor pool and deceased donation is by far the commonest source of donor organs [10]. In Latin America, adoption of LDLT faces logistical issues due to healthcare systems regulations. However, countries like Brazil and Argentina have reported excellent outcomes of their pediatric LT programs [11]. At present, India is probably the country characterized by the fastest growing experience, with nearly 1000 cases of LDLT performed yearly, of which about 25% are pediatric procedures [12].

In pediatric LDLT, the donor - most frequently a parent or an older relative - donates part of the liver to a pediatric recipient. As compared to deceased donor LT, LDLT is characterized by unique aspects concerning donor selection and preparation, operation planning, surgical technique, and outcomes. In particular, concerns about the possibility of donor morbidity and mortality have probably been among the most important barriers to a wider adoption of LDLT worldwide. In pediatric LDLT, further specificities are represented by indications for LT, size matching and vessel size.

In recent years, pediatric LDLT has seen the advent of minimally invasive surgery and advances in 3D modeling and printing, which have improved pre-operative planning, donor safety, and some aspects of postoperative course for both donors and recipients [13]. This led some centers to reconsider this option as an opportunity to expand donor pool and overcome the shortage of suitable organs for children.

This review will provide a general overview of fundamental aspects of pediatric LDLT, including donor selection and preparation, surgical technique, and outcome. Furthermore, it will summarize most recent advances in the field, including minimally invasive approaches, radiological 3D modeling, and applications of artificial intelligence for preoperative planning and outcome prediction.

Donor selection and safety

Surgical complications and donor safety

Donors safety is a major concern in adult-to-adult and pediatric LDLT. According to a 2013 survey, average donor morbidity rate was 24%, with five donors (0.04%) requiring transplantation. Donor mortality rate was 0.2% (23/11,553) and the incidence of near-miss events such as massive bleeding or respiratory failure was 1.1% [14]. In the report by Abecassis et al. [15] the most frequent cause of donor death was multi-organ failure linked to infection and sepsis.

One of the more relevant studies in the field is the A2ALL study [16], which investigated donor morbidity in a cohort of 760 liver donors over ten years. Thirty-three procedures in this series were full left lobes procurement. The authors reported a significant association between transfusion requirement and the development of a first complication of any type (HR = 1.38 per unit; $p < 0.0001$), and specifically with the occurrence of a bile leak (HR = 1.55; $p < 0.0001$) and infection (HR = 1.40; $p = 0.0011$). Intraoperative hypotension and higher pre-donation serum bilirubin level were identified as risk factors for any type of complications [17], suggesting the need for accurate donor assessment. Interestingly, neither center experience nor year of donation were associated with the risk of complications.

In 2016 Lauterio et al. [18] collected the experience in living donation of 7 Italian centers, analyzing data of 246 transplants, including 16 pediatric LDLT cases. Authors reported excellent donor outcomes, with only one patient requiring relaparotomy for surgical repair of a diaphragmatic hernia (Clavien grade > III), whereas three patients developed pulmonary embolism (n = 1) and surgical site infection (n = 2). In this series, hospital stay of pediatric LDLT donors was significantly shorter than adult cases, although the limited sample size did not allow for a meaningful comparison of right versus left lobe donation.

Other reports in the literature [15,17] have suggested that left lobe donation could be safer as compared to right lobe donation, which is characterized by a higher incidence of blood loss, pleural effusion, and biliary fistula [11,12]. Furthermore, right lobe donation is associated with an increased risk of postoperative hepatic insufficiency, although this complication has been infrequently reported (incidence = 0.1-4%), with most cases making a spontaneous recovery [12,14,16]. A recent meta-analysis of more than 25,000 liver donors has shown that right lobe donation

is associated with an increased risk of any complication, major complications, and prolonged hospital stay [19].
However, a recent consensus conference has highlighted how, despite the lower morbidity associated with left lobe donation, in adult LDLT right lobe donation is still referred because it is associated with a lower risk of small-for-size syndrome (SFSS) and recipient operation technically less challenging, with less vascular complications, better regeneration, and better patient survival [20].

