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Improving Safety in Living Liver Donation: Lessons From Intraoperative Adverse Events in 438 Donors Undergoing a Left Liver Resection

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Background. Donor safety is paramount in living organ donation. Left liver resections are considered safer than right lobe hepatectomies. However, unexpected intraoperative adverse events (iAEs), defined as any deviation from the ideal intraoperative course, can also occur during left liver resections and may be life threatening or lead to postoperative complication or permanent harm to the donor and recipient. **Methods.** Records of 438 liver living donors (LDs) who underwent 393 left lateral sectionectomies (LLSs) and 45 left hepatectomies (LHs) between July 1993 and December 2018 in a pediatric living-donor liver transplantation center were reviewed for the appearance of iAEs that could have influenced the donor morbidity and mortality and that could have contributed to the improvement of the LD surgical protocol. **Results.** Clinical characteristics of LLS and LH groups were comparable. Nine iAEs were identified, an incidence of 2%, all of them occurring in the LLS group. Seven of them were related to a surgical maneuver (5 associated with vascular management and 2 with the biliary tree approach). One iAE was associated with an incomplete donor workup and the last with drug administration. Each iAE resulted in subsequent changes in the surgical protocol. Donor outcome was at risk by 5 iAEs classed as type a, recipient outcome by 2 iAEs (type b) and both by 2 iAEs (type c). Postoperative complications occurred in 87 LDs (19.9%), with no differences between the LLS and LH groups ($P = 0.227$). No Clavien-Dindo class IVa or b complications or donor mortality (Clavien-Dindo class V) were observed. **Conclusions.** iAEs debriefings induced changes in our LD protocol and may have contributed to reduced morbidity and zero mortality. iAEs analysis can be used as a quality and safety improvement tool in the context of LD procedures, which may include right liver donation, laparoscopic, and robotic living liver graft procurement.

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The scarcity of size-matched pediatric deceased liver grafts has prompted alternative transplant techniques, such as split-liver and living-donor liver transplantation (LDLT), which are essential in pediatric liver transplantation.[1-3] Indeed, the chronic shortage of deceased pediatric liver grafts inspired the first attempts of LDLT using left liver grafts in the late 1980s.[4,5] The technique was then used to transplant adults some years later.[6,7] Since then, several studies have addressed

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the progress of LDLT techniques, as well as donor and recipient outcomes. In fact, liver living-donor (LD) procedures are not without risks; related morbidity varies from 18% to 49% depending of the study accuracy[8-13] and overall mortality is estimated at 0.2%,[14] varying from 0.1% for left liver resections (LLRs) to 0.5% for right hepatectomies (RHs).[14,15] Hence, LDLT poses an ethical dilemma when a potentially harmful procedure is inflicted on a healthy person. Arguably, the only likely benefit to the donor could be the psychological satisfaction of actively helping in the treatment of a loved one who has no other chance of being transplanted.[16] Therefore, LD procedures must be performed in accordance with the highest level of surgical care and a strict ethical approach with the goal of achieving the lowest possible morbidity and zero mortality. In general, LLR is considered a safer procedure with lower complication rates than RH.[11,17-19] However, according to literature data, at least 4 LDs who underwent an LLR died within 3 months after the procedure, with 2 of them within the first postoperative week due to complications associated with the surgical procedure.[20-22] We therefore hypothesized that unexpected and unreported intraoperative adverse events (iAEs) may also occur in donors undergoing LLRs, which may be life threatening, or may compromise donor or recipient outcome.[23,24] Furthermore, iAEs identification and analysis can be used as quality tools to improve LD surgical protocols. Here, we comprehensively reviewed the medical, anesthetic, and surgical records of LDs who underwent LLR for pediatric living-donor liver transplantation (PLDLT) at our center, focusing on the occurrence of iAEs to define their characteristics and potential impact on the donor and recipient outcomes.

MATERIALS AND METHODS

Clinical and surgical data from LDs undergoing LLR for a donation in the context of a PLDLT at the Cliniques Universitaires Saint Luc (CUSL)—Université Catholique de Louvain, Brussels, Belgium (UCL), were retrospectively obtained from paper and electronic medical records. The CUSL Ethic Committee (CUSL-EC) approved this study protocol (2018/05NOV/409). The study was conducted in accordance with both the Declarations of Helsinki (2013) and Istanbul (2018). iAEs were defined according to the ClassIntra score as any deviation from the ideal intraoperative course that may require treatment and may be life threatening or lead to complication or permanent harm to the donor and recipient (Table 1).[24] The suffix ***a*** was used after each iAE's ClassIntra rating to define whether the iAE represented a risk for the donor, the letter ***b*** if there was a risk for the recipient, and the letter ***c*** if both were at risk. All postoperative complications were graded using the 5-tier Clavien-Dindo classification 25, and patient overall morbidity was assessed using the comprehensive complication index (CCI).[25-27] From July 1993 to December 2018, 438 LDs underwent an LLR for a PLDLT in our center (Table 1). Morbidity was analyzed according to the type of LLR that was performed: left lateral sectionectomy (LLS) (segments II and III) and left hepatectomy (LH) (segments II, III, and IV, including the middle hepatic vein [MHV]).[28]

Donor Workup

The PLDLT protocol was approved by the CUSL-EC. The stepwise LD evaluation begins with a baseline hematological and biochemical blood test and examination of potential LD by a transplant team member. If no obvious contraindication was found, a full blood analysis including coagulation tests, thrombophilia screening (protein C and S, antithrombin III, and activated protein C resistance), lipid profile, and viral screening for hepatitis A, B, and C; Epstein-Barr virus; and cytomegalovirus was performed. Electrocardiogram, pulmonary function tests, and chest radiography were also performed. Finally, an internal medicine physician, independent from the transplant team, acted as a "medical advocate" by examining the LDs to rule out medical contraindications to the donation. A psychiatrist evaluated the LDs to detect any psychological perturbation or donor coercion. Liver imaging assessment included Doppler ultrasonography (DUS) to initially investigate the presence of steatosis or focal lesions and as a first summary analysis of vascular anatomy. Contrast-enhanced MRI (Gadoteric acid, Dotarem, Guerbet, Fr) was performed to estimate hepatic volumetry, investigate the presence of suspicious hepatic lesions, as well as to study vascular and biliary anatomy, and accurately reassess the presence of steatosis. In the presence of steatosis, potential donors are

TABLE 1.

