This is the peer reviewd version of the followng article:

Donor safety in living donor liver donation: An Italian multicenter survey / Lauterio, A; Di Sandro, S; Gruttadauria, S; Spada, M; Di Benedetto, F; Baccarani, U; Regalia, E; Melada, E; Giacomoni, A; Cescon, M; Cintorino, D; Ercolani, G; Rota, M; Rossi, G; Mazzaferro, V; Risaliti, A; Pinna, Ad; Gridelli, B; De Carlis, L. - In: LIVER TRANSPLANTATION. - ISSN 1527-6465. - 23:2(2017), pp. 184-193. [10.1002/lt.24651]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

12/10/2024 06:32

(Article begins on next page)

Title page

Title

Donor Safety in Living Donor Liver Donation: an Italian Multicenter Survey

Author List

Andrea Lauterio[1], Stefano Di Sandro[1,8], Salvatore Gruttadauria[2], Marco Spada[2], Fabrizio Di Benedetto[3], Umberto Baccarani[4], Enrico Regalia[5], Ernesto Melada[6], Alessandro Giacomoni[1], Matteo Cescon[7], Davide Cintorino[2], Giorgio Ercolani[7], Matteo Rota[9], Giorgio Rossi[6], Vincenzo Mazzaferro[5], Andrea Risaliti[4], Antonio Daniele Pinna[7], Bruno Gridelli[2], and Luciano De Carlis[1,10]

Affiliations:

[1]Division of General Surgery & Abdominal Transplantation; ASST Grande Ospedale Metropolitano Niguarda; Milan, Italy.

[2]ISMETT-UPMC; Palermo, Italy.

[3]HPB Surgery & Liver Transplantation Unit, University of Modena and Reggio Emilia; Italy.

[4]Liver Transplant Unit, Department of Medical & Biological Sciences, University Hospital; Udine, Italy.

[5]HPB Surgery and Liver Transplant Unit, Istituto Nazionale Tumori, IRCCS Foundation; Milan, Italy.

[6]Division of HPB Surgery and Liver Transplantation; Maggiore Hospital; Milan, Italy.

[7]Abdominal Organ Transplant Center, DIMEC; University of Bologna; Italy.

[8]Department of Experimental Medicine; University of Pavia; Italy.

[9]Department of Epidemiology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

[10]University of Milano-Bicocca, School of Medicine; Milan; Italy.

Corresponding Author

Andrea Lauterio, MD

Transplant Center; Division of General Surgery & Abdominal Transplantation; ASST Grande Ospedale Metropolitano Niguarda; Piazza Ospedale Maggiore, 3, 20162 Milan; Italy

andrea.lauterio@ospedaleniguarda.it

Keywords:

Living donor liver transplantation; donor outcomes; donor morbidity; liver transplantation; living donation

Abbreviations

LDLT, living donor liver transplantation; LD, living donation; LT, liver transplantation; RLV, remnant liver volume; ASA, American Society of Anesthesiology; RL, right lobe; LL, left lobe; LLS, left lateral segments; GRWR, graft to recipient weight ratio

Running title: Safety in Living Donor Liver Donation

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/lt.24651

This article is protected by copyright. All rights reserved.

Accepted Article

Abstract

Background: Major concerns about donor morbidity and mortality still limit the use of living donor liver transplantation (LDLT) to overcome the organ shortage.

Methods: The present study assessed donor safety in LDTL in Italy reporting donor postoperative outcomes in 246 living donation procedures performed by seven transplant centers. Outcomes were evaluated over two time periods using the validated Clavien 5-tier grading system, and several clinical variables were analyzed to determine the risk factors for donor morbidity.

Results: Different grafts were obtained from the 246 donor procedures (220 right lobe, 10 left lobe, and 16 left lateral segments). The median follow-up post-donation was 112 months. There was no donor mortality. One or more complications occurred in 82 donors (33.3%), and three of them had intraoperative complications (1.2%). Regardless of graft type, the rate of major complications (grade≥III) was 12.6% (31/246). The overall donor morbidity and the rate of major complications did not differ significantly over time: 25 donors (10.2%) required hospital readmission throughout the follow-up period, while 5 donors (2%) required reoperation. Prolonged operative time (>400 min), intraoperative hypotension (systolic <100 mmHg), vascular abnormalities, and intraoperative blood loss (>300 mL) were multivariate risk factors for postoperative donor complications.

Conclusion: From the standpoint of living donor surgery, a meticulous and well-standardized technique that reduces operative time and prevents blood loss and intraoperative hypotension may reduce the incidence of donor complications. Transparency in reporting results after LDLT is mandatory and we should continue to strive for zero donor mortality.

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

Introduction

Living donor liver transplantation (LDLT) has long been an established practice in Europe. Despite large differences across countries in the rate of living donation (LD), 4-5% of all liver transplants (LT) involved live donors (1,2). Nevertheless, initial enthusiasm gradually waned in Western countries as high rates of donor complications and fatalities were reported in both scientific literature and the popular press. Major concerns about donor morbidity and mortality still limit the use of LDLT to overcome the organ shortage. Although donor morbidity and mortality are probably underreported in the medical literature, the worldwide donor mortality rate ranges from 0.2 to 0.5% (3,4). A wide range of complication rates have been reported in donors after LDLT, reaching up to 78.3% in right lobe (RL) LD procedures (5). A clear understanding of all the potential risks to donors is mandatory to justify exposing a healthy adult to such a major surgical procedure.

Since LDLT was first introduced in Italy in 2001 for adult recipients, its risks have not been fully addressed. The lack of a national registry limits comprehensive data on donor morbidity, and most available information stems from single center series (6-8). In 2014, seven Italian transplant centers involved in LDLT (listed below) signed a cooperative research agreement with the specific aim to provide accurate and transparent information on the risks and benefits of LDLT in both donors and recipients. The current report retrospectively analyzed the predictors associated with donor postoperative complications and outcomes after LDLT in the seven transplant centers.

