

Review Article

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Confronting the Cadaveric Donor Liver Shortage: A Review of Split-Liver Transplantation

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Abstract

As the sole treatment for end-stage liver disease, Liver Transplantation (LT) must be maximized. With the stagnant number of donor liver allografts unable to account for the demand of the LT waiting list, expansion of the donor pool for both children and adults is essential. Split-Liver Transplantation (SLT) can mitigate the shortage of cadaveric donor livers by doubling the yield of a single allograft, enabling liver replacement in two recipients. Given the scarcity of size-matched cadaveric organs for children, the pediatric population stands to benefit most from SLT and the exploitation of the liver's segmental anatomy and regenerative capacity. We explore the evolution of SLT leading to its present state of outcomes, highlighting donor/recipient selection, surgical technique, and the most current results.

Abbreviations

LDLT	:	Living-Donor Liver Transplantation
LT	:	Liver Transplantation
MELD	:	Model for End-Stage Liver Disease
RLT	:	Reduced-Liver Transplantation
SLT	:	Split-Liver Transplantation
UCLA	:	University of California, Los Angeles
US	:	United States
WLT	:	Whole-Liver Transplantation

Background

Donor liver shortage prevents the necessary expansion of Liver Transplantation (LT). Owing to the liver's segmental anatomy and the fundamental principle that a component of the liver with a suitable vascular pedicle, bile duct, and venous drainage, along with sufficient functional hepatocyte mass, sustains equivalent hepatic function as a whole organ, the liver can be separated into two independent and transplantable anatomic units [1]. Realizing the

pediatric population's stringent need for donor-recipient size and weight homogeneity, compounded with the low number of pediatric donors, Bismuth and Houssin [2] spearheaded efforts in harnessing the liver's potential for size alteration. First described in 1984, they reported the feasibility of Reduced-Liver Transplantation (RLT) in pediatric recipients presenting with a deteriorating clinical picture for whom no whole allografts can be located. Dependent on size stipulations, the liver allograft may be tailored, with segments II and III (left lateral segment) and segments II, III, and IV (left lobe) most commonly used for pediatric patients [1]. Despite the greater complexity of RLT, in conjunction with the higher frequency of critically-ill recipients selected for the procedure, outcomes between RLT and Whole-Liver Transplantation (WLT) are now comparable [3-5]. Furthermore, there may be a lower incidence of hepatic arterial complications following RLT, attributable to the larger caliber of the adult hepatic artery [5,6]. While enlarging the relative donor pool for the pediatric population, RLT does not increase the total number of organs available for LT since there is an equivalent reduction of liver allografts available for adults.

Living-Donor Liver Transplantation (LDLT), in which a portion of the liver from a living donor is transplanted, was a natural evolution from RLT. Raia, et al. [7] and Strong, et al. [8]

first demonstrated the viability of this procedure leading to over 1,000 LDLTs worldwide in the ensuing decade. With comparable outcomes to WLT, experienced centers report survival rates exceeding 90% after 1 year [9-12]. Moreover, LDLT imparts additional benefits: the possibility to perform LT prior to the waning of recipient clinical condition, timing convenience and maximal preparation for both the transplant center and recipient, selected histocompatibility between donor and recipient, and psychosocial value for the donating party. While there are particular advantages to LDLT, unresolved risks for living donors, including bile leaks, liver insufficiency, and even death, persist [13]. Additionally, with LDLT being the predominant form of LT in most Asian countries, donor death and complications after LDLT bring forth ethical questions, especially in areas underutilizing cadaveric donation. This situation is exacerbated by the fact that donor morbidity/ mortality incidental to LDLT is underreported given the perceived threat to programs' survival ratings.