Psychological aspects of pediatric LDLT

In the Abecassis et al. [15] study, authors reported two cases death due to psychological issues leading to suicide or drug abuse. Both cases were reported after adult-to-adult LDLT, whereas the rate of psychological issues has traditionally been reported to be lower in pediatric LDLT [21] suggesting that a stronger bond between the donor and the recipient could help preventing the development of post-donation depression and anxiety. However, it is well-documented that pediatric LT determines a significant social and economic strain on donor families, with 30% reporting at least one material economic hardship (e.g., food insecurity or housing instability) [22].
Despite a number of studies having highlighted these potential issues, specific guidelines on how to evaluate psychological suitability to organ donation are lacking.
Most centers agree that informed consent, active involvement in multidisciplinary discussions, support by a live donor advocate, and the necessary period to metabolize the amount of received information are imperative steps, which should also take into account that the emotional bond with the recipient will inevitably influence donor decision-making process [21]. Spital and Taylor have argued that the dynamic of parent-child relationship complicates the attainment of rigorous informed consent from parental donors, whose decisions are predominantly influenced by emotions and not by logical information processing. Although parental donors must be thoroughly informed about the risks associated with donation, it may not be reasonable to assume that risk-benefit analysis will drive their decision, emotions and relationships holding greater weight [24].
On a separate note, Makota et al. [23] highlighted an issue observed in many liver transplant centers worldwide - the tendency to consider the living donor as a "non-patient". They emphasized the contrast with the extensive care provided to recipients, who are considered the "real" patients, absorbing the majority of attention and concern. This disparity in treatment appears to be significantly underestimated in clinical practice, with repercussions potentially persisting for years after donation. In their series including 15 pediatric LDLT cases, 30% of donors experienced marital problems post-donation, leading to divorce in two cases.
Recognizing these challenges, Dien et al. [25] conducted a study aimed at assessing pre-donation intervention to prevent psychosocial issues arising after donation. In contrast with its premises, this study concluded by recommending the implementation of a long-lasting post-donation monitoring protocol to detect and address potential difficulties and issues related to organ donation. Despite these concerns, however, Benzing et al. [26] reported excellent long-term outcomes in terms of the quality of life for live donors. In their comparative study, authors found that live donors exhibited superior results compared to the general population, particularly regarding self-esteem and overall quality of life. Thus, while the relevance of psychological aspects in pediatric LDLT should not be underestimated, this should not discourage LDLT practice.

Donor evaluation and selection

If psychological aspects are central in donor selection and evaluation [21], proper clinical assessment is even more important. Full clinical evaluation should include medical history, clinical examination, as well as laboratory and radiological findings (Fig. 1).
Considering that LDLT could reduce pediatric waiting list mortality to 3% [27], donor evaluation should be put into the context of how precious this opportunity could be for a children waiting for an organ.
For this reason, Kashara et al. [28] recently proposed a new point of view in parental liver donation, introducing the concept of "marginal parental donors". Authors stressed the necessity of avoiding any additional hazards in living donation and identified some rare conditions potentially dangerous for both the donor and the recipient, including rare genetical disorders such as congenital deficiency of protein C, Alagille syndrome and acute intermittent porphyria. These conditions must be carefully investigated and ruled out be in potential donors before start planning the donation process.
An unavoidable step is represented by the radiological work-up aimed at defining liver anatomy and quantifying the volume of future liver remnant (FLR). Eighty-eight percent of north American centers use a combination of computed tomography and magnetic resonance imaging in living donor preoperative study [29]. These techniques allow surgeons and radiologist to identify anatomic anomalies (surgical reconstructive techniques will be discuss later in this paper) and study liver parenchyma, which is important to exclude presence of unexpected liver lesions. Indeed, areas of focal nodular hyperplasia do not represent a contraindication to donation, whereas hepatic adenomas represent a contraindication due to the risk of bleeding and malignant transformation [30,31]. Graft and future liver remnant volume estimation are key objective of radiological work-up. From the recipient perspective,

graft weight should avoid both small-for-size and large-for-size syndromes. A large-for-size graft, especially in a pediatric recipient, may be associated with compression and inadequate blood supply [31]. From the donor perspective, insufficient FLR represent a major contraindication to living donation [32,34] even this is a frequent issue in adult rather than pediatric LDLT, in which the vast majority of grafts are represented by segments 2-3.

Surgical technique

Graft volume

Planning of donor operation is a paramount step in pediatric LDLT and it is driven by considerations on graft volume and anatomy. The liver represents 4-5% of body weight at birth, but only 2% in adults. The optimal proportion between graft and recipient weight (graft-to-recipient weight ratio, GRWR) has been widely debated. In 2021 Kusakabe et al. [35] have discussed the fact that the lower GRWR or standard liver volume ratio thresholds have been arbitrarily set by many transplant centers at 0.8% and 40%, respectively. However, many institutions have questioned the appropriateness of this limit, reporting similar incidence of SFSS in cases with GRWR < 0.8% [36,37]. This might be, in fact, a limited perspective, as there are many other factors influencing the possibility to develop SFSS, including donor age, steatosis, and recipient characteristics, especially the degree of portal hypertension. According to Kusakabe et al. [35], a pragmatic approach could be modulating the boundaries of GRWR based on the peculiarities of each case, accepting a minimum 0.6% GRWR in low-risk cases, whereas this should be ⩾ 0.8% in high-risk cases.

