FMUC FACULDADE DE MEDICINA
UNIVERSIDADE DE COIMBRA

Mestrado Integrado em Medicina – Trabalho Final

JOSÉ PEDRO FERNANDES DOS SANTOS

Poor Outcome Predictors and Donor Surgical Morbidity in Pediatric Living Donor Liver Transplant

Artigo Científico

Área científica de Cirurgia Pediátrica

Trabalho realizado sob orientação de:

Professora Doutora Maria Francelina Lopes

Dr. Ricardo Jorge Martins

Março 2019

Poor Outcome Predictors and Donor Surgical Morbidity in Pediatric Living Donor Liver Transplant

José Pedro Fernandes dos Santos[1]

Dr. Ricardo Jorge Teixeira Martins[1;2]

Professora Doutora Maria Francelina de Sousa Cruz Lopes[1;2]

[1]: Faculty of Medicine, University of Coimbra, Portugal

[2]: Centro Hospitalar e Universitário de Coimbra

e:mail – jose.pfdossantos@gmail.com

Index

List of abbreviations

ALT: Alanine Transaminase

AP: Alkaline Phosphatase

AST: Aspartate Transaminase

BMI: Body Mass Index

CHUC: Centro Hospitalar e Universitário de Coimbra

CT: Computed Tomography

GIQLI: Gastro Intestinal Quality of Life Index

HDH: Hybrid Donor Hepatectomy

IBT: Intraoperative Blood Transfusion

ICU: Intensive Care Unit

INR: International Normalized Ratio

IOC: Intra-Operative Cholangiography

LH: Left Hepatectomy

LHV: Left Hepatic Vein

LL: Left Liver

LLS: Left Liver Sectionectomy

MHV: Middle Hepatic Vein

MILDH: Minimally Invasive Living Donor Hepatectomy

MRCP: Magnetic Resonance Cholangiopancreatography

MRI: Magnetic Resonance Imaging

NAFLD: Non-Alcoholic Fatty Liver Disease

PE: Pulmonary Embolism

P-ESLD: Pediatric End-Stage Liver Disease

PHLD: Post-Hepatectomy Liver Dysfunction

P-LDLT: Pediatric Living Donor Liver Transplant

RH: Right Hepatectomy

RHV: Right Hepatic Vein

RL: Right Liver

RLV: Remnant Liver Volume

RS: Right Subcostal

SBP: Systolic Blood Pressure

TB: Total Bilirubin

Abstract

Introduction: Pediatric liver transplantation is the state-of-the-art treatment for children with end-stage liver disease (ESLD). Pediatric ESLD incidence is increasing and so is the number of children enlisted for liver transplant. Since 1991 the number of liver grafts from living donors could not keep up with the demand, mostly due to donor misinformation.

Methods: For this study, 18 years of Living Donor Liver Transplant (LDLT) were retrospectively analysed, matching 28 successfully procedures. Donor's data were collected, and surgical outcomes were categorized according to Clavien's Classification of Surgical Complications. Furthermore, a bibliographical review focusing on the factors that can interfere with the donor's operative prognosis was performed. These poor outcome predictors were collected and organized into 3 categories: pre-, intra- and postoperative.

Results: Twenty-eight per cent (n=8) of donors had surgical complications. According to Clavien's classification, 2 donors had major complications (Clavien grade ≥3); 4 donors had grade 2 complications and 2 donors had grade 1 complications. The present series reports no mortality. Literature review suggests that pre-operative important data gathered is donor's age and sex, smoking habits, obesity and hepatic steatosis, albumin concentrations, liver blood tests (Alkaline Phosphatase, Alanine Transaminase and Aspartate Transaminase), coagulation status, vascular anatomy variations and procedure urgency. Intra-operative important factors are blood transfusion, hypotension, remnant liver volume, hepatectomy length, type of hepatectomy and abdominal wall incision. Recent techniques as the use of minimal invasive liver surgery, Propofol and Terlipressin infusion, Portal vein pressure modulation, "softcoagulation" and bloodless donor hepatectomy may improve donor post-surgical outcome. Postoperative hyperbilirubinemia and increased INR should also be given due consideration as a predictor of poor surgical outcome.

Conclusions: CHUC's series shows that donor hepatectomy in P-LDLT is a safe and feasible procedure, without mortality. When assessing a potential donor, poor outcome predictors assessment should be done aiming to exclude patients and decrease surgical complication rates. Bearing in mind the *Primum non nocere* precept regarding donation, overall morbidity should be reduced, thus decreasing patient reluctance which may contribute to greater availability of organs and wider use of LDLT.

Keywords: Liver Transplantation; Living Donors; Donor Outcomes; Morbidity; Donor Safety.

Introduction

Pediatric liver transplantation is the state-of-the-art treatment for children with established or with high risk of end-stage liver disease (P-ESLD). Pediatric Living Donor Liver Transplant (P-LDLT) has become a viable and feasible strategy aiming to ameliorate the organ shortage experienced by centres around the world. P-LDLT is a treatment option when the risk of mortality by the disease itself overcomes the risk of death likelihood related with the transplant or a mortality risk due to liver failure in 1 year greater than 90% (1,2). Children's mortality rate is 15% in the first 5-years after transplant (1). This technique was first described in the Western world; however, it is especially prevalent in Asian countries were deceased donation rates are very low (3).

The first attempts of pediatric liver transplantation using a living adult donor were reported in 1988 by Raia *et al.* who described two complete procedures in which both recipients died (4). In 1989 Strong *et al.* described the first successful P-LDLT using a graft obtained from an adult (5).

Coimbra's Pediatric Hospital (CHUC) is a tertiary academic centre serving as the national reference centre for pediatric liver transplant since 1994. P-LDLT is performed since 2001 (6). Additionally, Coimbra's Pediatric Hospital is amongst the 18 European centres which integrate de ERN Transplant-Child (7).

The most common indications for Pediatric Liver Transplant worldwide are biliary atresia, fulminant hepatic failure, α-1-antitrypsin deficiency, Primary liver tumours (hepatoblastoma and hepatocellular carcinoma), cryptogenic cirrhosis, Alagille Syndrome, Tyrosinemia, Autoimmune hepatitis and Primary Sclerosing Cholangitis (8). For instance, the incidence of biliary atresia has increased at an average of 7.9% per year from 1997 to 2012 (9) and the incidence of hepatoblastoma has doubled from 0.8/million to 1.6/million in a 15-year analysis (10). Some reports show that the prevalence of pediatric non-alcoholic fatty liver disease (NAFLD) has increased substantially in the last two decades. NAFLD has become the most common cause of chronic liver disease in children (11). Reports show that patients with NAFLD often required a second transplantation before adulthood due to recurrence of the disease (12). In our centre, the most common aetiologies leading to P-LDLT are biliary atresia and α-1-antitrypsin deficiency.

Donor safety is a matter of paramount importance. Currently, donor death rate and surgical morbidity related to pediatric liver transplant are 0.13% and 10-40% respectively (13,14).

Morbimortality in donors is the main obstacle to the use and evolution of LDLT. Assuring donors' safety is the main priority and trying to avoid poor surgical outcome depends greatly on the procedure and patients' characteristics. Donor's safety depends on many aspects including preoperative selection, surgical technique and postoperative management. Knowing the aspects that may affect the procedure morbidity may be useful in preventing complications or exclude donors with higher risk.

Surgical technique's innovations and perfectioning and the increasing incidence of P-ESLD drove to an upsurge use of LDLT. The number of required surgeries has increased by 11-fold since 1991 and the number of donors did not follow this tendency. Due to shortage of donors, there is a significant delay in surgical timing which can be fatal for children (8).

National scientific literature regarding this important topic is scarce. This study aims to determine donor's surgical morbidity in Centro Hospitalar e Universitário de Coimbra (CHUC) and to gather the parameters that may interfere with donor surgical outcome by the relevant scientific literature review.