Methods

The study coordinators at each transplant center filled out a retrospective structured data collection form for each donation procedure using an electronic data entry system. Preoperative, intraoperative, and postoperative data were collected and analyzed by the coordinating center for all LDLT procedures performed from March 2001 to December 2014 at the seven transplant centers. Donation was absolutely voluntary in all cases. Only potential donors who met the universally accepted (9) primary selection criteria for LDLT were evaluated according to each local protocol with minor differences between centers. Details of the surgical technique applied in donor operations were described in previous reports by three of the institutions involved (6,10,11). In order to evaluate the changes in perioperative donor characteristics and outcomes over time, the patient cohort was further investigated over two time periods: [A] the initial period of LDLT activity (2001-2006); [B] the latest period (2007-

This article is protected by copyright. All rights reserved.

2014). Outcomes of donors who underwent graft procurement for pediatric LDLT were examined and reported separately due to the small number of cases.

Liver biopsy to exclude liver steatosis was not routinely performed, and some centers applied this invasive procedure only when steatosis was suspected from the donor's medical history, physical examination, and preoperative studies. Volumetric measurements of the donor liver were obtained using preoperative imaging. The ratio of the donor remnant liver volume (RLV) was expressed as a percentage of the estimated total liver volume, while the actual procured graft weight in grams was recorded on the back table after flushing with cold perfusion solution.

Surgical complications were evaluated and graded according to the updated 5-tier grading classification system proposed by Clavien and colleagues (12). For each recorded complication, the information required for grading according to the Clavien system, date of onset and resolution were recorded. Complications were tabulated by type and grade, using the highest grade for donors with multiple complications. Complications graded as III or more were considered major events. Although intraoperative complications are not graded by the Clavien classification, they were recorded and examined separately. Short-term complications were defined as those occurring within three months after LD, and long-term complications as those occurring more than three months after surgery. With reference to other published series, several clinical variables were analyzed to determine the risk factors for donor morbidity.

Participating institutions

1- Transplant Center; Division of General Surgery & Abdominal Transplantation; ASST Grande Ospedale Metropolitano Niguarda; Milan, Italy. 2- ISMETT-UPMC; Palermo, Italy. 3- HPB Surgery & Liver Transplantation Unit, University of Modena and Reggio Emilia; Italy. 4- Liver Transplant Unit, Department of Medical & Biological Sciences, University Hospital; Udine, Italy. 5- HPB Surgery and Liver Transplant Unit, Istituto Nazionale Tumori, IRCCS Foundation; Milan, Italy. 6- Division of HPB Surgery and Liver Transplantation; Maggiore Hospital; Milan, Italy. 7- Abdominal Organ Transplant Center, DIMEC; University of Bologna; Italy.

Statistical analysis

Donors' demographic information, operative characteristics and post-operative complications are presented as relative frequencies (%) for categorical variables and medians (ranges) for continuous variables. The chi-square test for categorical and the t-test for continuous variables were used to

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

compare characteristics across the two groups of donors. Univariate logistic regression analysis was performed to identify significant risk predictors of overall post-operative complications. Each predictor potentially associated (p-value≤0.20) with the outcome was then included in a multivariate model to identify any independent risk factor for postoperative complications. A backward predictors selection strategy with a removal p of 0.157 (as based on the Akaike information criterion) (13) was used to select the final multivariate model. A P value less than 0.05 was considered statistically significant. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA) and R version 2.11.1 for graphics.

Results

A total of 246 donor procedures for LDLT were fully performed and one aborted. As previously reported in detail (7,11), a potential right lobe LD was aborted after the beginning of surgery because of an abnormal venous outflow intraoperatively discovered by ultrasound and not detected at the preoperative imaging evaluation. No donor postoperative complications were observed after the aborted living donation. The aborted donor was not included in the subsequent analysis. Mean post-donation follow-up was 112 months (range 6-169 months). Different types of grafts were obtained: 220 right lobe (RL) donations (Couinaud segments 5-6-7-8) without the middle hepatic vein (MHV) and ten left lobe (LL) donations (Couinaud segments 2-3-4) including the MHV. Sixteen donors underwent left lateral segment (LLS) procurement for pediatric recipients. A minimally invasive approach was applied to LD in 11 donors in a single institution and no statistical analysis was performed concerning the surgical technique due to the small number of cases. Donor demographic characteristics for all donors and perioperative details over time (excluding LLS grafts) are summarized in Tables 1 and 2. Mean donor age was 32 years (18-64), and 117 (47.5%) were females. Donor and recipient were biologically related in 210 (85.4%) LDLT procedures. There were no significant differences in donor demographics between groups over time except for donor's overall physical status according to the classification system based on the score proposed by the American Society of Anesthesiologists (ASA), and previous abdominal surgery. Donor vascular and biliary abnormalities are reported in Table 1. Table 2 shows perioperative details. Regardless of graft type procured, the mean donor RLV was 39.9% (22.7%-87.6%). With the exclusion of LLS grafts, mean operative time (433 min versus 365 min; p<0.001), operative time longer than 400 min (91% versus 28%, p<0.001), and estimated intraoperative blood loss (400 mL versus 300 ml, p=0.002) as well as blood loss >300 mL significantly differed over time. No donor experienced intraoperative hypotension (defined as systolic blood pressure <100 mmHg for

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

more than 30 minutes) in the second time period (9% versus 0%, p=0.02). The mean length of hospital stay was eight days (3-45) and was comparable over time.