ClassIntra version 1.0 classification of intraoperative events

Grade	Definition
Grade 0	No deviation from the ideal intraoperative course
Grade I	Any deviation from the ideal intraoperative course: • Without the need for any additional treatment or intervention • Patient with no or mild symptoms
Grade II	Any deviation from the ideal intraoperative course: • With the need for any additional minor treatment or intervention • Patient with moderate symptoms, not life threatening, and not leading to permanent disability
Grade III	Any deviation from the ideal intraoperative course: • With the need for any additional moderate treatment or intervention • Patient with severe symptoms, potentially life threatening or potentially leading to permanent disability
Grade IV	Any deviation from the ideal intraoperative course: • With the need for any additional major and urgent treatment or intervention • Patient with life-threatening symptoms or leading to permanent disability
Grade V	Any deviation from the ideal intraoperative course with intraoperative death of the patient

Summary of the ClassIntra (Classification of Intraoperative events) version 1.0 grade developed by Dell-Kuster et al,[24] based on the CLASSIC (Classification of Intraoperative Complications) grade proposed by Rosenthal et al (*World J Surg.* 2015;39:1663–1671).

encouraged to lose weight, are evaluated by a dietitian, and are started on a more balanced, low-fat diet. The donor candidate could be reconsidered for donation, depending on weight loss and improvement of steatosis on sequential imaging evaluation. Regarding the volume of the graft, it is intended to consider grafts that result in a GRWR >1%, normally around 2% to 3% and never >4%. Finally, a donor consent form was signed at the end of the workup assessment.

Donor Liver Resection Technique

Only left liver grafts are used in our PLDLT program, and our LD surgical technique has evolved over time.[3,29] Briefly, the left liver is approached through a supraumbilical midline laparotomy (17–20 cm). After division of the falciform ligament, the anatomy of the hepatic veins is approached using intraoperative DUS. Hilar dissection is limited to the left elements. Dissection of the left hepatic artery (LHA) is carried out down to the bifurcation of the proper HA with the exposition of the origin of the right hepatic artery (RHA). The parenchymal transection, performed using ultrasonic dissection (CUSA-CV720-472-000; Valleylab, Inc., Boulder, CO), starts 0.5 cm on the right side of the falciform ligament in the case of LLS or just above and on the right side of the MHV in case of the LH. Intraoperative cholangiography is performed through the cystic duct before hilar plate transection. The left portal vein (LPV) is dissected, then 1000IU heparin is administered intravenously through the central line followed by the LPV clamping and catheterization. Once the LHA is divided, graft perfusion is started in situ through the LPV with 500 mL cooled heparinized Hartmann solution until complete transection of the left HV (LHV) and closure of its stump on the donor site. At the back table, perfused with 1 L of IGL-1 (Institute Georges-Lopez, Lyon, France) via the LPV. At this time, the LHV is digitally clamped for 10–15 min to retrogradely perfuse and wash the arterial vasculature.[3,30] A 5–7 cm segment of the inferior mesenteric vein (IMV) and the internal jugular vein (IJV) and a segment of the right gastroepiploic artery (RGEA) are procured if portoplasty, replacement of the retrohepatic vena cava, and an arterial graft interposition are required for graft implantation, respectively.

Postoperative Care

LDs are transferred to the intensive care unit for 24 h surveillance, and then to the ward. Postoperative analgesia is ensured either by peridural analgesia or morphine-derivate analgesia delivered in patient-controlled analgesia mode in combination with standard postoperative analgesia. Oral intake is restarted as soon as possible. Blood tests are performed daily, and routine DUS is performed on the first and on the fifth postoperative days (POD), when the abdominal drain is withdrawn. Deep vein thrombosis prophylaxis includes the use of intermittent pneumatic compression devices during operations, early postoperative mobilization, and treatment with low-molecular weight heparin in prophylactic doses within the first 2 wk postoperatively. LDs are usually discharged on the seventh POD with the first outpatient follow-up in a week with routine blood tests and DUS, and then at 1, 3, 6, and 12 mo and then yearly.

Clinical and Surgical Discussion Meetings

LD workup, the surgical strategy, and the postdonation outcome are discussed in a weekly multidisciplinary meeting. iAEs and changes to our routine protocol are also discussed during those meetings. Exceptionally, the occurrence of a donor major complication can also be discussed in mortality and morbidity meetings extraordinarily organized for this purpose.

Statistical Analyses

Statistical analyses and graphs were performed using IBM SPSS Statistics (version 26, Armonk, NY) and GraphPad Prism 7.0 (GraphPad Software, San Diego, CA), respectively. Continuous variables were analyzed by unpaired t-test or the Mann-Whitney *U* test for comparisons between 2 groups when indicated. Pearson's chi-square or Fisher's exact test was used for categorical variables. Results are reported as means and SDs or as medians and interquartile ranges (IQRs) when appropriate. *P* values <0.05 (2-tailed) were considered statistically significant.