The cutting-edge technique of SLT allows for division of a whole cadaveric organ into two functioning allografts, thereby increasing the total number of donor organs. First documented by Pichlmayr, et al. in 1988 [14] and shortly thereafter validated as sustainable and effective via the Rogiers et al. experience [15], SLT represents a promising method to decrease reliance on LDLT and relieve the strained supply of donor allografts. If half of potentially appropriate split-liver donors were made available for SLT, the entire unmet need for pediatric donor livers in the United States (U.S.) would be satisfied [16]. While recent studies have shown improved outcomes in SLT [17-20], < 10% of donors meeting SLT criteria between 1996 and 2006 were made available for splitting [21]. This inadequate utilization of split-liver allografts may in part be derived from early reports of unsatisfactory outcomes in adult recipients following SLT [19,22,23]. In the current liver allocation scheme, many high-quality, splittable livers are allocated to high Model for End-Stage Liver Disease (MELD), critically-ill adult patients. For the majority of these patients, SLT is not an option [18,20,24]. We believe liver allocation policy requires revamping in order to maximize the total number of livers and allow as many patients as possible to be transplanted and benefit from this limited resource.

Donor/Recipient Selection

Meticulous donor selection is critical for the success of SLT. Perhaps most important is accurate donor assessment from the procurement team, with careful consideration for the potential allograft's size, vascular and biliary anatomy, and parenchyma quality and quantity [25]. Normal color and texture, equal perfusion, and sharp edges are characteristic requirements of the cadaveric split-donor allograft [20]. While variations exist across transplant centers, criteria for optimal donor selection commonly include the following: younger age (40 ~ 10 years of age) with a body weight

above 60 kg, body mass index < 30, minimal hospitalization time (< 7 days) with an absent or scant arrest period (< 30 minutes), and in stable hemodynamic conditions along with liver function test results within 3 times the normal range [26,27]. Other factors that can affect donor suitability include vasopressor requirements (no more than single-agent) and serum sodium concentration (< 155 mEq/L).

Appropriate size-matching is essential to prevent postoperative small-for-size syndrome, with a minimum allograft weight/recipient weight ratio of 0.8% [28,29]. Maximum allograft size consideration is an even greater limiting factor in SLT, as the prospective pediatric recipient is often the index patient. It is very common to cancel a split procedure due to the excessive size of a left lateral segment, and in some desperate situations the left lateral segment is reduced further down to monosegment. In addition to allograft size requirements, illness severity is a significant constituent in recipient selection. For adult recipients, SLT is often reserved for patients who are not critically-ill (without marked portal hypertension and an excessive MELD score). Decompensated, portal-hypertensive adult patients overwhelm the split allograft due to a lack of sinusoidal space, which is unable to manage the increased portal flow associated with decompensated cirrhosis [20]. Given the scarcity of size-matched cadaveric organs for children, pediatric SLT recipients are often of greater acuity. As it has been reported that urgent SLT recipients have lower survival rates compared to nonurgent recipients [18], the greater proportion of acute pediatric recipients may explain the younger cohort's higher rate of mortality post-SLT [29].

Surgical Technique

Two types of SLT, *ex vivo* and *in situ*, have been described. Pichlmayr, et al. [14] first advocated SLT as an *ex vivo* procedure with liver preparation occurring at the recipient institution following standard rapid en bloc organ procurement. While *ex vivo* dissection lengthens cold ischemic time and exposes the allograft to rewarming during the splitting procedure, routine procurement practice at the donor hospital is preserved, minimizing the need for logistical coordination [25]. Moreover, *ex vivo* splitting enables a more complete evaluation of an allograft's vascular and biliary structures through imaging, e.g. angiography, cholangiography, and dilute methylene blue instillation, which assists in the identification of allograft split-suitability and splitting fidelity. On the other hand, *in situ* procurement derives from the principles of LDLT, with intention to curtail cold ischemic time and improve post-reperfusion hemostasis [15]. Hilar dissection and parenchymal transection take place in the heart-beating cadaver immediately prior to aortic cross clamp and organ cold perfusion. In addition, *in situ* SLT allows for assessment of the two allografts directly after parenchymal transection and before vascular interruption to confirm adequate perfusion. Upon allograft reperfusion, the

in-situ technique results in significantly less bleeding [26,30]. Furthermore, *in situ* procurement facilitates allograft sharing via direct shipment from the donor site [31,32].