Donor complications and outcomes

There were no donor deaths among the 246 donors in the study cohort. One or more complications were experienced by 82 donors (33.3%), while an aggregate 88 complications were recorded; six donors (2.4%) experienced multiple complications. Regardless of graft type, the rate of major complications (grade ≥III) was 12.6% (31/246). The overall donor morbidity and major complication rates did not differ significantly over time as reported in detail in Table 3. Short-term complications occurred in 70 donors (70/82, 85.4%), while long-term complications arose in 12 donors (12/82, 4.6%). Consequently, most complications occurred within three months after LD, and long-term complications were rare. Short and long-term complications requiring reoperation are discussed in detail below. Type of complication, number and Clavien grade are reported in Table 4.

Intraoperative complications included two cases of profuse hemorrhage (blood loss >1000 mL) due to vascular injury, and one common bile duct lesion. The common bile duct was sutured and paraffin T-tube drainage placed. This donor underwent T-tube removal after one month without any after-effects. All these events were repaired intraoperatively with no postoperative consequences.

Four donors (1.6%) required reoperations, and three of them were rehospitalized. One donor required surgical re-exploration for postoperative bleeding from the hepatic cut surface, one for a chylothorax related to central vein catheter placement treated by thoracic duct ligation and pleurectomy, one required surgical wound repair of a complex wound infection with dehiscence, and the fourth underwent open drainage of an abdominal abscess related to a biliary leak from the liver cut surface. Another donor who underwent LLS procurement required reoperation as mentioned below in the text.

Overall 26 donors (10.6%) were readmitted to hospital throughout the follow-up with a lower rehospitalization rate in the second period (13.0% vs. 8.1%, p=0.05). Sixteen donors were hospitalized for biliary leak requiring endoscopic and radiologic interventions. One donor was rehospitalized for transient portal vein thrombosis requiring anticoagulant therapy while another two needed readmission for pulmonary embolism. One donor suffered colitis and required antibiotic therapy. Another five donors required rehospitalization for percutaneous drainage of abdominal fluid collection in three cases, and pleurocentesis in two cases. One donor who had primary repair of an intraoperative bile duct injury was hospitalized for T-tube cholangiography before T-tube removal.

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

No donors experienced severe postoperative liver dysfunction; however transient hyperbilirubinemia (grade I) was observed in three donors while another five developed ascites (four grade I and one grade II). Deterioration of liver function after LD was resolved in all donors.

The results of logistic regression analysis to identify independent predictive factors for postoperative complications are listed in Table 5. Vascular abnormalities of the portal vein and hepatic veins, and intraoperative hypotension had significantly disadvantageous impacts on all complications. Moreover, intraoperative hypotension, and operative time >400 min were significantly associated with major postoperative complications as shown in Table 6. The multivariate risk factors for postoperative donor complications are listed in Table 7.

LLS outcomes

Sixteen donors underwent LLS procurement for adult-to-child LD by three of the participating institutions. Donor and recipient were biologically related (parent to child) in all cases except one. Mean donor RLV was 66.8% (60.2%-70.3%), and all donors had a RLV > 35%. Mean operative time was 302 min (286min -646 min), and in one donor the estimated intraoperative blood loss was 200 mL, with no need for blood transfusion. Five donors experienced intraoperative hypotension (<100 mmHg, systolic). The mean length of hospital stay was lower than for the adult-to-adult LD [6 days (6-10)]. The overall complication rate was 25% (three short-term complications, and one long-term complication). One donor showed a major complication (Clavien grade >III) and required rehospitalization for surgical repair of a diaphragmatic hernia. One donor suffered pulmonary embolism treated by anticoagulant therapy, while another two donors required prolonged medications to solve a skin wound infection.

Discussion

Donor safety must be mandatory in LDLT and all the clinicians involved have made every effort to minimize the risk of donor complications. However, in daily clinical practice, donor complications cannot be completely prevented.

One of the major aims of our study was to evaluate the predictors associated with donor postoperative complications, and some of our results confirm other literature reports. According to the Iida et al.'s (14) experience of surgery-related morbidity in more than 1000 LDs, prolonged operative time (> 400 min) was found to be an independent risk factor for complications by multivariate analysis (p=0.04;

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

OR 2.21). Conversely, the A2ALL study (15) found that operative time did not affect donor outcome, and advocated a meticulous and time-consuming dissection as a prudent approach for reducing donor surgical complications.

In line with another study (15), our analysis demonstrated that intraoperative hypotension (systolic blood pressure <100 mm Hg; >30 minutes) was associated with a higher risk of overall postoperative complications (p=0.02; OR 16.45) and multivariate risk factors for major complications (p<0.01; OR 8.08), irrespective of blood loss and transfusion requirements.

Our cohort study encountered vascular abnormalities in 79 (32.1%) donors with a comparable rate across the two different time periods. Vascular abnormalities can be considered a surrogate marker of donor surgery complexity, especially during hepatic hilar dissection and parenchymal transection. Our data showed this marker was an independent risk factor for postoperative complications (p=0.03, OR 2.04). When looking at the specific type of abnormalities, we found that portal (p=0.02, OR 2.72) and hepatic vein (p=0.01, OR 2.36) anatomic variations were associated with an increased risk for all, but not for major, postoperative complications in the univariate framework, whereas hepatic arterial variations did not confer an increased risk to donors in our series. The multivariate analysis revealed that only portal anatomic variations were independently associated with a higher risk of postoperative complications. Conversely, when considering the anatomy of the biliary tract, unlike other authors (16-18), we failed to demonstrate the negative impact of biliary anatomic variations on donor outcomes.

Other authors (19) found that BMI was significantly correlated to the risk of a grade IV complication after RL LD. In our experience, mean BMI was < 25 in all donors and few of them had a BMI ≥ 30. This is probably related to the strict selection applied in the donor evaluation process in our centers. Unlike other studies (14), we found no correlation between donor age and risk for complications even though donor age differed over time in our series. As reported by the A2ALL study group (15), intraoperative blood loss was significantly associated with the risk of postoperative donor complications (p=0.03; OR 2.43) by multivariate analysis with 54 donors experiencing intraoperative blood loss >300 mL.