RESULTS

Surgical and Clinical Characteristics

The LLS donors were younger and had a higher proportion of mothers compared with the LH group (Table 2). No donor hepatectomy was definitively aborted, the only temporarily interrupted procedure was completed later in the same day and was considered iAEs. The median operative time was 310 min (range, 158–714 min), and it was significantly shorter in the LLS group (307 min versus 365 min, $P < 0.001$). Graft weight was available for 337 grafts, and it was lower in the LLS group (277.64 ± 61 g versus 359 ± 68 g, $P < 0.001$) (Table 3). Vascular grafts were procured from 217 donors (49%), mainly in LLS donors (208 versus 9, $P < 0.001$) because of the need for special vascular reconstructions in small recipients. The 33 IJV grafts were used to replace the retrohepatic vena cava in recipients transplanted for unresectable liver malignancies. Of the 170 IMVs, 117 were used to perform portoplasty in recipients with portal hypoplasia, and 2 of the 15 RGEA grafts were used for arterial reconstructions. No complications related to vessels procurement were observed. The median overall length of hospitalization was 7 d (range, 5–14 d). LDs undergoing LLS presented significantly higher transaminase peaks, probably due to the devascularization of remnant segment IV (Figure 1). Only 2 (0.7%) LDs were transfused with red blood cells (RBCs) from the blood bank. Thirteen donors (4.57%) received their own units of RBCs collected before the operation, benefiting from the predonation protocol that was used until 1998. Two hundred eighty-two (64.38%) LDs received RBCs recovered and processed with the Cell-Saver system (Haemonetics, Braintree, USA) as part of our protocol to reinfuse the entire blood volume finally recovered (Table 3).

iAEs

Surgical, anesthetic, and nursing intraoperative records were exhaustively reviewed looking at any deviation of the ideal intraoperation course that met the iAEs criteria. In addition, senior LD surgeons were interrogated trying to capture any other iAEs. In doing so, 9 iAEs were identified, corresponding to an incidence of 2%, evenly distributed over the study period, all occurring in the LLS group. The first iAE occurred in the second PLDLT of our series. It was due to

TABLE 2.

Clinical characteristics of the study population

	Total population (438)			LLS (393)			LH (45)			
	n (%)	Median (IQR) (range)	Mean (SD)	n (%)	Median (IQR) (range)	Mean (SD)	n (%)	Median (IQR) (range)	Mean (SD)	*P*[a]
Age, y	438	33 (28–37) (19–56)	33.02 (±6.73)	393 (89.7)	32 (28–36) (19–56)	32.55 (±6.17)	45 (10.3)	37 (34–41) (23–51)	37.11 (±6.69)	0.000
Sex										
Female	225 (51.4)			207 (52.7)			18 (40.0)			0.107
Male	213 (48.6)			188 (47.3)			27 (60.0)			
BMI, kg/m^2	438	24 (22.0–26.0) (15–31)	23.51 (±2.7)	393	24 (22.0–25.5) (15–30)	23.43 (±2.69)	45	24 (21.5–26.0) (19–31)	24.16 (±2.84)	0.091
BMI < 18.5	17 (3.9)			17 (4.9)			0 (0.0)			0.238
18.5 ≤ BMI ≤ 24.9	252 (57.5)			229 (58.3)			23 (51.1)			0.357
25 ≤ BMI ≤ 29.9	167 (38.1)			146 (37.2)			21 (46.7)			0.213
BMI ≥ 30	2 (0.5)			1 (0.3)			1 (2.2)			0.195
Blood group										
O/A/B/AB	218/143/62/15			198/121/59/15			20/22/3/0			0.310
Preoperatory blood tests										
AST	359		20.75 (13.00)	325		20.61 (13.41)	34		22.06 (8.12)	0.538
ALT	342		20.77 (16.60)	310		20.40 (16.12)	32		23.79 (20.57)	0.266
Bil	334		0.76 (0.46)	302		0.77 (0.48)	32		0.69 (0.28)	0.341
INR	339		1.03 (0.07)	309		1.03 (0.68)	30		1.04 (0.07)	0.855
Hb	419		13.62 (1.56)	374		13.62 (1.55)	45		13.60 (1.67)	0.920
Ptls	420		251.33 (114.70)	375		251.68 (120.29)	45		246.67 (47.55)	0.773
Donor/recipient relationship										
Father	179 (40.9)			156 (39.7)			23 (51.1)			0.140
Mother	205 (46.8)			191 (48.6)			14 (31.1)			0.026
Uncles/aunts	37 (8.4)			32 (8.1)			5 (11.1)			0.568
Siblings	3 (0.7)			2 (0.5)			1 (2.2)			0.278
Cousins	4 (0.9)			2 (0.5)			2 (4.4)			0.054
Grandparents	5 (1.1)			5 (1.3)			0 (0.0)			1.000
Others[b]	5 (1.1)			5 (1.3)			0 (0.0)			1.000

IQR is presented as the 25th percentile–75th percentile.

[a]*P* value was calculated between the LLS and LH groups.

[b]Others: 2 godfathers, 1 godmother, 1 family friend, and 1 anonymous live liver donor.

ALT, alanine transaminase; AST, aspartate aminotransferase; Bil, bilirubin; BMI, body mass index; Hb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; LH, left hepatectomy; LLS, left lateral sectionectomy; Ptls, platelets.

TABLE 3.