In 2023, Kasahara and Sakamoto [32] reviewed the importance of age and body weight on transplant outcome, trying to define optimal GRWR in pediatric LDLT. In this review, a GRWR < 1.5% was associated with an increased risk of SFSS, especially in adolescent transplanted with a left lateral section (LLS) graft, suggesting that patients of this age may require larger grafts as compared to adults of similar weight. Authors proposed the following scheme to drive graft choice based on recipient weight (BW): BW < 5 kg: reduced LLS; 5 kg ⩽ BW < 25 kg: LLS; 25 kg ⩽ BW < 50 kg: left lobe (Couinaud segment II, III and IV with middle hepatic vein); BW ⩾ 50 kg: right lobe (Couinaud segment V, VI, VII and VIII without middle hepatic vein), ⩽ 50 kg.

Upper boundaries of GRWR are also important. A large-for-size (LFS) graft may lead to initial poor function due to compression and ischemia. Therefore, a thorough evaluation of the graft size and recipient abdominal cavity based preoperative imaging studies is crucial, especially in small infants without portal hypertension.

There are notable anatomical differences in the shape of the left-sided graft in potential donor candidates. To accommodate the graft in the small abdominal cavity of pediatric recipients, the practice of carving LLS grafts has been introduced. Kasahara et al. [32] have suggested that when estimated GRWR is > 4% a reduced LLS graft must be considered.

As a matter of fact, a LLS graft is most commonly used and fulfill metabolic requirements of the majority of patients. Furthermore, this choice undoubtedly represents the safest approach for the donor both in terms of FLR volume and surgical complications. Despite that, in some older children with higher weight, a LLS graft could be insufficient [36].

In this setting, Wan et al [38] reported their experience with the use of right posterior segments as an alternative to LLS for children weighing > 15 kg and living donors with a favorable anatomy, i.e., right posterior portal vein branching separately from the main portal vein, which accounts for about 20.3% of healthy adults. The authors reported their experience with 4 cases out of 1868 pediatric LDLT performed over 5 years, showing comparable outcomes to children undergoing LDLT with a classical LLS graft. Advantages of this approach include the preservation of middle hepatic vein in the donor and the position of the right posterior graft in recipient abdominal cavity, avoiding the risk of portal vein kinking.

Besides volume, portal flow and pressure are main factors associated with the risk of SFSS. There is substantial evidence indicating that elevated portal vein pressure

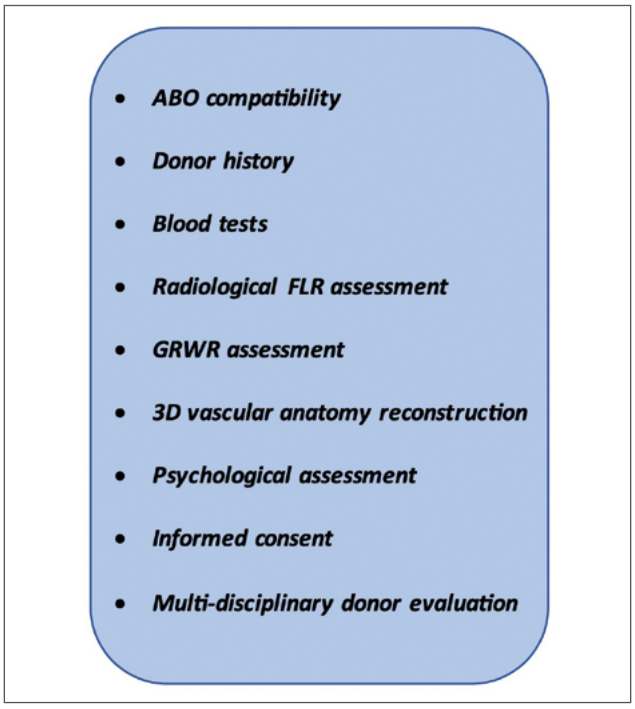

Figure. 1. Critical steps in donor work-up.