Splitting methodology depends on the recipients' age cohorts, either adult/pediatric or adult/adult. The vast majority of SLT procedures have been performed to treat one adult and one pediatric recipient. In these cases, the liver is split into a smaller portion (left lateral segment- segments II and III) for the pediatric recipient and a larger portion (extended right lobe- segments I, IV-VIII) for the adult recipient. This division necessitates isolation of the left hepatic artery and the left branch of the portal vein, while the left hepatic duct is not dissected prior to parenchymal transection. In an effort to avoid reconstruction of the left hepatic duct, the subsequent transection of the parenchyma is performed approximately 0.5-1 cm to the right of the falciform ligament, yielding two independent allografts. To prevent devascularization of the left hepatic duct, the left hepatic bile duct and hilar plate are divided sharply during hepatic parenchymal transection [33]. Generally, the left hepatic vein, the left portal vein, and the entire length of the celiac axis are retained with the left lateral segment while the middle hepatic vein, the main portal vein, and donor vena cava are preserved in the extended right lobe [28,31]. If needed, an external iliac artery extension graft can be placed on the donor right hepatic artery [34]. Although opinions vary as to which liver half should keep the entire hepatic/celiac trunk and main portal vein, the common bile duct is always retained with the right lobe for both adult/pediatric and adult/adult splits [1]. To prevent segment IV, V, and VIII venous congestion of the right-sided trisegmental allograft, care must be taken when closing the rent in the middle hepatic vein. In most cases, this is achieved via suturing a patch of donor iliac vein into the middle hepatic vein rent [35]. In adult/adult splits, transection occurs in the midplane of the liver (Cantlie's line), to the right of the middle hepatic vein, generating an anatomic right lobe (60% of the liver) and a left lobe (40% of the liver) to ensure sufficiently-sized allografts for two adult recipients. The middle hepatic vein is retained with the left lobe for sufficient draining of segments IV, V, and VIII. For ease of transplant, the full-length of the hilar vascular structures is often kept with the left lobe, as right-sided hilar structures are usually larger. In the right lobe, drainage of segments V and VIII may be compromised given the loss of the middle hepatic vein. However, this issue is easily resolved by tributary reconstruction on the back table with venous interposition grafts. Confirming adequate venous outflow for congestion prevention is paramount for success during the recipient operations [28]. Therefore, in adult/pediatric splits, an adult recipient receives the extended right lobe in the standard orthotopic manner with or without venovenous bypass utilizing a bicaval or piggyback technique

[18] Interposition vascular grafts may be used to establish a suitable source of inflow depending on vasculature division during

the splitting process. Biliary reconstruction may be performed using a choledochocholedochostomy with or without a T-tube/stent or by means of Roux-en-Y hepaticojjunostomy with or without stenting. The left lateral segment is implanted into a child, or smaller adult, in a fashion analogous to adult-to-pediatric LDLT, including microvascular reconstruction of the donor left hepatic artery or donor celiac trunk [34]. The patient receiving the left lateral segment will undergo biliary reconstruction via Roux-en-Y hepaticojjunostomy. In most cases, transected bile ducts need to be anastomosed to the Roux limb [33]. Described by Emond, et al. [36], size discrepancy may demand short and patulous anastomoses via various venoplasty stratagem to allow the allograft to rest comfortably in the hepatic fossa. Additionally, portal vein reconstruction must be individualized to the recipient's anatomy, as has been reported by Saad, et al. [37]. It must also be kept in mind that the left-sided allograft has to remain in its normal anatomic position in the recipient and cannot be allowed to fall into the empty right upper quadrant, as this may lead to vascular thrombosis and allograft loss. The final step in the transplant implantation procedure is to reapproximate the left triangular and falciform ligaments between donor and recipient, as originally described by Emond, et al. [38]. A unique set of patients that benefits dramatically from SLT are those with situs inversus. In these patients, where the stomach and spleen occupy the right upper quadrant, they are perfectly set up to receive a left lateral segment, as outlined by Maggard, et al. [39] originally utilizing a living donor.