Operative characteristics of 438 LDs

	Population (N = 438)			LLS (n = 393)			LH (n = 45)			
	LDs, n (%)	Median (range)	Mean (SD)	LDs, n (%)	Median (range)	Mean (SD)	LDs, n (%)	Median (range)	Mean (SD)	*P*[a]
Operative time, min	436 (99.54)	310 (158–715)	323.89 (±62.69)	391 (99.49)	307 (158–714)	317.75 (±57.32)	45 (100)	365 (280–715)	377.22 (±80.60)	0.000
Time from incision to graft perfusion, min	438 (100)	235 (96–637)	243.48 (±54.82)	393 (100)	229 (96–529)	237.44 (±48.50)	45 (100)	281 (188–637)	296.31 (±78.07)	0.000
Graft weight, g	337 (76.94)	280 (134–680)	286.65 (±68.70)	300 (76.33)	270 (134–630)	277.64 (±61.17)	37 (82.22)	340 (247–680)	359.73 (±68.69)	0.000
Transfusion, all types	284 (64.84)			254 (64.63)			30 (66.66)			0.786
Homologous transf., mL	2 (0.45)		484.50 (±304.76)	1 (0.25)		700 (/)	1 (2.22)		269 (/)	0.064
Predonation transf., mL	13 (2.96)		607.92(±203.80)	12 (3.05)		579.08 (±183.76)	1 (2.22)		954 (/)	0.075
Cell-saver RBCs, mL	282 (64.38)		409.33 (±271.32)	252 (64.12)	311 (120–2700)	391.28 (±237.82)	30 (66.66)	400 (150–1721)	560.90 (±444.06)	0.001
Vascular graft procurement	217 (49.54)			208 (52.93)			9 (20)			0.000
Inferior mesenteric vein	170 (38.81)			167 (42.49)			3 (6.66)			0.000
Internal jugular vein	33 (7.53)			28 (7.12)			5 (11.11)			0.337
Right gastroepiploic artery	15 (3.42)			14 (3.56)			1 (2.22)			0.000
Number procedures/surgeon										0.092
Surgeon A	62 (14.2)			50 (12.7)			12 (26.7)			
Surgeon B	71 (16.2)			62 (15.8)			9 (20.0)			
Surgeon C	11 (2.5.)			10 (2.5)			1 (2.2.)			
Surgeon D	284 (64.8)			262 (66:7)			22 (48.9)			
Others	10 (2.3)			9 (2.3)			1 (2.12)			
ICU stay >1 d	5			3 (3, 2, 2)[b]			2 (2, 2)[b]			0.028
Total length of stay, d	438	7 (5–14)	7.44 (±1.17)	393	7 (5–14)	7.43 (±1.20)	45	8 (6–10)	7.58 (±0.94)	0.417
Peak AST	364		361.18 ± 279.90	330		374.55 ± 287.62	34		231.32 ± 133.75	0.000
Peak ALT	339		553.61 ± 368.80	306		583.27 ± 367.99	33		278.61 ± 168.80	0.000
Peak total Bil	350		1.43 ± 0.85	317		1.42 ± 0.85	33		1.55 ± 0.77	0.631
Peak INR	374		1.27 ± 0.15	332		1.26 ± 0.15	42		1.33 ± 0.15	0.007
Peak platelets	367		428.10 ± 113.04	329		427.15 ± 113.47	38		436. 32 ± 119.30	0.637
Follow-up, d	347 (79)	456 (90–6297) (IQR = 183–414)		310 (78.9)	216 (90–6297) (IQR = 183–406)		37 (82.2)	313 (90–2471) (IQR = 197–531)		0.480

IQR is presented as the 25th percentile – 75th percentile.

[a]*P* value for comparison between the LLS and LH groups.

[b]Number of days that each patient spent in the intensive care unit.

ALT, alanine transaminase; AST, aspartate transaminase; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; LD, living liver donor; LH, left hepatectomy; LLS, left lateral sectionectomy; RBC, red blood cell; total Bil, total bilirubin;

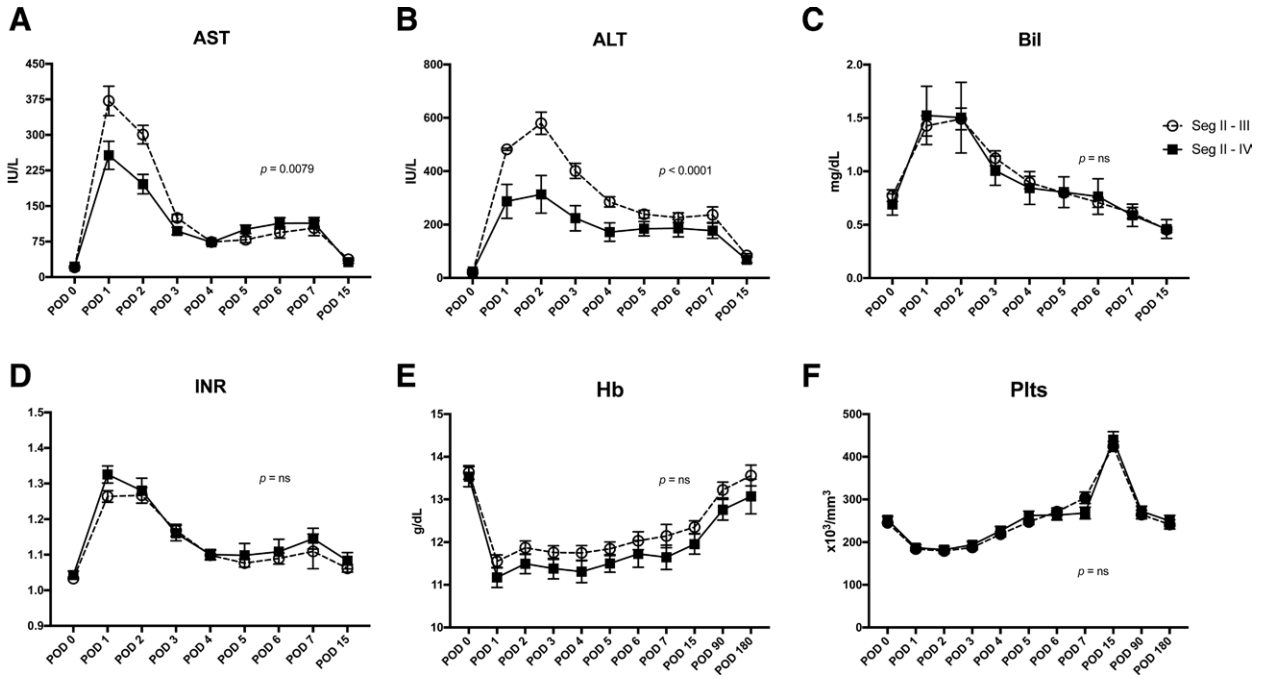

FIGURE 1. Biochemistry and hematologic postoperative evolution in living liver donors undergoing the left lateral liver segmentectomy including the segment II and III and the left hepatectomy, which comprises the segment II, III, and IV with the middle hepatic vein. A, Postoperative donor AST levels, (B) postoperative donor ALT levels, (C) postoperative donor Bil levels, (D) postoperative donor INR levels, (E) postoperative donor Hb levels, and (F) postoperative donor Plt levels. ALT, alanine transaminase; AST, aspartate aminotransferase; Bil, total bilirubin; Hb, hemoglobin; INR, international normalized ratio; Plt, platelet; POD, postoperative day.