This paper presents CHUC's experience regarding donors' surgical morbidity in P-LDLT. A retrospective analysis of surgical outcomes was made and categorized according to the Clavien *et al.* Classification of Surgical Complications (15). Additionally, an analysis of the most recent published literature was done, collecting the potential pre-, intra- and postoperative aspects that may have a positive or negative impact on the perioperative complication rate of living liver donors.

Patients and methods

Living Donation for Pediatric Liver Transplantation in CHUC

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Coimbra and followed the Institutional and European Commission rules and Helsinki's ethical standards of using deidentified and anonymized data for human medical research.

A retrospective revision of a single institution clinical records was performed, analysing the medical charts of all donors (n=28) who underwent hepatectomy in P-LDLT (recipients under 18 years of age) context in CHUC from April 27, 2001, to September 30, 2018. In addition, we collected pertinent data of recipient-donor pairs included in the pediatric liver transplant database. No donors were excluded from the study.

Collected data included demographic characteristics from both the recipient and the donor as sex; age and body mass index (BMI) and ABO compatibility, date of procedure, primary indication for P-LDLT. Surgical and imagiological data collected included type and volume of graft collected, total liver volume, remnant liver volume; postoperative surgical complications including morbidity and mortality within the first 90 days after donor hepatectomy.

Generally, healthy voluntary individuals, aged between 18 and 50 years old, ABO compatible with recipient, body mass index between 18 and 28 kg/m^2 and without medical or psychiatric illness are considered for donor evaluation.

Donors' preoperative study at CHUC follows an established protocol which includes a psychosocial evaluation, health status evaluation, exclusion of metabolic or infectious diseases, study of the hepatic vascular and biliary anatomy, evaluation of the total liver and graft volumes in order to determine the percentage of remnant liver volume (RLV).

Analytic pre-donation studies include a full blood count and biochemical study, a complete coagulation study and viral serology. Depending on the receptor's disease, α-1-antitrypsin dosing and plasmatic ceruloplasmin and copper dosing were performed.

Imaging study done prior to donor hepatectomy is performed using Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Angiography with hepatic 3D anatomical reconstruction. CT Angiography with 3D reconstruction is used to minutely analyse liver vascular anatomy. These imagiological studies are also valuable to calculate total liver and graft volume, essential to a complete pre-operatory study. MRI allows detailed evaluation of the biliary tract and it is useful for assessment of hepatic steatosis (sensitivity:81% and specificity:100%(16)). Percutaneous hepatic biopsy is done in selected cases (4 donors in our series) due to altered hepatic enzymology (n=2), receptor with cryptogenic cirrhosis (n=1) and 1 non-described justification.

Postoperative surgical complications were graded according to the Clavien *et al.* Classification of Surgical Complications, which is presented in Table 1 (15). A major complication is defined as the arouse of any kind of surgical morbidity with grade ≥3 in the Clavien *et al.* classification.

Table 1. Clavien *et al.* Classification of Surgical Complications. (15)	
Grade 1:	Any deviation from the normal postoperative without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade 2:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade 3:	Requiring surgical, endoscopic or radiological intervention: 3a: Intervention not under general anaesthesia; 3b: Intervention under general anaesthesia.
Grade 4:	Life-threatening complication (including CNS complications)* requiring IC/ICU management: 4a: Single organ dysfunction (including dialysis); 4b: Multiorgan dysfunction.
Grade 5:	Death of a patient.
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain haemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks. CNS: central nervous system; IC: intermediate care; ICU: intensive care unit.

Literature review

A literature search was developed through PubMed database using the keywords ("pediatric"[MeSH Terms]) AND ("living donors"[MeSH Terms] OR ("living"[All Fields] AND "donors"[All Fields]) AND ("liver transplantation"[MeSH Terms] OR ("liver"[All Fields] AND "transplantation"[All Fields]) OR "liver transplantation"[All Fields] OR ("liver"[All Fields] AND "transplant"[All Fields]) OR "liver transplant"[All Fields]). An analysis of results was performed from inception to December 2018. After a selection of the relevant articles for this study, 62 articles were reviewed.

Results

CHUC's Surgical Outcomes

Cohort Data

A total of 28 hepatectomies for P-LDLT were performed. There were no aborted donor operations. Each donor experienced complete recovery after the donation. There were no deaths or need for postoperative donor-liver transplant. Procedures performed throughout the years can be seen in Figure 1.

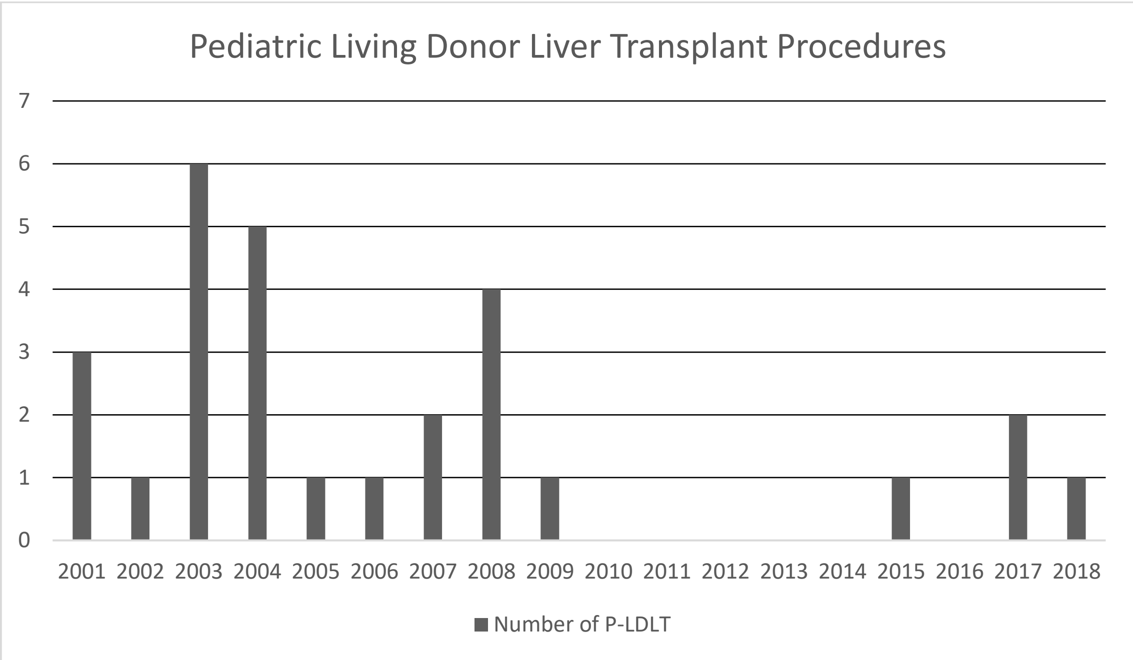

Figure 1. Pediatric Living Donor Liver Transplant Procedures since April 2001 to September 2018.

After analysis of the donor's medical charts and the prospective P-LDLT database (containing recipient-donor pairs pertinent information) several aspects regarding the demographic characteristics of our study population are presented in Table 2.

Table 2. Donor demographics.	
Characteristics	N=28
Age, mean (limits)	33.6 years (18-47)
Gender, n (%)	
Female	18 (64.3)
Male	10 (35.7)
Body mass index, mean kg/m^2	23.14 (18-31)
Indications for P-LDLT, n (%)	
Biliary atresia	11 (39.3)
α-1-antitrypsin deficiency	8 (28.6)
Cryptogenic cirrhosis	3 (10.7)
Multifocal hepatocarcinoma	1 (3.6)
Foetal hepatoblastoma	1 (3.6)
Type 1a glycogenosis	1 (3.6)
Acute hepatic failure	1 (3.6)
Wilsons' disease	1 (3.6)
Choledochal type I cyst	1 (3.6)
Relationship with recipient, n (%)	
Mother	18 (64.3)
Father	9 (32.1)
Uncle	1 (3.6)
ABO incompatibility, n (%)	0 (0)
Type of graft, n (%)	
Left Lateral Sectionectomy	20 (71.4)
Left Hepatectomy	6 (21.4)
Right Hepatectomy	2 (7.1)
Mean graft volume, cm3† / Mean Remnant liver volume (%)‡	
Left Lateral Sectionectomy	242.7 / 82.8
Left Hepatectomy	382.5 / 67.5
Right Hepatectomy	841 / 39.5
Days of hospital stay, mean (limits)	7.15 (6-12)
Overall within 90 days postoperative morbidity rate, n (%)	8 (29)
Postoperative liver insufficiency, n	0
Death, n	0

†: Graft volume was obtained pre-operatively in 26 patients with an average of 322 cm3, ranging from 179cm3 to 1051cm3.