(PVP) in a small-for-size graft can induce sinusoidal shear stress, disturb hepatic microcirculation, cause functional inadequacy in hepatocytes, lead to excessive hepatocyte regeneration, cellular damage, and subsequent cell death. This might be further aggravated by inadequate venous outflow, which could lead to graft congestion and reduced arterial perfusion, consequently limiting liver regenerative capacity and resulting in impaired liver function.
As proposed by the 2023 ILTS-LDLTS-LTSI recommendations 20 PVP should be maintained below 15 mmHg to prevent graft damage. However, some studies have suggested that even a PVP of 15-20 mmHg might not significantly increase SFSS risk, while there is a general consensus that a PVP exceeding 20 mmHg should be avoided.
Similarly, excessive portal venous flow, representing the volume of blood circulating through the liver, should be avoided. This might be an issue especially in patients with portal hypertension, who present a hyperdynamic splanchnic circulation due to the loss of vascular tone and altered hemodynamics. The upper threshold of portal venous flow is debated, as values between 250 and 360 ml/min/100 gr of liver parenchyma have been proposed [39].
Careful intraoperative monitoring of recipient systemic and splanchnic hemodynamics should dictate the decision to employ measures aimed at modulating portal vein flow, including splenic artery ligation, splenectomy, and portocaval shunts (HPCS) [17].

Vascular anatomy

Hepatic veins

Surgical reconstruction of venous outflow should follow Poiseuille law by which flow is proportional to the diameter of the vein and hence to the corresponding liver parenchyma territory [40]. Three-dimensional modeling has greatly enhanced the possibility to plan preoperatively venous outflow reconstruction (Fig. 2) [41].
In pediatric LDLT using LLS grafts, venous outflow reconstruction is influenced by anatomical variations of the left hepatic vein.
In most cases, LLS is drained by a single left hepatic vein (LHV), which is anastomosed to recipient inferior vena cava (IVC). However, in up to a third of cases, variations in venous drainage of segment 2 (V2) and 3 (V3) result in multiple outflow tracts.
Shankar et al. [42] reviewed vascular anatomy of 296 donors and proposed the following classification of LLS venous drainage:

- Type 1: a single LHV (n = 270; 91.2%), formed by the confluence of V2 and V3. This group was further subclassified into Type 1a and 1b based on LHV length > 9 mm;
- Type 2: V2 and V3 drain separately into IVC without forming a common LHV (n = 6; 2%);
- Type 3: V2 drains into IVC, whereas V3 drains into middle hepatic vein (n = 20; 6.8%).

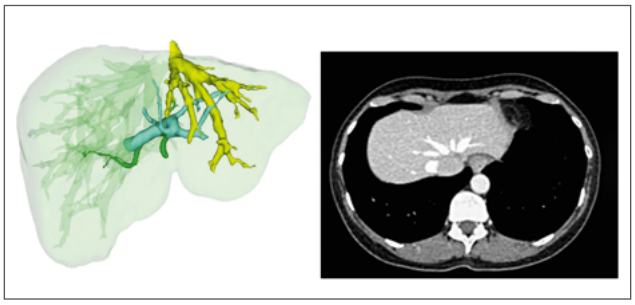

Figure. 2. A 3D-reconstruction of the venous outflow of a left lateral section (S2-S3) graft.

In Type 1 anatomy, and especially in type 1a, no venous reconstruction is generally needed.
In presence of type 2 or type 3 variations, venous outflow reconstruction may require performing a venoplasty (Type 2) or using a venous graft from a deceased donor (Type 3), depending on the distance between the venous stumps.

Hepatic artery

Incidence of arterial complications in LDLT is 15-25%, representing a significant cause of morbidity and mortality [43]. Yilmaz et al. [44] reported a rate of hepatic artery thrombosis (HAT) of 6.7 %. In the literature, incidence of HAT varies between 2 and 15%, representing the indication for about half of early retransplants, whereas other hepatic artery anastomosis-related complications such as pseudoaneurysm and bleeding are rare [43].
In LDLT, hepatic artery reconstruction differs from whole liver LT with regards to vessel caliper, orientation and structure in general.
In 2023 Salimi et al. [45] compared results of hepatic artery reconstruction using a continuous suture versus interrupted stitches in a series of 194 patients, in which a continuous suture was employed in the vast majority of cases (n = 178; 91.7%). In keeping with previous studies [46,47], Authors reported no differences in terms of HAT and other surgical complications. In contrast, Coelho et al. [48], in a series of 200 patients, reported higher rate of HAT associated with the continuous suture technique.
In 2019, Balci et al. [49] reviewed surgical techniques for hepatic artery reconstruction in LDLT, with particular reference to the use of a continuous suture versus interrupted stitches and the use of magnifying loupes *versus* microscope, concluding that surgical technique should be tailored to donor and recipient anatomy and surgeon preferences.
Several alternative techniques have been proposed. Okochi et al. [50], based on their experience with murine liver transplantation, proposed to perform the posterior

wall of hepatic artery anastomosis by a continuous suture, using interrupted stitches for the anterior wall. This technique was used in 13 patients in the period 2006-2010, none of which developed HAT during follow-up. Haberal et al. [51], in a series of 54 LDLT, proposed a combination of continuous sutures and interrupted stitches helped by the apposition of exposure stay sutures on the spatulated arterial stumps.