incomplete perioperative workup of the donor regarding their hematological profile, which resulted in a temporary abort of the procedure before hilar dissection, the abdomen was closed, and the donor was transferred to the intensive care unit. Later in the same day, after having ruled out possible thrombophilia, the donor's operation was resumed. Of the 7 iAEs related to a surgical procedure, 4 were associated with surgical bleeding or vessel injury, 2 hemorrhagic events were related to slippage of the vascular clamp securing the LHV stump in 1 case and slippage of the arterial clip, which closes the LHA stump. Although massive bleeding occurred in both situations, hemostasis was rapidly achieved without major consequences for the donors. Vascular injuries occurred in 2 other cases, in one the RHA was ligated and sectioned, mistaking it for the artery of segment IV; in the other, the hepatic artery of the graft was injured very close to the hepatic hilum as the artery crossed behind the LPV. The RHA was reanastomosed using microsurgery techniques, and the graft LHA was repaired during the back table. Two surgical iAEs were related to the approach to the bile duct. In one, the common bile duct was ligated and divided, as diagnosed by the intraoperative cholangiography. Roux-en-Y biliary bypass was performed without long-term complications. In the other, perioperative cholangiography showed an injury to a secondary bile duct on the graft side, which was repaired on the back table. In the last surgical case, a tension pneumothorax developed as identified during the abdominal procedure, and it was immediately drained. It probably happened during the insertion of the central line. The last iAE was due to a drug administration error; 25 000IU of heparin was administered before vessels clamping instead of 1000IU according to our protocol. Heparinization was immediately reversed by protamine administration (Table 4).

Postoperative Outcome

No mortality or Clavien-Dindo grade IVa or IVb complications were reported. In total, 97 complications (22.14%) occurred in 87 patients (19.9%). One complication was recorded in 78 LDs, 2 in 8 LDs, and 3 different complications occurred in only 1 LD. Grade IIIa and IIIb complications were noted in 12 and 16 LDs, respectively, whereas grades I and II were observed in 33 and 36 LDs, respectively. The majority of complications were abdominal (48.4% of the total), followed by infections (18.6%) and cardiovascular/thoracic (9.3%). Among the abdominal complications, 9 patients had biliary involvement (2.0%). Six cases of small bile leaks were treated conservatively by keeping the abdominal drainage until the bile leak stopped: 1 case with percutaneous drainage alone, another case with percutaneous drainage in combination with sphincterotomy, and the last with sphincterotomy and stenting. In addition, 4 cases of hepatic cut surface collection were drained percutaneously. No relaparotomy was necessary. There was only 1 case of significant postoperative hemoperitoneum, with a hemoglobin level of 5.6 g/dL, and the presence of free perihepatic fluid on DUS examination, but no signs of active bleeding on CT scan; this patient was treated conservatively with a good outcome. Eleven LDs presented with late incisional hernia. There was no statistical difference for all types of complications between the 2 groups of liver resection, except for deep vein thrombosis, since the 2 cases occurred in patients undergoing LH ($P < 0.001$). Based on the Clavien-Dindo score, both groups had similar complication rates, except for grade II, which was more frequent in the LH group (22.2% versus 3%, $P = 0.014$). In addition, there were no differences in the CCI between the 2 groups (Table 5).

TABLE 4.

Perioperative iAEs identified during 438 left liver resections

iAEs number	No. LDs[a] (year)	iAEs description	iAEs management/LD and/or recipient evolution	Hospital length of stay, d	Clavien-Dindo
1	2 (1994)	**Temporary hepatectomy abortion:** After dissecting the elements of the liver pedicle and before starting the parenchyma section, the surgical team received a phone call from the donor's family doctor informing that the donor's cousin, deficient in protein C, was hospitalized for thrombophlebitis with pulmonary embolism, and 2 donor aunts had a history of pulmonary embolism.	The procedure was aborted, and patient transferred to the ICU extubated. After ruling out the protein C and S deficiency, the team after a multidisciplinary discussion decided to proceed with the case, which was uneventful. No postoperative complication.	7	/
2	90 (2001)	**Section of common bile duct:** The perioperative cholangiography prior to the section of the hilar plate did not show the presence of contrast on the intrahepatic biliary tree.	The exploration of hepatic pedicle identified a section of the common bile duct, which was treated by a Roux-en-Y hepaticojejunostomy. No postoperative complication.	6	/
3	105 (2002)	**Slipping of arterial clip:** The clip securing the stump of the left hepatic artery on the donor-side slipped just before abdominal wall closure causing an extensive bleeding.	The artery was clamped and doubled tied off. 900 mL of blood was recovered, processed, and transfused to the LD. Patient developed an abdominal wall collection treated by drainage and antibiotics.	7	II
4	176 (2009)	**Lesion of seg II bile duct (graft side):** The perioperative cholangiography, performed just before sectioning the hilar plate, identified a lesion on secondary bile duct draining the seg II (graft side).	Injury repair at the back table. Postoperative outcome was uneventful; however, the recipient developed an anastomotic biliary stricture requiring a revision of the hepaticojejunostomy 8 y later.	20 (recipient)	IIIb (recipient)
5	182 (2009)	**Slipping vascular clamp left hepatic vein:** The vascular clamp securing the stump of the LHV slipped off, just after the liver graft was taken out causing an extensive immediate bleeding.	Immediate bleeding control by doing a Pringle maneuver and clamping the LHV stump with posterior suture. 2700 mL of blood was recovered, processed and transfused to the LD. No postoperative complication or further blood transfusions.	8	/
6	276 (2013)	**Intraoperatory hypertensive pneumothorax:** Following the puncture of the left subclavian vein, a perioperative hypertensive pneumothorax developed, being promptly diagnosed.	Treatment consisted of an urgent transdiaphragmatic puncture with a posterior chest drain insertion, which was taken out at POD4 under local anesthesia. Otherwise, no complications were observed in the outcome.	9	IIIa
7	350 (2015)	**Donor full heparinization before portal vein clamping:** Before vascular clamping, LD received an overdose of 10 000 IU of heparin instead of a protocoled 1000 IU.	Donor full heparinization was confirmed by the activating clotting time test, motivating the administration of protamine in perioperative. No hemorrhagic complications were observed in either the LD or the recipient. The LD presented an incisional hernia 2 years later.	8	IIIb
8	375 (2016)	**Section of RHA:** The RHA was inadvertently sectioned and tied at the end of the liver parenchyma division due to a hepatic vascular anatomy anomaly.	Treatment consisted of a microsurgical vascular reconstruction. Postoperative period was uneventful with normal sequential liver DUSs.	9	/
9	430 (2018)	**Injury of left hepatic artery (graft side):** During the section of the hilar plate, the LHA was partially sectioned close to the liver parenchyma on the graft side due to an aberrant position compared with the normal anatomy.	An ex situ arterial microsurgical reconstruction through a termino-terminal anastomosis with interrupted stiches was performed.	22 (recipient)	I (recipient)