The accuracy of estimating RLV should be considered the initial step toward donor safety (20). Although it has been reported that LD surgery with a RLV <30% could be safely performed in selected donors, we generally agree that donor safety requires more than 30% of the original liver volume with a complete vascular and biliary flow (9,21-24). In our experience, no more than 11 (4.5%) donors showed a RLV <30% with no significant difference over time. In line with previous reports, we failed to demonstrate a significant correlation between RLV <30% and the risk of postoperative

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

complications (16,20).

The preferred type of graft in this multicenter survey was RL without the MHV with no difference over time. Because of the small number of LL grafts, we deemed observations on the relative risk of complications from LL versus RL graft donation inconsistent. The choice of graft type has been analyzed in depth over the last decade with different donor outcomes, while a recent large study reported comparable outcomes for RL and LL donations (14,15,25). Data from other Far Eastern series previously validated a rate of 20% as the standard to achieve for donor morbidity after RL donation (26). Conversely, the A2ALL study group proposed 40% as the definitive figure for the risk of complications in the first year after RL donation (15). Very recently, the Seoul National University group published a large single center study investigating surgery-related donor morbidity over a period of 13 years reporting advancements over time (16). The overall morbidity rate decreased over time from 26.4% to 5.8% in the more recent period (2011-2012) when more than 200 donors underwent RL graft donation. Although LL donation has recently increased (27), we agree that the RL advantages in terms of graft size and perhaps easier surgical technique play a crucial role in the choice of graft type.

A minimally invasive approach was adopted by one of the participating institutions for 11 donor operations for adult-to-child LDLT. In addition, one living donor underwent a totally robotic right hepatectomy for an adult recipient. This small number of procedures precluded us from making any rational analysis and solid conclusion on the impact of the minimally invasive approach to donor outcome. Although a minimally invasive approach has become the standard in living kidney donation, its application still remains limited and controversial in LD. Very recent data from a multicenter study provide the first validation for a laparoscopic LLS, suggesting that the approach is feasible and should be considered a new standard practice for LLS graft procurement as it is for kidney LD (28). Therefore, the safety and effectiveness of the minimally invasive approach in the setting of major hepatectomy awaits further confirmation (29,30).

This Italian experience with 230 adult living donor livers is comparable to other published series where donor outcome was evaluated and graded by the latest Clavien 5-tier classification system (5,14,19,26,31-33) in preference to the original version (34). According to other authors, the new version avoids the underestimation of grade ≥III complications (16,35).

Our data showed a midway incidence of major donor complications of 12.6% in the range of 2-32% reported by other series (5,31,35-37) including those where outcomes were evaluated with a different Clavien grading system, with a rate of ≥III Clavien complications estimated at approximately 20-25% (15,38). Nevertheless, data from large Far Eastern centers with the lowest recipient morbidity and best

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

survival rates also report the lowest incidence of donor ≥III Clavien complications at <10% (26,34). According to the data reported by the A2ALL study group and the Toronto group, a range from 2 to 5% could be considered the definitive risk of intraoperative aborted living RL donation (15,38). Our survey found a lower rate of no-go hepatectomies with only one donor (1/247, 0.4%) procedure aborted.

In our experience, three donors had intraoperative complications, but all of them made a complete recovery thereafter. Intraoperative donor complications may be under-reported in the literature, and despite not being graded by the Clavien classification they remain an important issue in LD because they may have a negative impact on the immediate and long-term outcomes.

Accumulated center experience, including strict donor selection, advances in surgical technique, and post-donation patient care seems to play a crucial role in the improvement of donor outcomes (39,40,41). Nevertheless, this issue remains controversial (14-19,33), and the data from our analysis fail to demonstrate a trend toward decreasing overall morbidity or the risk of major complications over time, although there was some decrease in the severity of complications (less incidence of grade ≥III).

This is the first comprehensive survey on donor safety in LDLT in Italy thanks to a cooperative research agreement initiated by seven Italian transplant centers. Among the 313 LD procedures performed in Italy up to the end of 2014, 246 (78.6%) were retrospectively analyzed, providing data on donor outcomes and predictors associated with donor postoperative complications.

In our experience, living RL donation is the preferred choice and probably reflects the confidence and surgical experience gained in hepatobiliary surgery and split-liver transplantation by those institutions actively involved in LDLT. However, LD should not be limited by graft type, and different options must be considered based on graft size and anatomy as well as recipient characteristics. From the standpoint of LD surgery, a meticulous and well-standardized technique that reduces operative time, and prevents blood loss and intraoperative hypotension may reduce the incidence of living donor complications.

One surgeon who experienced a donor death claimed that what happened was an inevitable event for LDLT programs, and recently reported strategies to manage a donor death (42). A donor's death is a tragedy of unspeakable proportions for the recipient, the family and all the clinicians in the LDLT process, especially for the surgical team directly involved in the donation. Enormous efforts are required by all those involved to minimize the possibility of error at all levels and not only during the surgical procedure. Ongoing updates to the well-established donor and recipient evaluation process are mandatory to minimize and ideally eliminate errors.

Among the seven institutions participating in this study, three experienced centers performing both

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

hepato-pancreato-biliary and transplantation surgery and actively involved in both liver and kidney LD performed almost all the LD analyzed. Intriguingly, this setting could explain a kind of natural selection of centers where LD converges to make the best use of resources and knowledge.

Especially in Western countries, LDLT should be considered an additional resource to devote to those patients who may obtain the greatest benefit. A better understanding of the mechanisms affecting donor outcome, and advances in the management of donor postoperative complications should revive the initial enthusiasm surrounding LD, especially in those centers were the use of this option has declined. We should expect a national donor registry with periodical detailed reports of short- and long-term donor follow-up with a transparent analysis of any LD-related adverse events including all the psychological issues. Transparency in reporting results after LDLT is mandatory and we should continue to strive for zero donor mortality.