‡ : The average remnant liver volume, determined in 24 donors, was 76% (minimum of 35% to a maximum of 89%.

As Table 2 presents, female to male ratio preponderance was 1.8 and slightly elevated BMI average is noticeable. The only child who had not a parental relationship with the donor, received the graft from an uncle. The most common indication for P-LDLT was biliary atresia.

A total of 28 procedures were done, being Left Lateral Sectionectomy the most common one (n=20; 71.4%), followed by Left Hepatectomy (n=6; 21.4%) and Right Hepatectomy (n=2; 7.1%).

Overall postoperative morbidity rate within 90 days after donor´s hepatectomy was 29% (n=8 patients). However, these complications were mainly minor, except for 7% of the cases (n=2 with Grade ≥3 complications) (Table 3).

Table 3. Donors’ Complications according to the Clavien *et al*. Classification. (15)

Clavien Grade		Complication	n	Relative %	Absolute %
1		Partial Respiratory Insufficiency	1	3.6%	12.6%
		Paralytic Ileum	1	3.6%	12.6%
2		Bile leak	2	7.1%	24.8%
		Superficial incisional infection	2	7.1%	24.8%
3	3a	N/A	0	0%	0%
	3b	Incisional Hernia	1	3.6%	12.6%
4	4a	Hemoperitoneum	1	3.6%	12.6%
	4b	N/A	0	0%	0%
5		N/A	0	0%	0%
Total:			8	28.6%	100%

N/A: Not applicable.

Grade 1 complications arouse in 4 patients. One of the donors developed partial respiratory insufficiency treated with kinesiotherapy and Oxygen supplementation. One other patient experienced paralytic ileum that was solved with conservative treatment.

Grade 2 complications occurred in another 4 donors. Of these, two donors developed post-surgical bile leak and both were successfully managed with drainage maintenance and antibiotic therapy. The other 2 donors presented a superficial incisional infection which required antibiotic and ressuture with local anaesthesia.

Major complications arouse in 2 patients. One of the donors developed a postoperative abdominal hernia which required a surgical repair under general anaesthesia (Grade 3b). The incisional hernia was detected within the first 90 days after donation, but the relaparorraphy was performed after that period. One other donor experienced a hemoperitoneum followed by hypovolemic shock and was immediately taken to the Operating Room for urgent haemostasis (Grade 4a).

Data from Literature review: Surgical Outcome Predictors

Of the several references identified by searching the MEDLINE-PubMed database using the MeSH terms listed above in the Methods, 42 full-text studies containing information regarding the pre-, intra-, and postoperative aspects which may negatively or positively influence the perioperative outcome of live liver donors were selected for review (13-14, 17-22, 24-41, 43-59). Tables 4, 5 and 6 present the summarized factors which may modify donor morbidity rates, as well as the literature reference for each feature.

PRE-OPERATIVE

Pre-operative donor characteristics which may alter patient post-donation morbidity are described ahead and can be found summarized in Table 4.

Donor's Age

Although adult live donors younger than 50 years are generally chosen for P-LDLT, there is increased use of older donors due to the shortage of cadaveric organs for liver transplant (17).

Even though advanced donor age is generally related to poorer outcomes after hepatectomy, donor´s age as low as 40 years old is proved to be an independent risk factor for the development of bile leak and abdominal hernias in the donor (14). Donors age over 50 years old is associated with a higher rate of major complications (Clavien grade ≥3), especially after Right Hepatectomy (RH). In this type of procedure, if Middle Hepatic Vein (MHV) is harvested and Remnant Liver Volume (RLV) drops under 35%, donors over 50 years old should be excluded (18).

An impaired regenerative capability which may lead to hepatic dysfunction after procedure might be present in older patients. Elderly donors have worst post-hepatectomy liver regeneration than younger ones, either considering the transplanted graft or the remnant liver (19).

Contrarily, patients younger than 33 years have higher chances of developing early postoperative complications such as hemodynamic and respiratory instability and diarrhoea. Wakata *et al.* showed that a 1-year increase in age was associated with an 8.6% decrease in the risk of respiratory instability (20). Wang *et al.* reported younger donor age (with a mean age of 24.3 years) being associated with significantly higher rates of diarrhoea incidence and lower scores in GIQLI (Gastro-Intestinal Quality of Life Index), although no pathological relation between hepatectomy and development of diarrhoea was disclosed (21).

Donor's Sex

Donor's sex is a poorly understood surgical risk predictor in LDLT. Male sex seems to be an independent risk factor for incisional hernia after hepatectomy (14).

Renz *et al.* reported two donor deaths in P-LDLT in which both patients were women, who developed Pulmonary Thromboembolism. Furthermore, female sex is proved to be an independent risk factor for delayed recovery of the remnant donor liver (13,22).

Smoking habits

Two described deaths related to smoking in one centre lead to the exclusion of tobacco users as donors. Renz *et al.* reported two fatalities, both women who smoke who had a fatal pulmonary embolus. Furthermore, the occurrence of a similar, yet not fatal, case in one smoking male donor drove to the rejection of this kind of individuals (13).

Obesity and Hepatic Steatosis

Obesity and Hepatic Steatosis walk hand by hand. Individuals with BMI>27.5 kg/m^2 were most likely to show moderate steatosis than those with BMI<23kg/m^2 (who displayed no or mild steatosis) (23). Due to this correlation, all articles reviewed presented both these donors' characteristics together.

Series analysing surgical morbidity after right lobe liver donation verified that only obese (BMI>30kg/m^2 and documented macrovesicular hepatic steatosis) patients developed Clavien 4a complications (24). BMI>30kg/m^2 represents an independent risk factor for serious postoperative complications and longer hospital stay, even in less invasive surgeries. Mini-laparotomy or laparoscopic techniques showed positive results concerning donation safety except in obese patients due to technical difficulties when performing it on donors with larger body habitus (25).

An increment of 10kg in body weight (in relation to maximum weight of 25kg/m^2) rises the risk of bile leak by 22% (14).

Postoperative transaminase and bilirubin peak values may be used as markers of the extent of hepatic injury after donation. Irrespective the steatosis type (micro- or macro-vesicular), as long as mild degree steatosis is verified, values of post-donation

AST/ALT concentration are up to 6 times higher than normal (26). Furthermore, macro-vesicular steatosis constitutes an independent risk factor for greater post-donation bilirubin levels. Bilirubin concentration after donation was, on average, 80.5μg/mmol and 49.6μg/mmol in patients with and without steatosis, respectively (27). Higher bilirubin peak after hepatectomy is associated with worst donor surgical outcome as it will be discussed later (28).

Alkaline Phosphatase

Higher pre-donation alkaline phosphatase (AP) levels constitute an independent risk factor for the development of biliary complications after hepatectomy (29) (30). Donors with higher levels of AP activity had more than 3 times the odds of developing biliary pathology (leak or stricture) related to hepatectomy when comparing with donors with normal AP activity levels (14).

Alanine Transaminase (ALT), Aspartate Transaminase (AST) and Albumin

Donors with pre-donation transaminase levels 2 to 4 times the upper limit of normal or reduced albumin are prone to hepatic dysfunction and are significantly associated with developing cholestasis after hepatectomy (13).

Coagulation profile

Knowing a patient coagulation profile prior to any procedure is key to prevent thromboembolic events or haemorrhage. Living donor hepatectomy reported mortality is linked to pulmonary embolism (PE) and other serious events as portal vein or inferior vena cava thrombosis and intra-abdominal or gastrointestinal bleeding may arise after hepatectomy. Patients with coagulopathy have a higher risk of cholestasis and hepatic dysfunction after liver donation (13).

