FACULTY OF MEDICINE AND HEALTH SCIENCES

THE OUTCOME OF LEFT LATERAL AND EXTENDED RIGHT GRAFTS FOR SPLIT LIVER TRANSPLANTATION IN BELGIUM DURING THE MELD ERA

A RETROSPECTIVE MULTICENTRIC STUDY CONCERNING THE ROLE OF EXTENSION OF DONOR CRITERIA

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1. Preface

Writing a dissertation, as a part of the Master in Medicine at the University of Ghent, did not only provide the possibility to gain insight into the scientific research but also permitted us to contribute to the medical advance. The tremendous progress we were able to make on multiple competence levels would not have been possible without the support of several people we would like to thank. They have made it possible to shape and finish our scientific work.

First of all we would like to thank all the patients who participated in the study by permitting us to process their data. Without patient's cooperation medical evolution obtained by scientific research would be unthinkable nowadays.
The processing of the patient's data was assisted by the co-investigators and transplant coordinators of the Ghent University Hospital, University Hospitals Leuven and Catholic University of Louvain. Their support was greatly appreciated.
Looking back at the study's take-off, none of this would have been possible without the dedication of study coordinator Kathleen Segers, who we still owe a mojito for her extensive help and support.

A big thanks goes out to promoter prof. dr. Roberto Troisi for his patience, perseverance and active participation even across the border. His extensive and constructive feedback has made it possible to finish the work in its best way.
While writing this work we were confronted with the devastating news of the passing of co-promoter prof. dr. Xavier Rogiers who was more than important to us concerning multiple aspects of the work. His clear and realistic vision was indispensable at moments when we encountered difficulties and had lost track. He will always be remembered for his warm personality and his excessive medical passion.
The secondary assistance of prof. dr. Berrevoet, especially concerning the statistical difficulties, was very much appreciated as well. His insights and guidance were of great value to us.

Last but not least it has to be mentioned that the thesis did not only affect people signing up for it. We would like to thank family, friends and other involved ones emphatically for their support.

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3. Abstract

Background: Split liver transplantation enables, by splitting the liver into two grafts, the treatment of two patients instead of one, compared to the conservative technique. Resulting in a left lateral graft (segments II and III) and an extended right graft (segments I, IV- VIII) respectively transplanted in a pediatric and an adult patient. This technique has been developed because of the increasing discrepancy between liver graft supply and demands, which reflected itself in an unacceptably longer waiting list and an increased death rate. Therefore surgeons and physicians have been innovative in making the best use of those organs that are available. The possibility of treating two patients instead of one, in times where the shortage of donor organs is resulting in higher death rates on the waiting list, makes this subject currently interesting. Furthermore there have been multiple calls for research of this kind, substantiated by an extensive dataset. Even though the approach of splitting the liver is gaining prominence, the performance of the procedure is not adequately investigated. Most of the scientific evidence is based on single center trials. Major issues of this technique are represented by different allocation policies as well as non-homogeneous donor selection criteria.

Objectives: The study endeavored to evaluate the entire process associated with pediatric and adult recipients undergoing SLT, from standard brain death deceased donors, during the last decade. This period involves the MELD allocation policy in Eurotransplant. Extensive analyses were performed both for the left lateral grafts as the extended right grafts included in this study, permitting their separate evaluation. Contributing to the process of defining an operable 'donor-recipient match', it is obligated to perform an analysis of both the donor and recipient variables, the graft function, post-transplant biliary/vascular complications and their role in graft loss or dysfunction.

Methods: This retrospective multicentric study includes all adult and pediatric recipients who received a split liver transplantation performed from January 1st 2007 until December 31 2017, matching the selection criteria. This concerns all recipients who were treated with SLT in one of the three participating university hospitals (Ghent University Hospital, University Hospitals Leuven and the Catholic University of Louvain) in the last 11 years, either with the 'in situ' or 'ex situ'

technique. Exclusion criteria included a SLT performed with 'full left/ full right' split grafts and donors after circulatory death (DCD).
The processing of data, obtained from 42 patients, subdivided in 26 extended right grafts (ERG) and 16 left lateral grafts (LLG) was carried out with respect to the new General Data Protection Regulation (GDPR) legislation. The included patients were all eligible for extensive analysis.

Results: Multiple significant associations in the context of graft and patient outcome were observed. The overall ten-year patient and graft survival are respectively 92.3% and 76.9% for the LLG study population. The overall ten-year patient and graft survival are respectively 83.3% and 66.7% for the ERG study population. Left lateral grafts characterized by a cold ischemia time higher than 660 minutes were found associated with higher risk of graft loss, confirmed by both the univariate (p=0.034) and multivariate (p=0.034) analysis. The extended right graft receivers showed higher recurrences of graft loss for participants with infections before the transplantation (p=0.018), patients confronted with biliary (p=0.004) and/or cholangitis (p=0.026) related complications and for grafts featuring a prolonged warm ischemia time (p=0.009). Concerning the patient survival a significant impact of the donor's BMI was perceived. At multivariate analysis (p=0.046) a donor BMI >25 was associated with an increased risk of mortality in the ERG study population. Analysis of the coupled receivers provided the determination of possible donor factors related to unfavorable outcomes. This analysis was only performed in a descriptive way and can be seen as an attempt to endeavor for an ideal donor-recipient model.