With regards to the use of magnifying instruments, Elkomos et al. [52] reviewed 10 studies involving 1939 patients. When comparing magnifying loups versus microscope, no discernible differences were identified in terms of surgical complications and HAT rate, but using a microscope prolonged the time required to perform the anastomosis. Authors concluded that there is no additional benefit derived from the routine use of microscopic surgery in hepatic artery anastomosis in LDLT.

Portal vein

In standard cases, portal vein anastomosis is usually performed end-to-end using 5/0 or 6/0 polypropylene sutures [43]. In pediatric LDLT, difficulties in portal vein reconstruction most frequently arise from portal vein hypoplasia in the recipient. The Leuven group [53], in a series of 250 pediatric LDLT, has extensively reported on reconstruction techniques to deal with this issue. In patients with portal vein hypoplasia, they suggest a lower dissection, up to the origin of superior mesenteric vein, associated with an anterior portoplasty, the distance between the venous stumps possibly being bridged using a venous jump graft. In case of hypoplasia extending to the origin of superior mesenteric vein, a lateral portoplasty using a donor venous patch to enlarge recipient venous stump can be used, allowing the following anastomosis to be performed in a standard end-to-end fashion (Fig. 3).

Biliary anatomy and reconstruction

Biliary complications are considered the "Achille's heel" of liver transplantation [54]. Although some biliary complications arise as a consequence of impaired hepatic artery inflow or ischemia reperfusion injury [55], a complex surgical reconstruction can be associated with pos-toperative complications.

Over 20 years ago, Renz et al. [56] published a milestone paper describing four types of biliary anatomy in LLS grafts (Fig. 4). The most frequently observed anatomy (Type 1, 55%) is the union of segment II and III ducts to form the left lateral segment duct within 1 cm of the umbilical fissure. In 30% of cases, the LLS duct forms close to the umbilical fissure, followed by the union of 2 parallel ducts from segment IV to form the left hepatic duct. The third type (10% of cases) is represented by a single segment III duct that receives a duct from segment IV and joins segment II duct close to the hepatic hilum. The rarest

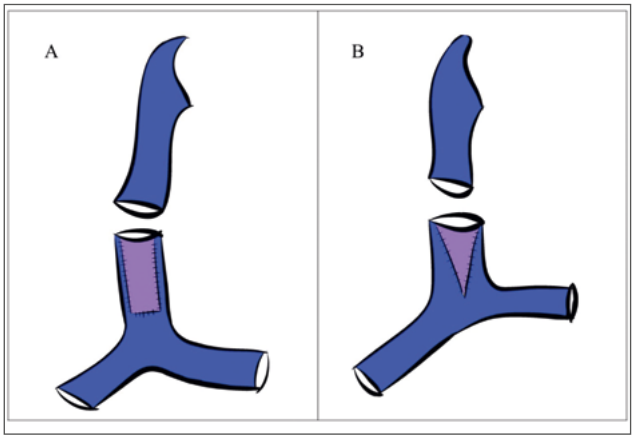

Figure 3. Examples of different portoplasty techniques to deal with portal vein hypoplasia.

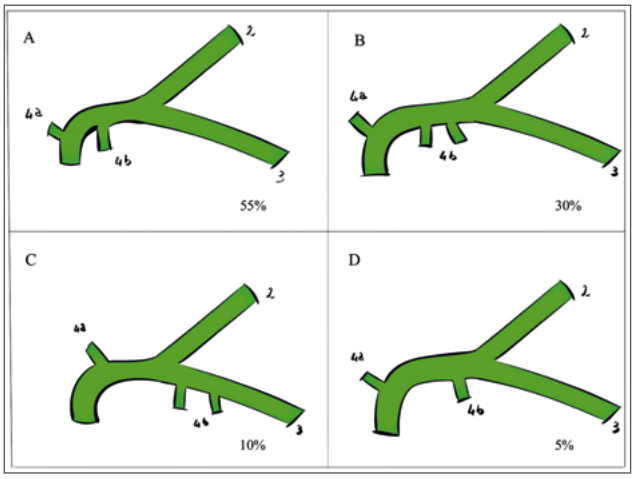

Figure. 4. Anatomical variations of left hepatic duct.

type of biliary drainage (5% of cases) is characterized by segment II and III ducts joining immediately to the right of the umbilical fissure to form a very short LLS duct, in which subsequently drains segment IV duct. Given this anatomy, Authors suggested that, if bile duct transection is performed 1 cm to the right of the umbilical fossa, performing a double biliary anastomosis is required in ≤ 10% of patients.