[a]No. LDs indicates in which living donor procedure in our consecutive LDLT series the iAEs occurred.

DUS, Doppler ultrasonography; iAE, intraoperative event; ICU, intensive care unit; LD, living donor; LDLT, living-donor liver transplantation; LHA, left hepatic artery; LHV, left hepatic vein; POD, postoperative day; RHA, right hepatic artery.

TABLE 5.

Postoperative complications observed in 438 LDs according to the Clavien-Dindo 5-tier score

Complications	Total population (N = 438)		Clavien-Dindo				LLS (n = 393)		Clavien-Dindo				LH (n = 45)		Clavien-Dindo				
	LDs[b] (n)	No. compl[c]	I	II	IIIa	IIIb	LDs[b] (n)	No. compl[c]	I	II	IIIa	IIIb	LDs[b] (n)	No. compl[c]	I	II	IIIa	IIIb	*P*[b]
Abdominal	32	37	17	3	5	12	29	33	15	3	4	11	3	4	2		1	1	0.513
Chylous ascites	(1)	(1)	(1)				(1)	(1)	(1)										0.735
Wound complications	(8)	(9)	(7)		(2)		(7)	(8)	(6)		(2)		(1)	(1)	(1)				0.933
Cut surface collection	(2)	(3)			(3)		(1)	(2)			(2)		(1)	(1)			(1)		0.187
Vascular	(2)	(2)		(2)			(2)	(2)		(2)									0.631
Intraabdominal bleeding	(1)	(1)		(1)			(1)	(1)		(1)									0.735
Ileus	(4)	(7)	(7)				(4)	(6)	(6)					(1)	(1)				0.725
Hyperamylasaemia	(2)	(2)	(2)				(2)	(2)	(2)										0.631
Appendicitis	(1)	(1)				(1)	(1)	(1)				(1)							0.735
Incisional hernia	(11)	(11)				(11)	(10)	(10)				(10)	(1)	(1)				(1)	0.896
Biliary complication	9	9		6	1	2	7	7		4	1	2	2	2		2			0.233
Bile leak	(7)	(7)		(6)		(1)	(5)	(5)		(4)		(1)	(2)	(2)		(2)			0.108
Biloma	(2)	(2)			(1)	(1)	(2)	(2)			(1)	(1)							0.631
Cardiovascular/thoracic	9	9	2	3	3	1	7	7	2	1	3	1	2	2		2			0.834
Deep vein thrombosis	(2)	(2)		(2)									(2)	(2)		(2)			0.000
Vasoplegic syndrome	(1)	(1)		(1)			(1)	(1)		(1)									0.735
Pneumothorax	(5)	(5)	(2)		(3)		(5)	(5)	(2)		(3)								0.447
Lung cancer	(1)	(1)				(1)	(1)	(1)				(1)							0.735
Infection	16	18		16	2		14	15		13	2		2	3		3			0.362
Neurologic	4	4	2	1		1	3	3	1	1		1	1	1	1				0.330
Pain	8	9	8		1		8	9	8		1								0.305
Psychiatric disorders	2	2		2			2	2		2									0.631
Others	7	9	4	5			5	7	3	4			2	2	1	1			0.834
Subtotal	87	97	33	36	12	16	75	83	29	28	11	15	12	14	4	8	1	1	
Clavien-Dindo I	28	33	33				25	29	29				3	4	4				0.716
Clavien-Dindo II	31	36		36			24	28		28			7	8		8			0.014
Clavien-Dindo IIIa	12	12			12		11	11			11		1	1			1		0.822
Clavien-Dindo IIIb	16	16				16	15	15				15	1	1				1	0.589
Total of complications		97						83						14					0.126
Total number of living donors with complications, n (%)	87 (19.9)						75 (19.1)						12 (26.7)						0.227
CCI (mean ± SD)	20.5 ± 9.6						20.5 ± 9.8						20.1 ± 8.3						0.868

[a]All *P* were calculated for the complications rates out the last one that was calculated for the number of LDs presenting complications. Values in parentheses are the subtotal for abdominal complications, biliary complications, and cardiovascular/thoracic complications.
[b]No. LDs indicates the total number of living donors presenting at least 1 postoperative complication. The highest Clavien-Dindo complication was considered in an LD presenting more than 1 complication. Seventy-eight LDs presented only 1 complication, 8 LDs presented 2 complications, and 1 LD presented 3 complications.
[c]No Compl indicates the number of times a type of complication occurred in the LD population that presented complications in its postoperative course. At the end of the study, 97 complications were reported to have occurred in 87 LDs.
CCI, comprehensive complication index; LD, living liver donor; LH, left hepatectomy; LLS, left lateral sectionectomy.