Conclusion: Not only does SLT provided a possibility to reduce the mortality rate on the waiting list for pediatric patients, also it has served as a driving force to develop alternative treatments, in order to encounter the treatment gap. Equal outcomes for SLT, compared to conservative interventions, can be seen when respecting the procedure's conditions. Nevertheless the split procedure only represents a minor part of the liver transplant techniques during the years 2007-2017. A negative trend in prevalence since implementation of the MELD policy has been observed. The significant risk factors associated with potential unfavorable outcomes, derived from our study, form a great addition and confirmation to the exclusion criteria which are described yet. This takes us closer towards an ideal donor-recipient model. Study models of this kind should be encouraged on a bigger scale study population. Besides further study concerning a conform donor-recipient model, centralization of the expertise and using a well-defined allocation policy seems necessary to promote and optimize the technique.

4. Introduction

Liver transplantation (LT) is the treatment of choice for end-stage liver disease in adult and pediatric population.

The increasing success of LT, in terms of increasing knowledge and experience over the last three decades, resulted in a greater number of patients who would meet the criteria for selection and benefit from the procedure (1). However, in many countries the number of donor organs available for transplantation has steadily fallen, in contrast to the advanced techniques and extended indications for transplantation.Because of the increasing discrepancy between liver graft[1] supply and demands, which reflected itself in an unacceptably longer waiting list and an increased death rate, surgeons and physicians have been innovative in making the best use of those organs that are available. Overall donor scarcity resulted in the use of liver grafts from marginal donors and donors after circulatory death or even the acceptance of living donors. Eventually the use of transplanting a single graft to two recipients (the split liver technique - SLT) originated.
Aim of this thesis is to subject the split liver transplantation to an extensive analysis by examining the results of the procedure in Belgium (2, 3).

The possibility of treating two patients instead of one, in times where the shortage of donor organs is resulting in higher death rates on the waiting list, makes this subject currently interesting. Furthermore there have been multiple calls for research of this kind, substantiated by an extensive dataset. Even though the approach of splitting a liver is gaining prominence, the performance of the procedure is not adequately investigated. Most of the scientific evidence is based on single center trials. Major issues of this technique are represented by different allocation policies as well as non-homogeneous donor selection criteria. Striving for generalized donor criteria, based on multicentric reviews, should be encouraged (3, 4).

[1] A patient's diseased liver is replaced with a whole or partial healthy liver from another person (allograft).

4.1 Graft allocation

Before the transplantation of a donor organ occurs, this challenging type of surgery is preceded by a complex selection procedure, namely 'graft allocation'. During the evolution of liver transplantation, the consideration to allocate an organ to a suitable receptor became more and more understood, resulting in a more adjusted and safer way of donor allocation and distribution.

Currently liver allocation is determined by wait-time and Model for End-stage Liver Disease (MELD) score. Before the introduction of the MELD in 2002, patients were listed for liver transplantation based on their United Network of Organ Sharing (UNOS) status. During the UNOS era the waiting list for liver transplantation approached a total of 20 000 patients. In addition, on the waiting list there were ,for example, only three categories present for patients with cirrhosis: status 2A, status 2B and status 3. The most important determinant of who would receive a liver graft became the waiting time on the transplant waiting list. In consequence patients with a high risk of mortality but an unrepresentative waiting time obtained a disadvantage during this policy. MELD algorithm is able to rank patients with cirrhosis and listed for a transplant procedure, in an accurate way depending upon their risk of mortality while waiting on a suitable graft. Originally the MELD was created to predict survival after the elective placement of transjugular intrahepatic portosystemic shunts (TIPS) in patients who suffered from complications of portal hypertension. MELD uses three objective patient variables, which are determined in the clinical laboratory: the international normalized ratio (INR), serum creatinine and serum bilirubin. The MELD score can be calculated on handheld electronic devices. Its utilization caused an immediate reduction in liver transplant waiting list registrations. Moreover the mortality on the waiting list reduced with almost 15 %. Today almost all of the organ sharing organizations (OSO), including Eurotransplant, uses MELD for prognosis and prioritizing allocation of liver transplants (5-8)

To fully understand the MELD score, one should assume that the calculated score is not representative for every disease in terms of urgency of transplantation. Examples are diagnoses as hepatocellular carcinoma, cholestatic liver diseases, biliary atresia, non-metastatic hepatoblastoma, etc. For these specific situations the use of the 'standard exceptional MELD' (SE MELD) is indicated (2). Appendix 1 provides a list of the specific diseases in which the SE MELD is used. Important to note is that the implementation of exceptions varies between the different OSO's.

Besides these noticeable improvements, the quality of the donor allograft is only considered in a limited way. In addition to the importance of the various donor factors, such as ABO compatibility, age, liver function, size-match, vasopressor requirements and serum sodium, one should never lose sight of the receiver and its influencing factors since also the clinical state of the recipient can influence outcomes (3, 9).