In any case, a careful preoperative evaluation of biliary anatomy is required to plan biliary transection plane [57].

Outcomes

Pediatric LDLT has traditionally been associated with excellent outcomes [1,58-60].

Kashara et al. [61] reported one of the largest cohorts worldwide, collecting data from 2224 recipients transplanted from 1989 to 2010 in Japan. Patient survival at 1, 5, 10 and 20 years post-LDLT was 88.3, 85.4, 82.8 and 79.6%,

respectively. ABO incompatibility, recipient age, etiology of liver disease and transplant era were significantly associated with survival, while recipient-liver graft size matching was significantly associated with a successful outcome.

Similar results were reported by Zhang et al. in Bejing (China) [60]. This group compared outcomes of pediatric transplantation from deceased versus living donors reporting similar survival rates but with a higher incidence of vascular complications in recipients of a graft from a cadaveric donor.

Song et al. [62] from Shanghai (China) focused their work on pediatric LDLT in children with metabolic disease. Authors showed a lower rate of early allograft dysfunction in recipients of LDLT when compared to deceased donor LT; however, patients in this group had significantly longer recovery, which could be correlated to the younger age of patients in this group.

In 2017, the Indian group coordinated by Mohan et al. [63] collected data from 200 pediatric LDLT cases, including 2 domino LT. Retransplantation rate was 1.5% in this series, whereas 1- and 5-year actuarial patient survival was 94 and 87%, respectively. Interestingly, 57 LDLT were performed for acute liver failure thanks to the ability to complete donor assessment in 6-8 hours.

As compared to LT with a split liver from a deceased donor, pediatric LDLT has been associated with similar 1-, 3-, and 5-year survival [64]. In a UNOS database analysis by Dalzell et al. [64], data about 911 consecutive pediatric LT were analyzed, showing a lower rate of primary nonfunction and graft dysfunction, and shorter hospital stay in LDLT recipients; on the other hand, patients in this group had a higher rate of overall vascular complications, although HAT rate was similar between the two groups.

Biliary complications still remain a major concern in pediatric LDLT, affecting about 20% of recipients [65] Sanada et al. [66] reported 54 cases of biliary complications after pediatric LDLT, the vast majority of them (n = 46) being anastomotic strictures. Authors proposed a management algorithm based on recipient weight and intrahepatic biliary dilatation, suggesting a "step-up" approach including balloon dilatation, rendezvous approach and, only in case of failure of all other approaches, redo surgery. Authors also proposed routine placement of a biliary stent during hepaticojejunal anastomoses and stressed the importance of early diagnosis of biliary complications in children.

Expanding on Sanada recommendations, Yoshizumi et al. [54] proposed double balloon enteroscopy as the treatment of choice for biliary strictures after pediatric LT.

Innovations in pediatric LDLT

Minimally invasive donor surgery

Minimally invasive approach to living donation has become standard of care at many high-volume centers [67,68] with a growing number of reported cases (Tab. I). In pediatric LDLT, early strides towards a minimally invasive approach leveraged literature on oncologic surgery, showing the superiority of laparoscopic versus open LLS resection in terms of hospital stays, blood losses, patient recovery, and surgical complications [69]. In 2002, Cherqui et al. [70] first described laparoscopic living donor hepatectomy in pediatric LDLT as safe and feasible. Although this experience was encouraging, the growth of laparoscopic donation was perhaps slower than anticipated, possibly reflecting the reluctance to apply a technique that was still considered as experimental to the delicate setting of living donor surgery. Thanks to the accumulating evidence on the benefits of laparoscopic liver surgery, which fostered a progressive acceptance and expansion of the technique, also minimally invasive donor surgery gained popularity [71]. In 2014, the second international consensus on laparoscopic liver resection held in Morioka (Japan) [72] concluded that left lateral sectionectomy for pediatric transplants is associated with the advantages of minimally invasive surgery without compromising donor safety [73,74].

In 2015, Lee et al. [68] reviewed 480 cases from 32 series and identified three different techniques for laparoscopic left lateral sectionectomy: pure laparoscopic, hand-assisted, and hybrid techniques.