DISCUSSION

Although surgical outcome can be seriously affected by the occurrence of an iAE, its definition is currently very heterogeneous and confusing, since it sometimes overlaps with the definition of postoperative complications. In fact, in a recent review, more than 16 definitions and 12 grades of severity were reported, making any attempt of series comparisons extremely challenging.[31] In addition, it is more difficult to define and grade iAEs in the context of living-donor procedures, wherein the occurrence of an iAE involving the graft may lead to consequences for the recipient. By using ClassIntra score, which was originated from a prospective multicenter study specifically designed to define and classify surgery- and anesthesia-related iAEs, we identified 9 iAEs that changed the normal planed intraoperative course, in which 5 iAEs were considered potentially harmful for the donor, 2 were for the recipient, and 2 were for both. To the best of our knowledge, this is the first study to systematically, openly, and clearly address the issue of the occurrence of life-threatening intraoperative adverse events in the context of living liver donation.

Although our first iAE can be considered anecdotal in aborting a donor hepatectomy due to a phone call emphasizing the donor's family history of hematologic disorders, it warns how an incomplete donor evaluation can influence the outcome. This prompted us to perform a stricter preoperative donor evaluation. In addition to the risk of thromboembolic complications, the donor underwent an unplanned second anesthesia and surgery. Furthermore, aborting the donation procedure could have affected the recipient's outcome if any of the recipient's major liver structures were already divided at the time of donation interruption. However, it should be noted that it was the only aborted procedure in our 438 LDs (0.22%), although temporarily, whereas other studies reported a donor hepatectomy abortion rate of 1.3% to 4.7%.[32,33] In the 2 iAEs referred to as possible biliary complications, both lesions were diagnosed using routine cholangiography. Previous descriptions of intraoperative donor bile duct lesions include thermal injury of the bile duct, reported by the Toronto group, and treated with a choledochojejunostomy repair without specifying whether it was performed during donor hepatectomy or later.[34] Tanemura et al described 2 bile duct lesions treated with duct-to-duct reconstruction protected by T-tube insertion.[35] The mishap of our 2 biliary injuries could have caused serious consequences to the donor in 1 case and to the recipient in the other. Failure to identify donor bile duct ligation could have resulted in postoperative biliary obstruction. Subsequent surgical treatment would be challenging as biliodigestive diversion would be carried out with inflamed tissues. In fact, it could lead to other postoperative complications, such as bile leaks and infections, which could increase donor morbidity. Likewise, the mishap of the left bile duct injury in the graft could result in posttransplant bile leakage. Surgical treatment would be riskier in a weakened transplanted child under immunosuppressive treatment. In the absence of perioperative cholangiography, the diagnosis is likely to be made later as a true complication and its consequences. Therefore, we continue to perform routinely perioperative cholangiography, which is the standard in many LDLT centers worldwide.[36] Four iAEs were found to be associated with intraoperative vascular accidents. Following the Hemo-lok iAE, similar clipping accidents were reported, including the fatal course of a kidney donor who underwent a laparoscopic nephrectomy.[37] Since then, we have used double-metal clipping. The iAE, caused by the slipping of the LHV vascular clamp, led us to change the surgical protocol. So that instead of completely dividing the LHV in 1 step, we switched to a progressive division of the LHV with its concomitant stump closure using a continuous 4/0 Prolene suture. A similar iAE has already been described during a right lobe resection for an adult LDLT, resulting in blood loss of more than 1 liter without specifying if the donor outcome has been impacted.[38] Hwang et al described a similar technical improvement after a major vascular accident, which involved the placement of a traction stitch in each corner of the hepatic vein before its division.[39] Two vascular iAEs were associated with arterial injuries: RHA transection and partial LHA injury on the graft side. After debriefing of the RHA-iAE, we found that the RHA ran alongside the LHA up to the hilum, where it turned to the right. In addition, because of the vasospasm induced by surgical dissection, it was mistaken as the artery for segment IV. Since then, we have used to dissect the LHA and the origin of the RHA. In addition, we used to wrap the arteries in a piece of Surgicel soaked with papaverine to avoid vasospasm. The partial transection of the LHA close to the liver graft was due to an anatomic variation in its course, running just behind the LPV before entering the parenchyma. Since then, we have paid more attention to such variations before transectioning the hilar plate and the LPV. The occurrence of 2 pneumothoraxes as consequence of invasive hemodynamic monitoring was also previously described during LD procedures.[38] Although the placement of a central venous line has been abandoned by some authors during donor hepatectomy,[40] we routinely use it for better perioperative monitoring and fluid infusion. However, after our IJV iAEs, the puncture is now performed under ultrasound guidance. Surprisingly, only 1 iAE was associated with inappropriate drug administration. In this case, full-dose heparinization exposed the donor to the risk of developing serious perioperative bleeding, as well as the recipient after graft implantation. This event made us adopt a "navy" way of verifying the heparin doses by team members saying out loud the dosage, first by the main surgeon, then the first assistant, and finally, the anesthesiologist immediately before administration. Collectively, these 9 iAEs prompted us to modify and improve our LD protocol over time in a manner similar to that recommended by the "root cause analysis" (RCA) systematization. The methodology can be roughly summarized in 3 questions: What happened? Why did it happen? What can be done to prevent it from happening again?[41] RCA has already been used as an enhancement tool for liver transplant recipients.[42] Based on RCA system, we interrogated what led to the occurrence of each iAE, and what could have happened in case of the iAEs not being recognized and treated in time, this systematization helped us to improve our LD intraoperative care. When compared with the ClassIntra study, our 2% (9 of 438) incidence of iAE is much lower than the 24% incidence reported in 2520 patients recruited from 12 different surgical specialties. In fact, in their prospective study, 18.4% of the iAEs were classified as grade I or II, whereas in our series, all iAEs were considered grade III or IV (Table 6), suggesting that it was not possible to capture the low-grade iAEs in a retrospective data search. In contrast, Kaafarani et al, using a different but quite similar iAE classification, reported 181 iAEs in a series of 9292 patients from different surgical specialties (1.94% incidence), with >60% of their iAEs being classed as grade I or II.[23] In the context of liver living donation, few studies looked at the occurrence of iAEs. In a retrospective study, Araz et al used a very strict iAE classification to specifically look at anesthesia-related iAEs during an LD liver procedure and reported that 50% of donors experienced at