Outcomes

In an initial series of 9 *ex vivo* SLT procedures from the University of Chicago in 1990, Emond, et al. [38] demonstrated the feasibility and future potential of SLT. While overall patient and allograft survival rates were slightly inferior to WLT, accompanied by a higher incidence of biliary complications, primary nonfunction and arterial thrombosis frequencies were comparable between SLT and WLT. Given this promising preliminary experience and the anticipated technical improvements to mitigate the elevated risk of biliary complications, SLT garnered great enthusiasm for making more livers available. However, this eagerness quickly dissipated upon publication of the expanded University of Chicago series in 1991 [40], which failed to indicate improved SLT outcomes relative to WLT or LDLT. Optimism for SLT viability remained static until reporting of the European Split Liver Registry in 1995 [41], with data chronicling 98 SLT patients. This series revealed significantly improved SLT recipient and allograft survival with rates equivalent to European WLT.

Encouraged by the European experience, numerous American transplant centers expanded SLT implementation. University of California, Los Angeles (UCLA) published the first American SLT case series [33] following the 1995 European

Split Liver Registry. This study consisted of 15 *in situ* split-liver procurements resulting in 28 SLTs. 6-month and 1-year actuarial patient survival rates were 92% and 92%, respectively, while the 6-month and 1-year actuarial allograft survival rates were 86% and 86%, respectively. In the wake of these exciting prefatory outcomes, UCLA has grown to become the largest *in situ* SLT center with more than 100 procedures performed [20]. Despite SLT accounting for approximately 10% of adult and 40% of pediatric liver allografts at UCLA, it only amounts to 2% of LT throughout the U.S. [42]. As recent evidence suggests outcomes following SLT are likely commensurate to WLT for both pediatric and adult recipients [43-45], SLT application must be widened. Status 1 adult patients represent a potential anomaly to this procedural outcome equivalence with a recent study concluding critically-ill, adult SLT recipients have greater occurrence of allograft failure [24]. Another study concedes to the lower patient survival rate in high-risk SLT recipients relative to nonurgent SLT recipients; although, they found these inferior results were equivalent to those expected with WLT in urgent, high-risk patients [18]. Regarding technique, *ex vivo* vs. *in situ*, numerous early studies, such as Reyes, et al. [46], reported heightened clinical efficaciousness with *in situ* procurement. However, comparable morbidity and mortality have been revealed in the present-day, apart from a higher incidence of postoperative hemorrhage using the *ex vivo* technique [47]. Nevertheless, few studies exist that have directly compared the techniques, as most centers performing SLT use a single procurement method for optimization and standardization of results [15,20,26,29,33].

Conclusion

As the only modality to treat end-stage liver disease, LT must be optimized. The persistent donor allograft shortage has led to an unacceptable waitlist mortality. SLT has emerged as a means to alleviate donor allograft scarcity by generating two transplantable allografts from a single donor liver, with the potential to satisfy the entire unmet need of pediatric donor allografts. In view of the equivalent SLT patient and allograft survival rates compared to WLT and LDLT and the absence of donor risk incurrence, SLT warrants expansion from its 2% contribution to U.S. LT. However, numerous obstacles impede the further utilization of SLT, including rigorous donor and recipient selection. Smaller centers lack surgical experience with the complex technical variant. Logistical coordination is also a significant obstacle, extending to organ procurement organizations and allocation policy. At present, only a select group of centers contribute to the majority of SLT. Resources must be made available to centers wishing to actualize SLT in order to make the practice ubiquitous. While poor initial results with SLT prompted slow acceptance, the current data suggests SLT has equivalent outcomes and is ready for expansion. While the barriers are still significant, SLT can considerably

enlarge the donor liver pool, especially for children.

Disclosure Information

The authors of this manuscript have no conflicts of interest to disclose.

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