Disclosure

The authors of this manuscript have NO conflicts of interest to disclose as required by the Liver Transplantation journal.

Accepted Article

John Wiley & Sons, Inc.

This article is protected by copyright. All rights reserved.

Accepted Article

REFERENCES

1. European Liver Transplant Registry. Available from: www.eltr.org
2. Dutkowski P1, De Rougemont O, Müllhaupt B, Clavien PA. Current and future trends in liver transplantation in Europe. Gastroenterology 2010 Mar; 138(3):802-809.
3. Trotter JF, Adam R, LO CM, Kenison J. Documented deaths of hepatic lobe donors for living donor liver transplantation. Liver Transpl 2006;12:1485-1488.
4. Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. Liver Transpl 2013; 19(5):499-506.
5. Yi NJ, Suh KS, Cho JY, Lee HW, Cho EH, Yang SH, et al. Three-quarters of right liver donors experienced postoperative complications. Liver Transpl 2007;13:797-806.
6. Dazzi A, Lauro A, Di Benedetto F, Masetti M, Cautero N, De Ruvo N, et al. Living donor liver transplantation in adult patients: our experience. Transplant Proc. 2005 Jul-Aug;37(6):2595-2596.
7. Gruttadauria S, Pagano D, Cintorino D, Arcadipane A, Traina M, Volpes R, et al. Right hepatic lobe living donation. A 12 years single Italian center experience. World J Gastroenterol. 2013 Oct 14;19(38):6353-6359.
8. Lauterio A, Poli C, Cusumano C, Di Sandro S, Tripepi M, Mangoni I, et al. Living-donor liver transplantation: donor selection criteria and postoperative outcomes. A single-center experience with a 10-year follow-up. Transplant Proc. 2013 Sep;45(7):2680-2683.
9. Barr ML, Belghiti J, Villamil FG, Pomfret EA, Sutherland DS, Gruessner RW, et al. A report of the Vancouver Forum on the care of the live organ donor: lung, liver, pancreas, and intestine data and medical guidelines. Transplantation. 2006 May 27;81(10):1373-1385.
10. De Carlis L, Lauterio A, Giacomoni A, Slim AO, Pirotta V, Mangoni J, et al. Adult living donor liver transplantation with right lobe graft: the venous outflow management in the Milan-Niguarda experience. Transplant Proc. 2008 Jul-Aug;40(6):1944-1946.
11. Pagano D, Spada M, Cintorino D, Li Petri S, Ricotta C, Bonsignore P, et al. Evolution of surgical technique in conventional open hepatectomy for living liver donation over a 12-year period in a single center. Transplant Proc. 2014 Sep;46(7):2269-2271.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-213.
13. Sauerbrei W. The use of resampling methods to simplify regression models in medical statistics. Applied Statistics 1999; 48: 313-329.
14. Iida T, Ogura Y, Oike F, Hatano E, Kaido T, Egawa H, et al. Surgery-related morbidity in living donors for liver transplantation. Transplantation. 2010 May 27;89(10):1276-1282.
15. Abecassis MM, Fisher RA, Olthoff KM, Freise CE, Rodrigo DR, Samstein B, et al. Complications of living donor hepatic lobectomy--a comprehensive report. Am J Transplant. 2012 May;12(5):1208-1217.
16. Suh KS, Suh SW, Lee JM, Choi Y, Yi NJ, Lee KW. Recent advancements in and views on the donor operation in living donor liver transplantation: a single-center study of 886 patients over 13 years. Liver Transpl. 2015 Mar;21(3):329-338.
17. Shio S, Yazumi S, Ogawa K, Hasegawa K, Tsuji Y, Kida M, et al. Biliary complications in donors for living donor liver transplantation. Am J Gastroenterol 2008; 103:1393-1398.
18. Yuan Y, Gotoh M. Biliary complications in living liver donors. Surg Today 2010;40:411-417.
19. Marsh JW, Gray E, Ness R, Starzl TE. Complications of right lobe living donor liver transplantation. J Hepatol. 2009 Oct;51(4):715-724.
20. Facciuto M, Contreras-Saldivar A, Singh MK, Rocca JP, Taouli B, Oyfe I, et al. Right hepatectomy for living donation: role of remnant liver volume in predicting hepatic dysfunction and complications. Surgery 2013 May;153(5):619-626.
21. Kim SH, Kim YK, Lee SD, Park SJ. Selection and outcomes of living donors with a remnant volume less than 30% after right hepatectomy. Liver Transpl. 2013 Aug;19(8):872-878.
22. Taner CB, Dayangac M, Akin B, Balci D, Uraz S, Duran C, et al. Donor safety and remnant liver volume in living donor liver transplantation. Liver Transpl. 2008 Aug;14(8):1174-1179.
23. Reichman TW, Sandroussi C, Azouz SM, Adcock L, Cattral MS, McGilvray ID, et al. Living donor hepatectomy: the importance of the residual liver volume. Liver Transpl 2011;17:1404-1411.
24. Cho JY, Suh KS, Kwon CH, Yi NJ, Lee HH, Park JW, et al. Outcome of donors with a remnant liver volume of less than 35% after right hepatectomy. Liver Transpl 2006;12:201-206.
25. Uchiyama H, Shirabe K, Nakagawara H, Ikegami T, Toshima T, Soejima Y, et al. Revisiting the safety of living liver donors by reassessing 441 donor hepatectomies: is a larger hepatectomy complication-prone? Am J Transplant. 2014 Feb;14(2):367-374.
26. Chan SC, Fan ST, Lo CM, Liu CL, Wong J. Toward current standards of donor right hepatectomy for adult-to-adult live donor liver transplantation through the experience of 200 cases. Ann Surg. 2007 Jan;245(1):110-117.
27. Saidi RF, Jabbour N, Li Y, Shah SA, Bozorgzadeh A. Is left lobe adult-to-adult living donor liver transplantation ready for widespread use? The US experience (1998-2010). HPB (Oxford). 2012 Jul;14(7):455-460.
28. Soubrane O, de Rougemont O, Kim KH, Samstein B, Mamode N, Boillot O, et al. Laparoscopic Living Donor Left Lateral Sectionectomy: A New Standard Practice for Donor Hepatectomy. Ann Surg. 2015 Nov;262(5):757-761; discussion 761-763.
29. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg. 2009 Nov; 250(5):825-830.
30. Cauchy F, Schwarz L, Scatton O, Soubrane O. Laparoscopic liver resection for living donation: where do we stand? World J

This article is protected by copyright. All rights reserved.