There is a haemostatic system dysregulation after hepatectomy. Early postoperative increase in von Willebrand factor and VIII factors associated with a decrease in anticoagulants molecules such as Antithrombin and Protein C were verified. The same report shows that there were increased prothrombotic markers 10 to 30 times the normal in thrombin-antithrombin complexes and an increase in sP-Selectin by 2 times (31).

An exhaustive coagulation study prior to the hepatectomy is strongly recommended as it may contribute to the embolic events' reduction, therefore increasing donors' safety (32).

Vascular Anatomy Variations

It is of utmost importance to know vascular anatomy, particularly during hepatic hilar dissection and parenchymal transection. Lauterio *et al.* concluded that vascular anatomy variations constitute an independent risk factor for postoperative complications in donors. This study also shows that portal vein deviancies have a greater contribution to the risk of donor surgical morbidity than hepatic vein or hepatic artery abnormalities. Therefore, the complete assessment of liver vasculature, using new imaging techniques and 3D model reconstruction should be performed to assure and improve donor safety (33).

Venous dominance is determined by establishing V and VIII venous territory drainage, in the majority of cases, mainly to the Right Hepatic Vein. Donors submitted to Left Hepatectomy (LH) usually have the middle hepatic vein (MHV) harvested, thus compromising to some extent venous outflow of the V and VIII segments. Those with MHV dominance had significantly worse remnant liver regeneration rate than patients with RHV dominance mainly due to MHV-LHV clamping during the procedure (34).

Procedure Urgency

The impact of performing an urgent donor hepatectomy is related with the scarce study of the potential donor. Due to the lack of pre-procedure time, precise liver anatomy or complete coagulation studies are not addressed and skipping these important steps is clearly linked with a higher risk of complications. When comparing a non-urgent with an urgent procedure, the risk of hemodynamic instability is 12.82 times higher in the latter (20).

Table 4. Pre-operative surgical morbidity predictors			References
Age	Older	Impaired regenerative capability; >40 years: Higher risk for Bile Leak and Abdominal hernia; >50 years: Higher rate of any type of surgical complication.	(14,18,19)
	Younger	Hemodynamic instability and diarrhoea.	(20,21)
Sex	Male	Higher risk for hernia.	(14)
	Female	Delayed recovery of remnant liver; Development of PE.	(13,22)
Smoker		Development of PE.	(13)
Obesity and Hepatic Steatosis		Higher risk for any type of complications with greater liver enzymology levels post-donation.	(14,24,26,27)
Higher AP		Higher rate of biliary complications.	(14,29,30)
Higher ALT/AST and Lower Albumin		Higher risk for hepatic dysfunction and cholestasis.	(13)
Coagulopathy		Higher risk for hepatic dysfunction and cholestasis; Prothrombotic post-donation status.	(13,31)
Vascular Anatomy Variations		Higher risk for any type of complications; Worst liver regeneration after LH in MHV dominant liver.	(33,34)
Procedure Urgency and shorter donor evaluation time		Higher risk for any type of complications, especially hemodynamic instability.	(20)

PE: Pulmonary Embolus; AP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Transaminase; LH: Left Hepatectomy; MHV: Middle Hepatic Vein.

INTRA-OPERATIVE

Intra-operative aspects and techniques which may alter patient post-donation morbidity are described ahead and can be found summarized in Table 5.

Factors that may have a negative impact on donor´s postoperative outcome include the following:

Intraoperative blood transfusion

Intraoperative blood transfusion (IBT) is significantly associated with greater risk of developing surgical complications. A study conducted by Ghorbial *et al*. concluded that donors who were transfused had approximately 3 times the risk of developing biliary complications than those who did not require transfusions. Receiving 1 unit of blood increases the odds of developing biliary pathology by 2.7 times, 2 units of blood rises the risk up to 4.5 times when compared to non-transfused patients (35). Abecassis *et al.* report that blood transfusion is related specifically to an increased risk of bile leak and surgical site infection (14).

The preoperative study may predict an intra-surgical need for blood transfusion. Lower haemoglobin concentration and high graft to donor weight ratio (>0.94%) mean a greater risk of requiring intraoperative blood transfusion (36).

Intraoperative hypotension

Systolic Blood Pressure (SBP) inferior to 100mmHg (>30 minutes) is correlated with higher incidences of all kinds of surgical complications in donor hepatectomy. An increment of 48% rate of surgical complications is verified, especially major complications (Clavien grade ≥3), regardless of the blood loss or requirement for transfusion (14,33).

Remnant Liver Volume

Remnant liver volume (RLV) depends on both donor characteristics and receptor requirements which will determine the type of hepatectomy performed and graft collected. Donors with less than 30% remnant liver volume had 4 times greater relative risk of post-surgical morbidity and showed higher values in liver enzymology and INR after the procedure (28). It is suggested that only the smallest amount of liver required

to provide adequate recipient graft function should be collected. The remnant liver volume should be measured fastidiously (37).
The extension of the resected liver is correlated with bilirubin peak level after donation. A larger hepatectomy leads to a higher post-operative peak bilirubin level (and increased incidence of major surgical morbidity.

Facciuto *et al*. suggested that a remnant liver volume of no less than 30% should be guaranteed to assure donor safety based on their reports on the role of remnant liver volume in predicting hepatic dysfunction and surgical complications (38).

Patients with a lower percentage of RLV have impaired liver function in the early postoperative period. It has been found that post-hepatectomy liver dysfunction (PHLD) is more noticeable in patients with a substantial lower residual liver volume. Also, donors with PHLD had more post-surgical morbidity and hospital stay (39).

Procedure Length

Neuropraxia is defined as an injury to the myelin sheath only with axonal preservation and no Wallerian degeneration. This type of lesion is usually a consequence of stretching or compressing the donors' brachial plexus consequence of the patients' mispositioning on the operating table during the procedure. Mean surgical time of hepatectomy in donors who developed brachial plexus neuropraxia was 530 minutes vs. 455 minutes in those without neuropraxia symptoms (35).
The increment on donor hepatectomy time is directly linked with a higher risk of all type of complications. Operation time over 400min has a strong impact on donor surgical related morbidity and leads to increasingly adverse effects. A 1-hour increment in the procedure has increased the risk of respiratory instability by 74.4% (20,40).

Hepatectomy type

Regarding living donor liver transplant, several types of resections are usually performed. It is important to have in mind the different aspects regarding liver anatomy, most importantly, the concept of functional (or Couinaud's) segmentation of the liver. In the centre of each of these segments there is a branch of the hepatic artery, bile duct and portal vein (portal triad structures). Figure 2 shows the Couinaud's segments and their anatomical relations. Regarding hepatic resections, the functional division of the liver and comprehending this internal segmental anatomy and its relationship to the major vascular structures is paramount. Besides Monosegment and Hyper-reduced left lateral segment hepatectomies, the most common types of living liver donor surgery are shown in Figure 3 and 4. Detailed procedure techniques for both recipient and donor can be found fully described in the Broelsch *et al.* study (41).