Kim et al. [13] reported their experience with the systematic use of ultrasonic dissectors and radiofrequency energy in a series of 31 donors, showing that the laparoscopic approach was associated with a lower rate of surgical complications and shorter hospital stay.

The first series of robotic donor hepatectomy was reported in 2012 by Giulianotti et al. [75]. Robotic living donor hepatectomy was also slow to implement, likely due to the limited availability of the technology and its costs. A 2017 review [76] on robotic liver surgery included only two series of robotic donor hepatectomy, of which none in the setting of pediatric LDLT.

In 2022, Broering et al. [77] reviewed the literature on robotic donor hepatectomy, reporting data from three Asian centers (including their own) comparing robotic versus open donor hepatectomy [78-80]. The robotic approach was consistently associated with lower blood losses, lower incidence of postoperative complications, and shorter recovery. They suggested that, as compared to the standard laparoscopic approach, the advantages of robotic surgery are linked to enhanced ergonomics, stable visualization, improved dissection, and the ease of performing intracorporeal sutures, allowing the operating surgeon to closely reproduce the same steps performed during open surgery by a minimally invasive approach. In Authors experience, the unavailability of robotic ultrasonic dissectors was largely compensated by the increased ergonomics

Table I. Relevant articles on applications of minimally invasive techniques in LDLT.

Author	Year	Type	No.	Setting	Technique	Results
Cherqui et al. [70]	2002	Case report	2	Pediatric	Laparoscopy	Laparoscopic donor hepatectomy was safe and feasible
Park et al. [68]	2015	Review	480	Adult - pediatric	Laparoscopy	Comparable outcomes between different techniques
Kim et al. [69]	2021	Case series	31	Pediatric	Laparoscopy	Laparoscopic approach was associated with shorter hospital stay and less complications
Suk-Suh et al. [84]	2021	Case report	1	Adult	Laparoscopy	Fully laparoscopic donor hepatectomy and recipient operation were safe and feasible
Giulianotti et al. [75]	2012	Case report	1	Adult	Robotic	Robotic donor hepatectomy was safe and feasible
Broering et al. [77]	2022	Review	100	Adult - pediatric	Robotic	Robotic donor hepatectomy was associated with shorter hospital stay and less complications
Lee et al. [79]	2021	Case report	1	Adult	Laparoscopic and robotic	Laparoscopic donor hepatectomy followed by robotic implant was safe and feasible
Troisi et al. [82]	2021	Retrospective cohort study	75	Pediatric	Laparoscopic and robotic	Laparoscopic and robotic donor hepatectomy showed comparable outcomes, with a faster learning curve for the robotic approach

and visualization, causing no increase in bleeding during parenchymal transection. These advantages were reflected by the increasing prevalence of robotic donor hepatectomy at Authors centers, which was limited only by logistic issues [77]. Furthermore, it should be underlined that a robotic ultrasonic dissector might become available in the near future.

The increasing interest in robotic surgery as applied to abdominal transplantation was highlighted by a 2023 bibliometric analysis by Rawadesh et al. [81] which identified 160 articles from 2001 to 2021, with a peak of 22 articles published in 2018. The global attention on this topic was reflected by the high number of citations (n = 2287), averaging 14.9 citations per article.

In the setting of pediatric LDLT, Troisi et al. [82] compared robotic versus laparoscopic left lateral sectionectomy, concluding that the robotic approach was safe and yielded comparable outcomes to the laparoscopic approach in terms of donor morbidity and recipient outcomes. This study also highlighted a shorted learning curve associated with the robotic approach, which was partially referred to the fact that surgeons who embarked in the robotic program had already completed their training in laparoscopic surgery.

Minimally invasive recipient surgery

Almost twenty years after the first report of laparoscopic donor hepatectomy [83]. Sun et al. published in 2021 the first report of pure laparoscopic living donor liver transplantation, during which graft implantation was performed by instruments inserted through laparoscopic ports, after introducing the liver in the abdomen through a suprapubic incision [84]. Authors reported optimal recovery for both donors and recipients, considering this procedure as a milestone.

However, despite the interest generated by the application of minimally invasive techniques in the setting of recipient operation in LT [85] it is unclear whether these could be applied to a significant proportion of recipients [75].

Similarly to what has been observed in the setting of donor hepatectomy [80], it is possible that the enhanced dexterity and visualization allowed by the robotic platform could contribute expanding the indications for a minimally invasive approach in recipient operation.

Artificial intelligence and LDLT

Artificial intelligence and deep learning techniques are expected to significantly enhance outcomes and training in LDLT, their application having been made possible by the amount of information generated by modern health data systems.