Gastroenterol. 2014 Nov 14;20(42):15590-15598.
31. Gali B, Findlay JY, Plevak DJ, Rosen CB, Dierkhising R, Nagorney DM. Right hepatectomy for living liver donation vs right hepatectomy for disease. Intraoperative and immediate postoperative comparison. Arch Surg 2007; 142: 467–472.
32. Azzam A, Uryuhara K, Taka I, Takada Y, Egawa H, Tanaka K. Analysis of complications in hepatic right lobe living donors. Ann Saudi Med 2010; 30: 18–24.
33. Azoulay D, Bhangui P, Andreani P, Salloum C, Karam V, Hoti E, et al. Short- and long-term donor morbidity in right lobe living donor liver transplantation: 91 consecutive cases in a European Center. Am J Transplant. 2011 Jan;11(1):101-110.
34. Clavien PA, Camargo CA Jr, Croxford R, Langer B, Levy GA, Greig PD. Definition and classification of negative outcomes in solid organ transplantation: Application in liver transplantation. Ann Surg 1994; 220: 109–120.
35. Tamura S, Sugawara Y, Kukudo N, Makuuchi M. Systematic grading of morbidity after living donation for liver transplantation. Gastroenterology. 2008 Nov;135(5):1804.
36. Hwang S, Lee SG, Lee YJ, Sung KB, Park KM, Kim KH, et al. Lessons learned from 1000 living donor liver transplantations in a single center: how to make living donations safe. Liver Transpl 2006;12:920–927.
37. Khalaf H, Al-Sofayan M, El-Sheikh Y, Al-Bahili H, Al-Sagheir M, Al-Sebayel M. Donor outcome after living liver donation: a single-center experience. Transplant Proc 2007;39:829–834.
38. Shah SA, Cattral MS, McGilvray ID, Adcock LD, Gallagher G, Smith R, et al. Selective use of older adults in right lobe living donor liver transplantation. Am J Transplant 2007;7:142–150.
39. Shin M, Song S, Kim JM, Kwon CH, Kim SJ, Lee SK, et al. Donor morbidity including biliary complications in living-donor liver transplantation: single-center analysis of 827 cases. Transplantation 2012;93:942-948.
40. Broering DC, Wilms C, Bok P, Fischer L, Mueller L, Hillert C, et al. Evolution of donor morbidity in living related liver transplantation: a single-center analysis of 165 cases. Ann Surg 2004;240:1013-1024.
41. Hashikura Y, Ichida T, Umeshita K, Kawasaki S, Mizokami M, Mochida S, et al. Donor complications associated with living donor liver transplantation in Japan. Transplantation 2009;88:110-114.
42. Miller C, Smith ML, Fujiki M, Uso TD, Quintini C. Preparing for the inevitable: the death of a living liver donor. Liver Transpl 2013 Jun;19(6):656-660.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

TABLES

Table 1: Donor demographic characteristics over time

	All donors N=246	Period (01-06) N=133	Period (07-14) N=113	P
Age, years	32 (18-64)	31 (18-64)	33 (18-63)	0.21
Age >50 years (%)	26 (10.6)	10 (7.5)	16 (14.2)	0.09
Sex F vs M				0.06
Female, N(%)	117 (47.6)	56 (42.1)	61 (54.0)	
Male, N(%)	129 (52.4)	77 (57.9)	52 (46.0)	
BMI kg/m^2 %(range)	23.9 (16.0-34.0)	24.4 (18.3-33.9)	23.7 (16-34)	0.65
BMI≥30 kg/m^2	9 (3.7)	4 (3.0)	5 (4.4)	0.54
ASA score N(%)				0.001
ASA 1	215 (87.4)	125 (94.0)	90 (79.7)	
ASA 2	30 (12.2)	8 (6.0)	22 (19.5)	
Missing	1 (0.4)	0 (0)	1 (0.9)	
Previous abdominal surgery, N(%)	46 (18.7)	16 (12.0)	30 (26.6)	0.001
Relatedness to recipient				0.08
Biologically related				
Parent	25 (10.2)	9 (6.8)	16 (14.2)	
Child	138 (56.1)	83 (62.4)	55 (48.7)	
Sibling	44 (17.9)	25 (18.8)	19 (16.8)	
Other biological	3 (1.2)	2 (1.5)	1 (0.9)	
Not Biologically related				
Spouse	26 (10.6)	9 (6.8)	17 (15.0)	
Other	10 (4.1)	5 (3.8)	3 (2.7)	
Presence of steatosis, N(%)	79 (32.1)	43 (32.3)	36 (31.9)	0.35
Macrosteatosis >10%, N(%)	12 (4.9)	7 (5.3)	5 (4.4)	0.61
Vascular abnormalities, N(%) (*)	79 (32.1)	40 (30.1)	39 (34.5)	0.13
Arterial	52 (21.1)	25 (18.8)	27 (23.9)	0.54
Portal	29 (11.8)	18 (13.5)	11 (9.7)	0.04
Hepatic veins	44 (17.9)	13 (9.8)	31 (27.4)	<0.001
Biliary abnormalities, N(%)	50 (20.3)	27(20.3)	23 (20.4)	0.84

(*) 20 donors had more than 1 vascular abnormality.