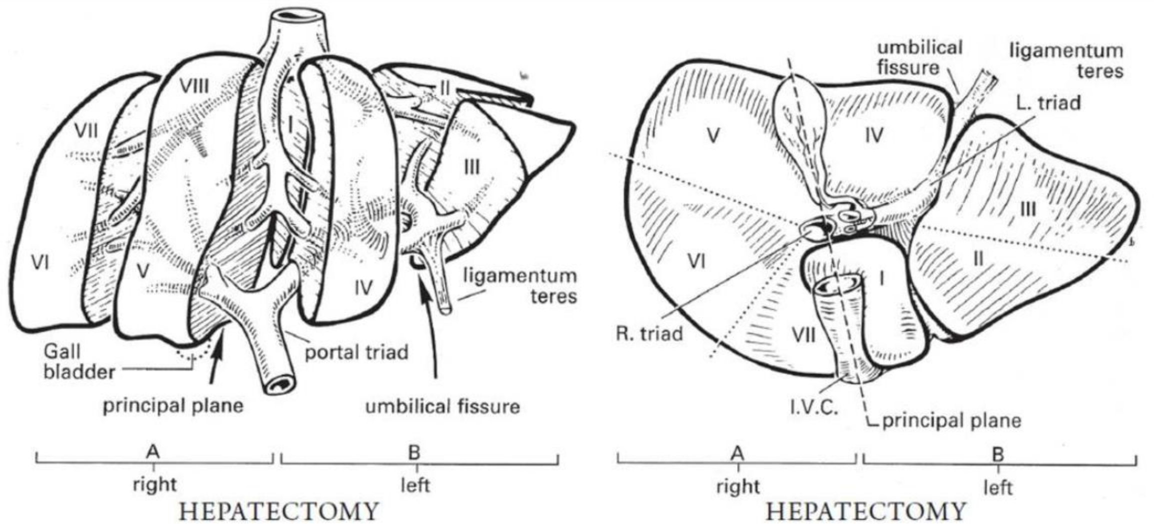

Figure 2. Liver Segmentation. Functional liver division separated by Cantlie's line ("principal plane") and anatomical lobes separated by the Umbilical Fissure. (42)

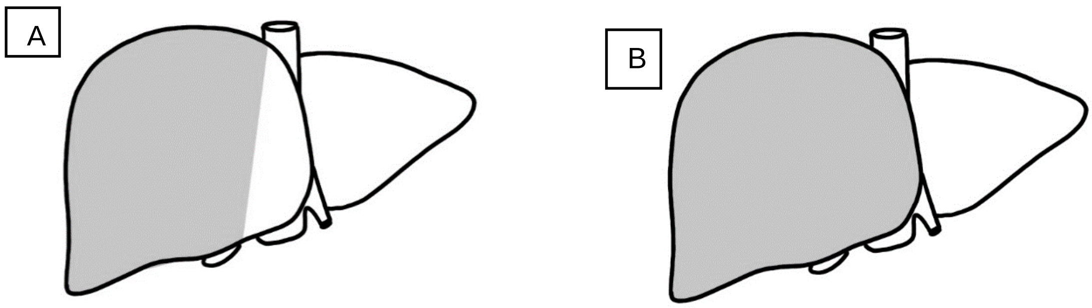

Figure 3. Grey marks the retrieved graft.

A - Right Hepatectomy (RH) graft: Segments V, VI, VII and VIII;

B - Extended Right Hepatectomy (ERH) graft: Segments IV, V, VI, VII.

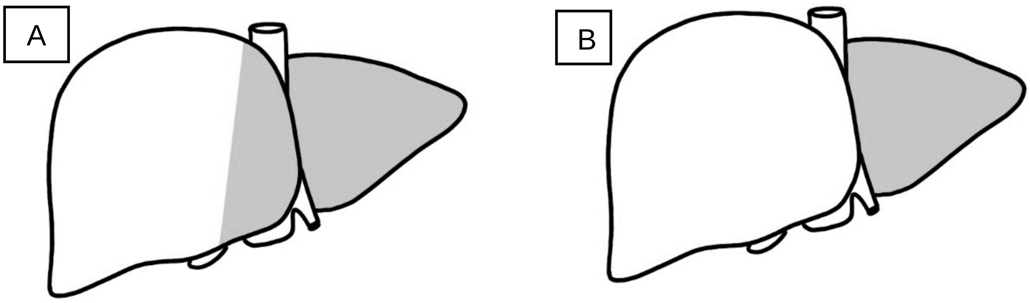

Figure 4. Grey marks the retrieved graft.

A - Left Hepatectomy (LH) graft: segments II, III and IV;

B - Left Lateral Sectionectomy (LLS) graft: segments II and III.

RH has been associated with a higher incidence of major complications (Clavien grade ≥3). Major complication rates in donors submitted to ERH was 15.6%, RH was 13.3% and left liver surgery (including LH and LLS) was 2.2%. RH grafts are more voluminous than LH grafts and the extent of liver resected is significantly associated with higher peak bilirubin level after donation, greater prothrombin time and intensive care unit stay (due to major complications) (37,43). Donors submitted to RH were hospitalized for a mean of 19.7 days, 5.7days more than those submitted to LH (mean of 14 days) (44). Not only the overall complication rate was higher in the RH than LH (44.2% vs. 18.8%), complication severity was also worse in right liver donations (40). Moreover, the mortality rate depends on the amount of parenchyma resected. Death likelihood after RH reaches 0.5%, higher than the 0.1-0.3% verified after LH (45).

Right biliary anatomy is more complex than the left lobe, and the type of hepatectomy may be the most important risk factor for the development of donor biliary complications (40). The abovementioned complications' rate differences are the cause for the shifting paradigm that is being noticed in liver transplant. Nowadays, the number of left graft hepatectomy surgeries is increasing while the right hepatectomy and extended right liver grafts are declining gradually (14,45).

Although graft volume is usually low in LLS hepatectomy, postoperative liver regeneration rates are greater in right hepatectomized patients. Gradual atrophy of segment IV is verified when segments II and III are resected (46).

LH was recently significantly associated with duodenal ulcer development in the donor, especially in male donors. However, this complication is not commonly mentioned as a donor surgical morbidity cause (47).

Factors that may have a positive impact on donor´s postoperative outcome include the following:

Abdominal wall incision

Midline incision has a lesser incidence of abdominal herniation compared to a subcostal (Kocher) incision (13). Smaller midline incisions (<10 cm) have a significantly shorter hospitalization and lower postoperative liver enzymology levels when compared to a large (15 cm) subcostal incision. Clinical outcomes such as operation time and length of hospital stay were comparable or significantly reduced with the smaller incision (48).

Intraoperative Cholangiography

Complex abnormal biliary tract anatomy may require a different transection cutting plane, so routinely intraoperative cholangiography (IOC) is recommended. Jeng *et al.* endorse using IOC in order to avoid injury to the donor remnant bile ducts, therefore, improving donor safety (biliary complications are the most common morbidity arising after hepatectomy). IOC sensitivity and negative predictive value are higher than magnetic resonance cholangiopancreatography (MRCP) (49).

Portal vein pressure modulation

This technique might be used in both recipient and donor in LDLT as it may contribute for a beneficial postoperative prognosis for both. Targeting for portal vein pressures inferior to 15mmHg had a favourable effect in donor surgical complication rate as it decreased from 13.8% to 9.3% (50).

Propofol use

Propofol may have protective effects against ischemic lesions on both the graft and remnant donor liver that might arise after Pringle manoeuvre. Propofol inhibits lipid peroxidase generation and improves glutathione antioxidant system thus counteracting oxidative stress in liver parenchyma. There are statistically significant differences when comparing the use of Propofol infusion versus control when comparing serum Total Antioxidant Capacity and Oxidative Stress Index (51).

Terlipressin infusion

Terlipressin infusion induces higher Systemic and Pulmonary vascular resistance, thus preventing intraoperative hypotension. Intra-operatory hypotension is associated with an increment of 48% of any type of complication (14). Intra-operatory Terlipressin infusion (> 2.0μg/kg/h) lead to shorter hospital stay (average of 6 days) (52).

"Softcoagulation"

Liver transection using SOFT COAG (ERBE Elektromedizin, Tübingen) shows a statistically significant difference in intraoperative blood loss when compared to the use of bipolar dissection (435.2mL vs. 763.9mL). However, prospective data gathered in this article showed no difference regarding postoperative liver function or incidence of surgical complications (53).

Bloodless donor hepatectomy

Precocious counter-clockwise liver rotation and hanging manoeuvre during the procedure lead to a significant reduction in intraoperative blood loss (to as low as 30mL), thus reducing the need for intra-operatory blood transfusion. Average haematic depletion using this technique is 353±46mL, minor than 733±91mL verified when it is not used (54).