TABLE 6.

Potential consequences for donors and recipients in case of nonimmediate detection and treatment of iAEs and their classification according to the ClassIntra grade

iAEs (y)	iAEs	Risk for the donor or recipient and/or potential evolution in case of not treating the iAEs	Changes in the surgical protocol	iAEs grade[a]	Potential risk[b] (donor, recipient, both)
1 (1994)	Temporary hepatectomy abortion	Performing a second surgical procedure theoretically increases the risk of complications, such as anesthetic and surgical complications, developing an incisional hernia, and infections. If the abortion occurred later, it could occur at the time when an important structure in the recipient was already divided.	Improving hematologic LD preoperative screening	III	***c***
2 (2001)	Section of common bile duct	If the common bile duct ligation is not detected, the patient could have developed chronic biliary obstruction with all its consequences, which may include reintervention for biliary diversion and even the risk of developing secondary biliary cirrhosis.	Confirmed the utility of preoperative cholangiography	IV	***a***
3 (2002)	Slipping of arterial clip	If not recognized immediately, the donor could have developed severe hypovolemic shock with all its consequences, including cardiac arrest.	Change of the vascular clip type	IV	***a***
4 (2009)	Lesion of seg II bile duct (graft side)	If not repaired, the lesion could be the cause of a post-transplant biliary leakage.	Biliary stricture developed 8 y later requiring surgical revision	III	***b***
5 (2009)	Slipping vascular clamp left hepatic vein	If not recognized immediately, the donor could have developed severe hypovolemic shock with all its consequences, including cardiac arrest with a perioperative death.		IV	***a***
6 (2013)	Intraoperatory tension pneumothorax	If not drained immediately, the tension pneumothorax could have progressed to respiratory failure and cardiac collapse.	Insertion of central line under DUS guidance	III	***a***
7 (2015)	Donor full heparinization before portal vein clamping	Whole-body heparinization puts the patient at risk of developing serious perioperative bleeding as well as stroke. Increased risk of bleeding after graft implantation.	Implementation of a checking system before heparin administration	III	***c***
8 (2016)	Section of right hepatic artery	If unrecognized, the RHA ligation could have caused massive necrosis and failure of the remaining liver, which could require a liver transplant. Also, it could be the cause of biliary tree necrosis with all of its consequences.	Dissection of the origin of the RHA in a routine basis for a better visualization of its trajectory	IV	***a***
9 (2016)	Injury of left hepatic artery (graft side)	If not treated, the LHA injury on the graft side could be the cause of bleeding after implantation and or cause of a pseudoaneurysm of the artery in the long-term.	Careful dissection of the LHA when there are anatomic variations, and with special attention to the moment of division of the hilar plate	III	***b***

[a]iAE ClassIntra grading.
[b]iAE potential risk: ***a***: donor life-threaten or potential risk of complications to the donor; ***b***: risk of postoperative complications for the recipient; ***c***: risk of postoperative complications for the donor and the recipient.
DUS, Doppler ultrasonography; iAE, intraoperative event; LD, living donor; LHA, left hepatic artery; RHA, right hepatic artery.

least 1 episode of hypothermia, hypo/hypertension, or required a blood transfusion.[43] In a prospective study, Dondero et al included 127 LDs and reported an incidence of 12% with the occurrence of 15 surgical- and anesthesia-related iAEs.[38]

Despite that the Clavien-Dindo classification of postoperative complications is widely accepted, the reported complication rates and classification after living liver donation remain highly variable and heterogeneous.[25,44] Overall donor morbidity ranges from 10% to 40% in different studies.[9,14,19,44-46] In the current study, complications occurred in 19.9% of LDs, which is slightly lower than the average rate of 23% LH donor morbidity described in a recent metaanalysis,[44] and similar to the 20% complication rate in the only study exclusively for LLR in said meta-analysis.[46] Morbidity rates were similar between the 2 groups of liver resections. Furthermore, there were no grade IV complications, and only 6.4% of the patients had grade III complications. Only 9 LDs (2.05%) presented biliary complications, a relatively lower rate when compared with studies describing donor LH biliary complications, which range from 2.8% to 11.7%, as reviewed recently.[47] It should be noted that there were no donor bile duct strictures, but only small to moderate bile leaks or bilomas. These good results can be attributed to intraoperative cholangiography; due to the additional tests performed after graft removal, as the injection of methylene blue is injected through the catheterized cyst duct, a white swab is placed on the liver cut surface aiming to identify any open small terminal bile duct.

In conclusion, despite its limitations, the review of our series of LLS/LH living donations for a PLDLT allowed us to identify 9 majors iAEs that induced changes in our donor

perioperative care. This systematic iAEs debriefing policy contributed to the lower morbidity and zero mortality over time in our series by improving our LD surgical protocol. The use of an iAE differentiation system according to their potential risk for donors and recipients may facilitate comparison between different series of LDLT. Multicentric studies will be required to further improve such quality assessment in a living liver donation surgery, which could be extended to right liver donation and alternative surgical approaches including laparoscopic and robotic procurements.

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