This article is protected by copyright. All rights reserved.

Accepted Article

Table 2: Graft and operative characteristics over time (1)

	All donors N=246	Period (01-06) N=131	Period (07-14) N=99	P
DRWR (%)	1.0 (0.6-12.5)	1.0 (0.6-1.9)	1.0 (0.6-1.6)	0.06
Graft type (%)				0.005
RL	220 (89.4)	121 (91.0)	99 (87.6)	
LL	10 (4.1)	10 (7.5)	0 (0.0)	
LLS	16 (6.5)	--	--	
Actual graft volume (g)	780 (150-1482)	798.5 (220-1432)	790 (470-1482)	0.51
GRWR (%)	1.2 (0.3-4.1)	1.2 (0.3-2.5)	1.2 (0.5-3.0)	0.35
GRWR <0.8% (%)	21 (8.5)	11 (8.4)	9 (9.1%)	0.75
Remnant liver volume (%)	39.9 (22.7-87.6)	39.0 (23.3-80.9)	38.7 (22.7-67.3)	0.45
Remnant liver volume <30% (%)	11 (4.5)	7 (5.3)	4 (4.0)	0.60
Blood loss, mL	300 (10-1680)	400 (50-1680)	300 (10-1115)	0.002
Blood loss >300 mL	54 (22.0)	35 (26.7)	19 (19.2)	0.01
Intraoperative transfusion (%)	38 (45.5)	27 (20.6)	10 (10.1)	0.07
Units of transfused blood (%)				0.08
0	180 (73.2)	94 (71.8)	71 (71.7)	
1	16 (6.5)	9 (6.9)	6 (6.1)	
2	9 (3.7)	8 (6.1)	1 (1.0)	
3	9 (3.7)	8 (6.1)	1 (1.0)	
>4	2 (0.8)	2 (1.5)	0 (0.0)	
Missing	30 (12.2)	10 (7.6)	20 (20.2)	
Intraoperative hypotension (%)	12 (4.9)	12 (9.0)	0 (0.0)	0.002
Operative time, min	403 (270-754)	433 (295-754)	365 (270-705)	<0.001
Operative time>400 min (%)	132 (53.7)	91 (69.5)	28 (28.3)	<0.001
Length of stay, days	8 (3-45)	8 (6-34)	8 (3-45)	0.99
Hospital LOS >13 days (%)	22 (8.9)	14 (10.7)	8 (8.1)	0.53

(1) LLS excluded from the analyses over time; DRWR, donor-to-recipient weight ratio; RL, right lobe; LL, left lobe; LLS, left lateral segment; GRWR, graft-to-recipient weight ratio.

This article is protected by copyright. All rights reserved.

Table 3: Intra- and post-operative donor complications over time (1)

	All donors N=246	Period (01-06) N=131	Period (07-14) N=99	P
Intraoperative complications (%)	3 (1.2)	1 (0.8)	2 (2.0)	0.42
Postoperative medical complications (%)	30 (12.2)	13 (9.9)	17 (17.2)	0.11
Postoperative surgical complications (%)	52 (21.1)	26 (19.9)	23 (23.2)	0.53
Postoperative complications (%)	82 (33.3)	38 (29.0)	38 (38.4)	0.13
Major postoperative complications (2) (%)	31 (12.6)	19 (14.5)	11 (11.1)	0.45
Clavien-Dindo major complications grade (%)				0.83
IIIa	15 (48.4)	9 (47.4)	6 (54.6)	
IIIb	13 (41.9)	8 (42.1)	4 (36.4)	
IV	2 (6.5)	1 (5.3)	1 (9.1)	
IVa	1 (3.2)	1 (5.3)	0 (0.0)	
Rehospitalization (%)	26 (10.6) (*)	17 (13.0)	8 (8.1)	0.05
Reoperation (%)	4 (1.6) (*)	3 (2.3)	1 (1.0)	0.46

(1) LLS excluded from the analyses over time; (2) grade≥III; (*) including LLS.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 4: Type and severity of all complications graded by the 5-tier Clavien system

88 complications in all 246 LD (3 complications not graded)		Clavien grade				
	No. Donors	Grade I	Grade II	Grade III	GradeIV	Grade V
Intraoperative complications	3 (1.2%)	-	-	-	-	-
Intraoperative hemorrhage	2	-	-	-	-	-
Common bile duct injury	1	-	-	-	-	-
Postoperative complications						
Ascites	5	4	1	-	-	-
Fever	9	8	1	-	-	-
Arterial hypertension	1	-	1	-	-	-
Skin rush	1	1	-	-	-	-
Nausea+pain	1	1	-	-	-	-
Hyperbilirubinemia	3	3	-	-	-	-
Pleural effusion	20	14	2	4 IIIa	-	-
IVU	3	-	3	-	-	-
Pneumonia	1	-	1	-	-	-
Clostridium difficile colitis	1	-	1	-	-	-
Wound infection/dehiscence	6	-	5	1 IIIb	-	-
Portal vein thrombosis	1	-	-	-	-	-
Pulmonary hembolism	3	-	2	-	1	-
Bile leak/biloma	16	1	5	4 IIIa+6 IIIb	-	-
Biliary stricture	2	-	-	2 IIIa	-	-
Intraabdominal collection/abscesses	8	-	1	7 IIIa	-	-
Intraabdominal bleeding	1	-	-	1 IIIb	-	-
Incisional hernia	1	-	-	1 IIIb	-	-
Chylothorax	1	-	-	1 IIIb	-	-
Diaphragmatic hernia	1	-	-	1 IIIb	-	-
Pancreatitis	2	-	-	-	2 IV (**)	-
Total	88 (*)	34	23	28	3	-

(*) 6 donors had more than 1 complication; (**) 2 donors had acute pancreatitis as a consequence of other complications.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 5: Independent risk factors for postoperative donor complications (1)