Minimal invasive hepatectomy

Minimally invasive living donor hepatectomy (MILDH) is proved to be a safe, effective and feasible procedure. Comparing it with the laparotomy approach, fewer donor postoperative complications, less intraoperative blood loss, reduced hospital stay and analgesic requirement are significantly associated to MILDH procedures. Furthermore, graft volume obtained using this technique is similar when compared with the conventional approach (25,55,56). Laparoscopic approach for LH has significantly longer operative time than the conventional approach (459min vs. 403min); however, scar discomfort self-assessment rates were significantly higher in the latter (57). Comparing the hybrid technique (mini-laparotomy with midline incision 7 to 10cm with laparoscopic visualization) with pure laparoscopic hepatectomy, the latter had a significantly lower mean blood loss (81.07g vs. 238.50g) but longer procedure time (454.93min vs. 380.4min) than the former (58). However, Safwan *et al.* reported that hybrid techniques are difficult to perform in donors with larger body habitus showing no positive results concerning donation comparing with the conventional approach (25).

Table 5. Intra-operative surgical morbidity predictors.			
Negative impact			References
Intraoperative blood transfusion		Higher risk for biliary complications and surgical site infections.	(14,35)
Intraoperative hypotension		Higher risk for any kind of major complications.	(14,33)
Remnant Liver Volume <30%		Higher risk for any kind of major complications.	(28,39)
Longer procedure length		Higher risk for neuropraxia and respiratory instability.	(20,35,40)
Type of hepatectomy	RH	Higher risk for any kind of major complications, longer ICU and hospital stay.	(37,43–45)
	LH	Lower remnant liver regeneration rate; Higher risk for duodenal ulcer.	(46,47)
Positive impact			References
Smaller abdominal wall incision		Shorter hospital stay; Lower abdominal hernia risk.	(13,48)
IOC		Lower remnant bile duct lesion rate.	(49)
Portal Vein Pressure Modulation		Lower donor surgical morbidity rate.	(50)
Propofol use		Lower evidence of ischemic lesion during hepatectomy.	(51)
Terlipressin infusion		Lower intraoperative hypotension risk.	(52)
“Softcoagulation”		Lower intraoperative blood loss vs. Bipolar parenchymal dissection.	(53)
Bloodless donor hepatectomy		Lower intraoperative blood loss.	(54)
MILDH		Lower intraoperative blood loss, hospital stay and analgesic requirement vs conventional approach; Longer procedure time.	(55–57)

RH: Right Hepatectomy; LH: Left Hepatectomy; ICU: Intensive Care Unit; IOC: Intraoperative Cholangiography; MILDH: Minimally Invasive Living Donor Hepatectomy.

POSTOPERATIVE

Intra-operative aspects and techniques which may alter patient post-donation morbidity are described ahead and can be found summarized in Table 6.

High Bilirubin peak and INR

A higher post-procedure total bilirubin (TB) concentration is associated with greater incidence of major complications, and it is prone to affect patients with a lower remnant liver volume and the ones who have mild or severe hepatic steatosis prior to donation (37).

Besides high TB, INR evaluation should also be considered. Post-hepatectomy Liver Failure (PHLF) may arise in 1.2-32% after hepatectomy, and it's defined by the International Study Group for Liver Surgery (ISGLS) as "A postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cut-off levels defined by the local laboratory) on or after postoperative day 5." (59).

Table 6. Postoperative surgical morbidity predictors		References
Postoperative high bilirubin peak	Linked to greater incidence of major complications	(37)
Postoperative increase in INR	Linked to liver insufficiency	(59)

Discussion

P-LDLT interventions are growing due to both the increasing incidence of pathology which leads to P-ESLD and easier access to specialized LT centres. However, the availability of organs could not keep up with the demand mainly due to donor reluctance. Hesitation is frequent in the pre-donation scenario, and it might be linked to insufficient information about procedure safety and morbimortality (60).

Donor safety is a matter of paramount importance in LDLT. Complications arise in up to 40% of the patients within the first year after transplant. However, 95% of procedure-related morbidities is solved within the first postoperative 90 days (14). Large retrospective series reported that 21% of donors experience only one complication after the procedure and 17% develop two or more surgical complications. The most common surgical morbidity verified after donor hepatectomy are: biliary leak - 36.9%, bacterial infection - 12% and incisional hernia - 6%. Pulmonary effusion, neuropraxia and intrabdominal abscess account for 11% of the surgical morbidity reported (35). Our series report the existence of the same most common complications as the ones reported in the literature, except for neuropraxia or intrabdominal abscess.

Although there is a relatively short number of surgeries in CHUC, donor morbidity rate is comparable with results obtained worldwide. Within the first 3 months after donation, the complication rate verified was 28.6%, however Abecassis *et al.* report that surgical morbidity, namely hernia, bowel obstruction and psychological complications, may develop as late as 5 to 10 years post-transplant (14). Besides the short number of surgeries (due to both low demand of this kind of procedures and prioritization of cadaveric grafts for pediatric liver transplant), the retrospective analysis of donors' data was also a limitation in this study. Medical charts did not have a complete informative description of some procedure details.

In CHUC's series, the 8 donors who developed complications were submitted to conventional left hepatectomy (either LH or LLS) through subcostal or inverted T incision. The donor who developed partial respiratory insufficiency had abnormal liver anatomy which may have led to longer procedural time. Both donors who developed superficial wound infection were obese (BMI=27kg/m^2 and 28kg/m^2). Both, patients who developed major complications were men. These are the only links found between the literature review results and the morbidity verified in CHUC. However, it is important to note that not all the collected variables from the bibliographic review were completely studied or reported in our donors' charts. Furthermore, with such a small number of cases, it is difficult to establish a relationship between a potential poor predictor and morbidity development. It is important to note that the surgical morbidity predictors collected in this work result from the analysis of articles that report living liver donation for both adults and children. Although several procedure aspects in adult-to-adult LDLT may differ from adult-to-child LDLT, the articles analysed report the results together. Additionally, the increasing incidence of pediatric NAFLD is driving to higher procedure rates in older children (12). In these cases, the procedure technique is similar to the one performed for adult recipients.

Scrutinizing the factors that might be involved in poor surgical outcome may decrease donor morbidity rate thus increasing intervention safety. Predictors which are correlated with postoperative morbimortality should be minutely analysed as they may be useful to prevent complications or treat them more efficaciously.

Aspects that may influence post-hepatectomy surgical morbidity, such as pre-donation analysis and intra-operative manoeuvre description, are not clearly registered in the donor's medical file. The goal, as in any surgery, is to achieve the lowest complication rate possible. A proper description of the variables that influence post donation morbidity is key to prevent them through a stricter exclusion criterion for potential donors.

Therefore, a standardized document gathering all the information about the pre-, intra- and postoperative relevant data should be included in the patient's charts. A network between transplantation centres has been recently implemented with the goal to aggregate this kind of information. CHUC is part of this European Reference Network since May 2017, integrating 18 healthcare providers who are part of Transplant-Child.

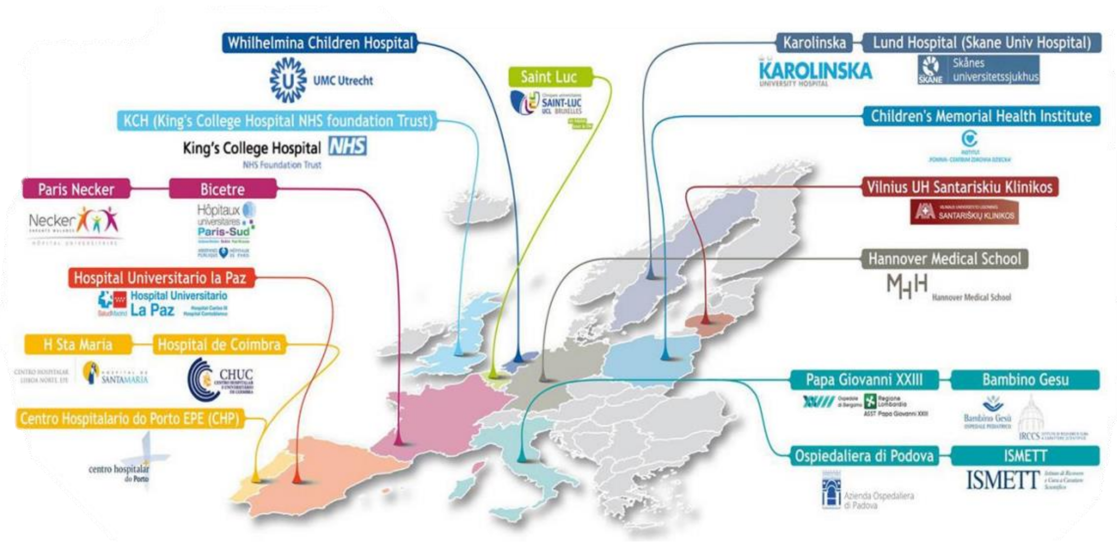

Figure 5. ERN Transplant-Child Centres (Adapted from (61)).