In 2022, Park et al. [86] reported on the well-known feasibility of CT-based liver volume prediction in preoperative planning for liver donation and introduced the potential for automated liver segmentation using software equipped with deep learning algorithms, an approach which would facilitate and automatize precise preoperative planning.

Deep learning techniques have been extensively explored in donor identification and screening. In 2023, Sauthier et al. in 2023 [87] proposed an algorithm based on a machine learning model to identify potential organ donors. The model successfully identified 397 ideal potential donors among 19,000 patients within the system, relying on blood tests, imaging, and medical charts. This preliminary experience suggests the capacity of machine learning algorithms of minimizing human intervention in donor selection.

Recently, Bondoc et al. [88] reviewed machine learning and deep learning algorithm applications in liver transplantation, which include optimization of waiting list priority and organ allocation, psychosocial evaluation, quantification of allograft steatosis, as well as prediction of survival, rejection, complication and recurrence of disease after transplantation.

It is likely that these models will facilitate data-driven decisions also in the field of pediatric LT. For example, Rajanayagam et al. [89] using an artificial neural network approach, developed a model predicting a negative outcome (death or need for transplant) in pediatric patients presenting with acute liver failure. This model was characterized by an area under the ROC curve of 0.96, 82.6% sensitivity and 96% specificity, and outperformed PELD and MELD scores. Machine learning algorithms have also been used to predict an ideal outcome at 3 years post-LT (patient alive with normal ALT and GGT, no retransplant, normal glomerular filtration rate, no cytopenia and no post-transplant lymphoproliferative disease) based on recipient characteristics and early complications [90]. Taken together, these models pave the way for increased personalization and precision in transplant medicine and surgery.

3D Printing in LDLT

Imaging software have proven highly beneficial in pediatric LDLT planning by enabling the printing of three-dimensional models of grafts. In our experience [41], this led to a more precise and "spatial" understanding of donor anatomy during LLS donor hepatectomy (Fig. 5). The 3D model was particularly useful to define vascular relationships at the hilar plate and to plan the transection point of the left bile duct (Fig. 2).

Figure 5. A 3D printed model of a left lateral section (S2-S3) graft.

In 2016, Soejima et al. [91] described a similar experience, in which real-size 3D printing models of the LLS graft and recipient abdominal cavity were created, simulating positioning of the graft in the abdomen during the transplant to reduce the risk of small-for-size or large-for-size syndromes.

In the series by Park et al. [92], three different models of the abdominal cavity were created to prevent large-for-size syndrome during implantation in small recipients. Notably, authors stressed the possibility to generate these models in under 10 hours, suggesting their potential use even in unplanned transplants and beyond the scopes of living donation.

In 2022, Cheng-Yen-Chen et al. [93] reported data on 30 consecutive pediatric LT, representing one of the first series of LDLT conducted with a routine use of 3D models for pre-operative planning. As compared to "classic" pediatric LDLT, the group in which 3D model were routinely used was characterized by lower body weight and a higher graft volume reduction rate, with all recipients receiving modified LLS grafts. This supports the utilization of 3D models to attain an ideal "tailored graft".

CONCLUSIONS

Pediatric LDLT is characterised by an inherent complexity at different levels, from donor selection and interaction with the recipient and his family, to planning and performing donor and recipient surgery, and managing postoperative course of LT in the short and long term.

Improvements in imaging and radiological workup (including 3D modeling and printing), a better understanding of liver anatomy and refinements in surgical technique and postoperative management have contributed to making pediatric LDLT a highly successful treatment, characterized by excellent recipient survival and donor safety.

Recent advancements like the introduction of the laparoscopic and robotic approaches for donor hepatectomy have further lowered the rate of surgical complications and reduced the functional and esthetic consequences of donation. In the near future it is expected that machine learning approaches will help tailoring decision making to each individual patient necessities, improving donor identification and workup, better informing the indication for LT, and personalising monitoring schedules.

This will help achieving the ultimate goal of pediatric LDLT, which is zero mortality on the pediatric waiting list worldwide and excellent survival and health-related quality of life for pediatric LT recipients [94-96].

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

DC: performed literature review, prepared artwork and drafted the manuscript; SC: assisted in literature review and manuscript drafting; GL: prepared artwork and revised the manuscript; AN, MP, PLC, LP, MS: revised the manuscript for important intellectual content; DP: designed the study and contributed to manuscript drafting and revision; RR: revised the manuscript and supervised production.

Ethical consideration

Given the nature of this manuscript, formal Ethical Approval by an appropriate Committee was not sought.

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