	Presence of complications (N=76)	No Complications (N=154)	OR (95% CI)	P
Age >50 years	12 (15.8%)	14 (9.1%)	1.88 (0.82-4.28)	0.14
Sex (M vs F)	42 (55.3%)	80 (52.0%)	1.14 (0.66-1.98)	0.64
BMI≥30 kg/m^2	2 (2.6%)	7 (4.6%)	0.58 (0.12-2.86)	0.50
ASA score (II vs I)	10 (13.2%)	15 (9.7%)	1.40 (0.60-3.29)	0.44
Previous abdominal surgery	18 (23.7%)	28 (18.2%)	1.32 (0.67-2.61)	0.42
Relatedness to recipient (not biological vs biological)	62 (81.6%)	133 (86.4%)	0.72 (0.34-1.53)	0.39
Steatosis	29 (38.2%)	44 (28.57)	1.66 (0.91-3.01)	0.10
Macrosteatosis >10%	3 (4.0%)	8 (5.2%)	0.78 (0.20-3.06)	0.72
Vascular abnormalities	33 (43.4%)	44 (28.6%)	2.04 (1.09-3.81)	0.03
Arterial	17 (22.4%)	34 (22.1%)	1.08 (0.54-2.16)	0.83
Portal	15 (19.7%)	14 (9.1%)	2.72 (1.21-6.13)	0.02
Hepatic veins	21 (27.6%)	22 (14.3%)	2.36 (1.20-4.65)	0.01
Biliary abnormalities	17 (22.4%)	33 (21.4%)	1.12 (0.57-2.20)	0.74
Graft type (LL vs RL)	2 (2.6%)	8 (5.2%)	0.49 (0.10-2.38)	0.38
GRWR <0.8%	5 (6.6%)	15 (9.7%)	0.67 (0.23-1.94)	0.46
Remnant liver volume <30%	4 (5.3%)	7 (4.6%)	1.23 (0.35-4.36)	0.75
Blood loss (>300 mL)	23 (30.3%)	31 (20.1%)	1.62 (0.77-3.39)	0.20
Intraoperative transfusion	12 (15.8%)	25 (16.2%)	0.99 (0.46-2.11)	0.97
Intraoperative hypotension (systolic<100 mmHg; >30 minutes)	11 (14.5%)	1 (0.7%)	25.89 (3.28-204.70)	0.002
Operative time (>400 min)	46 (60.5%)	73 (47.4%)	1.64 (0.94-2.85)	0.08
Period (07-14 vs 01-06)	38 (50.0%)	61 (39.6%)	1.60 (0.91-2.80)	0.10

(1) LLS excluded from the analyses; LL, left lobe; RL, right lobe; GRWR, graft to recipient weight ratio.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 6: Independent risk factors for major (1) postoperative donor complications (2)

	Presence of complications (N=30)	No Complications (N=200)	OR (95% CI)	P
Age >50 years	3 (10.0%)	23 (11.5%)	0.86 (0.24-3.04)	0.81
Sex (M vs F)	16 (53.3%)	106 (53.0%)	1.01 (0.47-2.19)	0.97
BMI≥30 kg/m^2	1 (3.3%)	8 (4.0%)	0.86 (0.10-7.12)	0.89
ASA score (II vs I)	4 (13.3%)	21 (10.5%)	1.31 (0.42-4.12)	0.64
Previous abdominal surgery	7 (23.3%)	39 (19.5%)	1.22 (0.48-3.10)	0.68
Relatedness to recipient (not biological vs biological)	25 (83.3%)	170 (85.0%)	0.82 (0.29-2.33)	0.71
Steatosis	11 (36.7%)	62 (31.0%)	1.44 (0.63-3.33)	0.39
Macrosteatosis >10%	1 (3.3%)	10 (5.0%)	0.62 (0.08-5.02)	0.65
Vascular abnormalities	10 (33.3%)	67 (33.5%)	1.14 (0.47-2.80)	0.77
Biliary abnormalities	5 (16.7%)	45 (22.5%)	0.67 (0.24-1.87)	0.45
Graft type (LL vs RL)	0 (0.0%)	10 (5.0%)	Not estimable	--
GRWR <0.8%	1 (3.3%)	19 (9.5%)	0.32 (0.04-2.49)	0.28
Remnant liver volume <30%	2 (6.7%)	9 (4.5%)	1.53 (0.31-7.50)	0.60
Blood loss (>300 mL)	10 (33.3%)	44 (22.0%)	2.05 (0.72-5.79)	0.18
Intraoperative transfusion	5 (16.7%)	32 (16.0%)	0.92 (0.33-2.59)	0.87
Intraoperative hypotension (systolic<100)	6 (20.0%)	6 (3.0%)	8.08 (2.41-27.07)	<0.001
Operative time (>400 min)	21 (70.0%)	98 (49.0%)	2.31 (1.01-5.30)	0.048
Period (07-14 vs 01-06)	11 (36.7%)	88 (44.0%)	0.74 (0.33-1.63)	0.45

(1) Grade≥ III; (2) LLS excluded from the analyses; LL, left lobe; RL, right lobe; GRWR, graft to recipient weight ratio.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Table 7: Multivariate risk factors for postoperative donor complications (1)

Variable	P	Odds Ratio	95% CI
All postoperative donor complications			
Portal vein abnormalities	0.02	2.95	1.22-7.15
Blood loss >300 mL	0.04	2.43	1.06-5.58
Intraoperative hypotension (systolic<100)	0.02	16.45	1.65-163.85
Operative time (>400 min)	0.04	2.21	0.93-4.17
Major (2) postoperative donor complications			
Intraoperative hypotension (systolic<100)	<0.001	8.08	2.41-27.07

(1) LLS excluded from the analyses; (2) Grade ≥III.

This article is protected by copyright. All rights reserved.