The ERN Transplant-Child has, among other objectives, this abovementioned mission aiming to extract statistically significant data, giving knowledge to every individual taking part in the transplantation process and to provide easier access to a donor medical consultation (7). Furthermore, post-donation consultations should take into consideration the reviewed aspects in this work.

New techniques will definitively contribute to improving donor safety. Minimally invasive hepatectomy and entirely robotic hepatectomy are revolutionizing liver donation, promoting a safer procedure. Advanced anatomical liver studies, as 3D reconstruction and virtual liver partitioning aiming to an individualized resection approach based on specific donor anatomic characteristics, will improve donor safety as well (62). Furthermore, improvement in hepatocyte transplantation techniques will definitely improve donor safety as a considerably less invasive procedure is performed (63).

Even though the donor's death is a rare event (0,5% for RH and 0.1-0.3% for LH (13,14)), it should be addressed as a catastrophe as it affects the recipient, both families and all the clinicians engaged in the LDLT process. From 1999 to 2017, 23 deaths worldwide were reported (45). All efforts should aim to minimize the possibility of donors' death. Accumulated centre know-how, full pre-donation study as well as strict donor selection criteria, new surgical techniques and intra-operative management and qualified postoperative patient care are crucial to the improvement of donor outcomes (33).

Conclusion

LDLT performed in our centre is a safe and feasible treatment option in selected pediatric cases. Rate and type of surgical morbidity were inferior to the data gathered from the literature.

Bearing in mind the *Primum non nocere* precept, maximum effort should be made to avoid any donor complication and mortality. Complication and mortality rates reduction should be a worldwide goal in living donor surgery. The abovereported data may be useful to bring morbidity rates down, that is, improve procedure safeness. An extensive patient pre-, intra- and postoperatively study should be carried out. Patients' and surgical characteristics should be minutely analysed and sceptically to foresee the chances of morbimortality. Recognizing the aspects that may influence procedure prognosis is critical to decreasing rates of morbimortality and reducing reluctance prior to donation. Studies like ours, show that the live donation process is a safe option of treatment with minor complications for the donors.

Bibliography

1. Cuenca AG, Kim HB, Vakili K. Pediatric liver transplantation. Semin Pediatr Surg. 2017;26(4):217–23.
2. Rawal N, Yazigi N. Pediatric Liver Transplantation. Pediatr Clin N Am 64. 2017;64(3):677–84.
3. Rela M, Reddy MS. Living donor liver transplant (LDLT) is the way forward in Asia. Hepatol Int. 2017;11(2):148–51.
4. Raia S, Nery J, Mies S. Liver transplantation from live donors. Lancet. 1989;334(8661):497.
5. Strong R, Lynch S, Ong T, Matsunami H, Koido Y, Balderson G. Successful Liver Transplantation from a Living Donor to her Son. N Engl J Med. 1990;322(21):1505–7.
6. Maciel J. Transplante Hepático Pediátrico com Enxerto de Dador Vivo - Experiência do Centro de Referência em Portugal. Faculty of Medicine, University of Coimbra; 2013.
7. Laezza N, Pessanha I, Lopes JP, Cunha C, Lopes MF. Experience report from a Center integrated in an European Reference Network. In: I Encontro Internato Médico da Zona Centro. 2018.
8. Holcomb G, Murphy J, Ostlie D, St. Peter S. Ashcraft's Pediatric Surgery. 6th ed. Elsevier; 2014. 607-631 p.
9. Hopkins PC, Yazigi N, Nylund CM. Incidence of Biliary Atresia and Timing of Hepatoportoenterostomy in the United States. J Pediatr. 2017;187:253–7.
10. Herzog CE, Andrassy RJ, Eftekhari F. Childhood Cancers : Hepatoblastoma. Oncologist. 2000;5:445–53.
11. Kumar P, Selvakumar C, Nasser M, Alkhouri N. Nonalcoholic Fatty Liver Disease in Children : Not a Small Matter. Pediatr Drugs. 2018;20(4):315–29.
12. Alkhouri N, Hanouneh IA, Zein NN, Lopez R, Kelly D, Eghtesad B, et al. Liver transplantation for nonalcoholic steatohepatitis in young patients. Transpl Int. 2016;29(4):418–24.
13. Renz JF, Roberts JP. Long-Term Complications of Living Donor Liver Transplantation. Liver Transplant. 2000;6(6):73–6.

14. 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;12(5):1208–17.

15. 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;240(2):205–13.

16. Rinella ME, Mccarthy R, Thakrar K, Finn JP, Rao SM, Koffron AJ, et al. Resonance Imaging to Quantify Hepatic Steatosis : Implications for Living Liver Donation. Liver Transplant. 2003;9(8):851–6.

17. Rauchfuss F, Voigt R, Dittmar Y, Heise M, Settmacher U. Liver Transplantation Utilizing Old Donor Organs: A German Single-Center Experience. Transplant Proc. 2010;42(1):175–7.

18. Dayangac M, Taner CB, Yaprak O, Demirbas T, Balci D, Duran C. Utilization of elderly donors in LDLT; When more is less? Liver Transplant. 2011;17:548–55.

19. Tanemura A, Mizuno S, Wada H, Yamada T, Nobori T, Isaji S. Donor age affects liver regeneration during early period in the graft liver and late period in the remnant liver after living donor liver transplantation. World J Surg. 2012;36(5):1102–11.

20. Wakata T, Nakashima N, Akinobu T, Shirabe K, Maehara Y, Akihito H. Factors Associated With the Postoperative Status of Donor Patients for Living Donor Liver Transplantation. Liver Transplant. 2007;13(3):465–6.

21. Wang SH, Ming YZ, Lin PY, Wang JY, Lin HC, Hsieh CE, et al. Predictors of diarrhea after hepatectomy and its impact on gastrointestinal quality of life in living donors. PLoS One. 2016;11(11):4–11.

22. Choi SS, Cho SS, Ha TY, Hwang S, Lee SG, Kim YK. Intraoperative factors associated with delayed recovery of liver function after hepatectomy: Analysis of 1969 living donors. Acta Anaesthesiol Scand. 2016;60(2):193–202.

23. Peng CJ, Yuan D, Li B, Wei YG, Yan LN, Wen TF, et al. Body Mass Index Evaluating Donor Hepatic Steatosis in Living Donor Liver Transplantation. Transplant Proc. 2009;41(9):3556–9.

24. Marsh JW, Gray E, Ness R, Starzl TE. Complications of right lobe living donor liver transplantation. J Hepatol. 2009;51(4):715–24.

25. Safwan M, Nagai S, Collins K, Rizzari M, Yoshida A, Abouljoud M. Impact of Abdominal Shape on Living Liver Donor Outcomes in Mini-Incision Right Hepatic Lobectomy: Comparison Among Three Techniques. Liver Transplant. 2018;24:516–27.

26. Shin YH, Ko JS, Kim GS, Gwak MS, Sim WS, Lee AR, et al. Impact of hepatic macrovesicular and microvesicular steatosis on the postoperative liver functions after right hepatectomy in living donors. Transplant Proc. 2012;44(2):512–5.

27. Nagai S, Fujimoto Y, Kamei H, Nakamura T, Kiuchi T. Mild hepatic macrovesicular steatosis may be a risk factor for hyperbilirubinaemia in living liver donors following right hepatectomy. Br J Surg. 2009;96(4):437–44.

28. Shi Z-R, Yan L-N, Du C-Y. Donor safety and remnant liver volume in living donor liver transplantation. World J Gastroenterol. 2012;18(48):7327–32.

29. Yoon YI, Shin MH, Kim WJ, Kim SH, Lee SG. Donor Safety and Recipient Liver Function After Right-Lobe Liver Transplantation From Living Donors With Gilbert Syndrome. Transplant Proc. 2015;2830:10–3.

30. Yuan Y, Gotoh M. Biliary Complications in Living Liver Donors. Surg Today. 2010;40:411–7.

31. Bezeaud A, Denniger M, Dondero F, Saada V, Venisse L, Huisse M, et al. Hypercoagulability after partial liver resection. Thromb Haemost. 2007;67(6):14–21.

32. Kamei H, Onishi Y, Kurata N, Ishigami M, Ogura Y. Donor selection and prophylactic strategy for venous thromboembolic events in living donors of liver transplantation based on results of thrombophilia screening tests. Ann Transplant. 2017;22:409–16.

33. Lauterio A, Poli C, Cusumano C, Sandro S Di, 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;45(7):2680–3.

34. Tung YC, Cheng YF, Huang TL, Chen TY, Ou HY, Yu CY, et al. Impact of Different Dominant Hepatic Vein Patterns in Left-Lobe Donors of Adult Living Donor Liver Transplantation. Transplant Proc. 2016;48(4):1012–4.

35. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, et al. Donor Morbidity After Living Donation for Liver Transplantation. Gastroenterology.

2008;135(2):468–76.

36. Choi SS, Cho SS, Kim SH, Jun IG, Hwang GS, Kim YK. Factors associated with blood transfusion in donor hepatectomy: Results from 2344 donors at a large single center. Transplantation. 2013;96(11):1000–7.

37. 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 Transplant. 2011;17(12):1404–11.

38. 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;153(5):619–26.

39. Elshoubary M, Shehta A, Salah T, Sultan AM, Yassen AM, Abdulrazek M, et al. Predictive Factors of Liver Dysfunction After Right Hemihepatectomy for Adult Living Donor Liver Transplantation. Transplant Proc. 2018;50(4):1114–22.

40. 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;89(10):1276–82.

41. Broelsch CE, Whitington PF, Emond JC, Heffron TG, Thistlethwaite JR, Stevens L, et al. Liver transplantation from living related donors. Ann Surg. 1991;214(4):428–37.

42. Aragon RJ, Solomon NL. Techniques of hepatic resection. J Gastrointest Oncol. 2012;3(1):28–40.

43. Tsang LLC, Tung YC, Hsu HW, Ou HY, Yu CY, Huang TL, et al. Impact of Graft Type in Living Donor Liver Transplantation: Remnant Liver Regeneration and Outcome in Donors. Transplant Proc. 2016;48(4):1015–7.

44. Umeshita K, Fujiwara K, Kiyosawa K, Makuuchi M, Satomi S, Sugimachi K, et al. Operative morbidity of living liver donors in Japan. Lancet. 2003;362:687–90.

45. Brige P, Hery G, Chopinet S, Palen A, Azoulay D, Gregoire E. Morbidity and Mortality of Hepatic Right Lobe Living Donors : Systematic Review and Perspectives. J Gastrointestin Liver Dis. 2018;27(2):169–78.

46. Ibis C, Asenov Y, Akin M, Azamat IF, Sivrikoz N, Gurtekin B. Factors Affecting Liver Regeneration in Living Donors After Hepatectomy. Med Sci Monit. 2017;23:5986–93.

47. Kadohisa M, Sugawara Y, Shimata K, Kawabata S, Narita Y, Uto K, et al. Duodenal Ulcer as a Postoperative Complication in the Donor in Living-Donor Liver Transplantation. Transplant Proc. 2018;50(4):1129–31.

48. Shinoda M, Tanabe M, Itano O, Obara H, Kitago M, Abe Y, et al. Left-side hepatectomy in living donors: Through a reduced upper-midline incision for liver transplantation. Transplant Proc. 2014;46(5):1400–6.

49. Jeng KS, Huang CC, Lin CK, Lin CC, Chen KH, Chu SH. Repeated introperative cholangiography is helpful for donor safety in the procurement of right liver graft with supraportal right bile duct variants in living-donor liver transplantation. Transplant Proc. 2014;46(3):686–8.

50. Cheng YF, Yu CY, Ou HY, Tsang LLC, Huang TL, Chen TY, et al. Living donor liver transplantation: The Asian perspective. Transplantation. 2014;97(8):S3–6.

51. Ucar M, Ozgül U, Polat A, Toprak HI, Erdogan MA, Aydogan MS, et al. Comparison of antioxidant effects of isoflurane and propofol in patients undergoing donor hepatectomy. Transplant Proc. 2015;47(2):469–72.

52. Hong SH, Lee JM, Choi JH, Chung HS, Park JH, Park CS. Perioperative assessment of terlipressin infusion during living donor liver transplantation. J Int Med Res. 2012;40(1):225–36.

53. Ishiko T, Inomata Y, Beppu T, Asonuma K, Okajima H, Takeiti T, et al. An Improved Technique for Liver Transection Using a New Device for Soft Coagulation in Living Donor Hepatectomy. Hepatogastroenterology. 2012;59(118):1907–10.

54. Sadamori H, Yagi T, Shinoura S, Umeda Y, Yoshida R, Satoh D, et al. Bloodless Donor Hepatectomy in Living Donor Liver Transplantation: Counterclockwise Liver Rotation and Early Hanging Maneuver. J Gastrointest Surg. 2013;17(1):203–6.

55. Li H, Zhang J-B, Chen X-L, Fan L, Wang L, Li S-H, et al. Different techniques for harvesting grafts for living donor liver transplantation: A systematic review and meta-analysis. World J Gastroenterol. 2017;23(20):3730.

56. Zhang B, Pan Y, Chen K, Maher H, Chen MY, Zhu HP, et al. Laparoscopy-assisted versus open hepatectomy for live liver donor: Systematic review and meta-analysis. Can J Gastroenterol Hepatol. 2017;2017:1–12.

57. Kitajima T, Kaido T, Iida T, Seo S, Taura K, Fujimoto Y, et al. Short-term

outcomes of laparoscopy-assisted hybrid living donor hepatectomy: a comparison with the conventional open procedure. Surg Endosc. 2017;31(12):5101–10.

58. Takahara T, Wakabayashi G, Nitta H, Hasegawa Y, Katagiri H, Umemura A, et al. The First Comparative Study of the Perioperative Outcomes between Pure Laparoscopic Donor Hepatectomy and Laparoscopy-Assisted Donor Hepatectomy in a Single Institution. Transplantation. 2017;101(7):1628–36.

59. Rahbari NN, Garden OJ, Padbury R, Brooke-smith M. Posthepatectomy liver failure : A definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149:713–24.

60. Sharma A, Ashworth A, Behnke M, Cotterell A, Posner M, Fisher RA. Donor selection for adult-to-adult living donor liver transplantation: Well begun is half done. Transplantation. 2013;95(3):501–6.

61. Transplant-Child. Transplantation in Children [Internet]. European Reference Networks. 2018 [cited 2019 Mar 15]. Available from: https://www.transplantchild.eu/en/

62. Radtke A, Sgourakis G, Molmenti EP, Schroeder T, Cicinnati VR, Beckebaum S, et al. The “carving” liver partitioning technique for graft hepatectomy in live donor liver transplantation: A single-center experience. Surg (United States). 2013;153(2):189–99.

63. Anderson TN, Zarrinpar A. Hepatocyte transplantation: past efforts, current technology, and future expansion of therapeutic potential. J Surg Res. 2018;226:48–55.