4.2 Combined donor-recipient model

Since the outcome after liver transplantation depends both on donor and recipient risk factors, the adequate donor/recipient matching has become a fundamental debate in the transplant community.

The mentioned expansion of graft use, caused by the deficit of donor organs, gives origin to a rather controversial situation in which risks for the patients are taken by using a wider supply in grafts. This is considered in an attempt to meet the huge demand for liver grafts and increase the chance of being able to offer as much patients as possible the essential transplantation. The importance of adequate donor/recipient matching is therefore emphasized since its direct correlation with a lower complication rate and the best outcome (10, 11).
Nonetheless, there is no universal definition of an extended criteria donor (ECD)[2]. Attempts were made to define a score that assesses the donor risk for transplantation. An example of such a score is The Eurotransplant Donor Risk Index in Liver Transplantation (ET-DRI). This Index is useful to receive an objective indication of the quality of the liver allograft and has a high predictive value for the outcome. It finds its use as an aid in difficult allocation situations in order to find the most favorable donor-recipient combination. Although its valid scoring capacity, a more appropriate approach is still acquired for allocation purposes, especially in high demanding procedures like SLT (9, 11).

A combined donor-recipient model (DRM) would allow getting a more complete image of the overall risk and would provide a combined positive effect of such a model. It consists both of donor risk factors and basic recipient factors. The result is a more complete score which contains all relevant factors that have a repercussion on the outcome after LT (11).

[2]Both general and more specific liver ECD criteria determine an ECD.The general criteria include hepatitis B or C, tumor, sepsis, drug abuse and meningitis whereas the more specific criteria include high BMI, steatosis, donor age greater than 65 years, high levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin, hypernatremia and intensive care unit (ICU) stay greater than 7 days.

Several risk indicating models combining donor, transplant, and recipient characteristics have been proposed previously. Briefly there would be a combination of the previous debated ‘ET-DRI’ and ‘simplified recipient risk index’ (sRRI), resulting in a ‘donor recipient model’ correcting for the sickness and/ or physical conditions where transplant patients may suffer from. The problem with these models are the few variables included and the lack of validation in an extensive data set (11).

Multiple recent study results confirm the importance of this match in the context of outcome after liver transplantation and survival benefit. Besides, the impact of the ‘pretransplant recipient risk’ is even more powerful than the donor quality. With the aim of achieving the highest survival benefit, particular donor livers should be transplanted in specific selected recipients (2, 9, 11).

4.3 General anatomy of the liver

Due to the work of the French surgeon and anatomist Claude Couinaud the internal anatomy of the liver was unraveled. He described the liver segmental anatomy, which is based on biliary and vascular relationships in a functional way, rather than external surface anatomy (the concept of plates and vascular biliary sheets). As a surgeon he performed the first ‘controlled’ hepatectomy and achieved the first biliary bypass to the left hepatic duct and the first ‘segment III bypass’. His scientific manuscript ‘Le Foie: Etudes Anatomique et Chirurgicales’ is considered to be the bible of the hepatobiliary surgery (12). Ever since then the practice of hepatic surgery evolved more and more to the contemporary interventions, based on the functional anatomy, instead of the lobar anatomy (13).

Couinaud described the 8-segment scheme of the liver: he divided the liver into 8 segments clockwise, starting with the caudate lobe as segment I. Each segment is supplied by terminal vessels. He used the portal vein branching as the basis for the segmental anatomy. In comparison with the hepatic artery and the biliary tree, the divisions of the portal vein are more consistent. Resulting in an independent vascular and biliary irrigation for each segment, where the vascular biliary elements move through the umbilical and hilar plates, obtaining a fibrous sheath that includes all three elements (hepatic artery, portal vein and bile duct) (12).

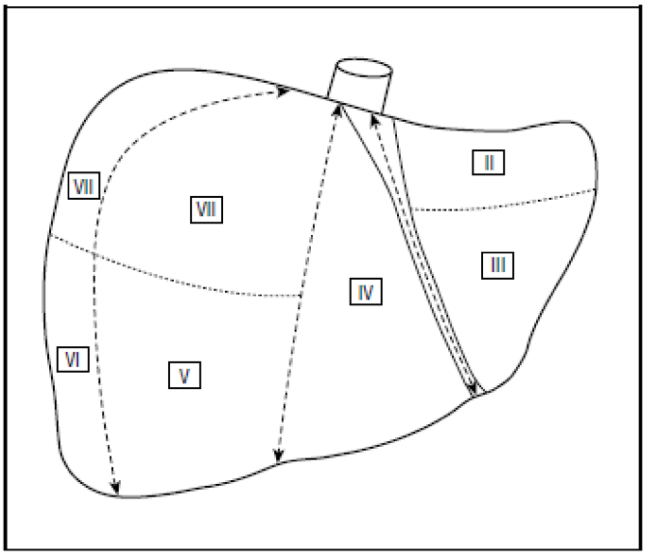


Fig.1. The segmental anatomy by Prof. Cuinaud. The segments are illustrated by Roman numerals. Segment I is the caudate lobe and is not seen in the anterior view (12).

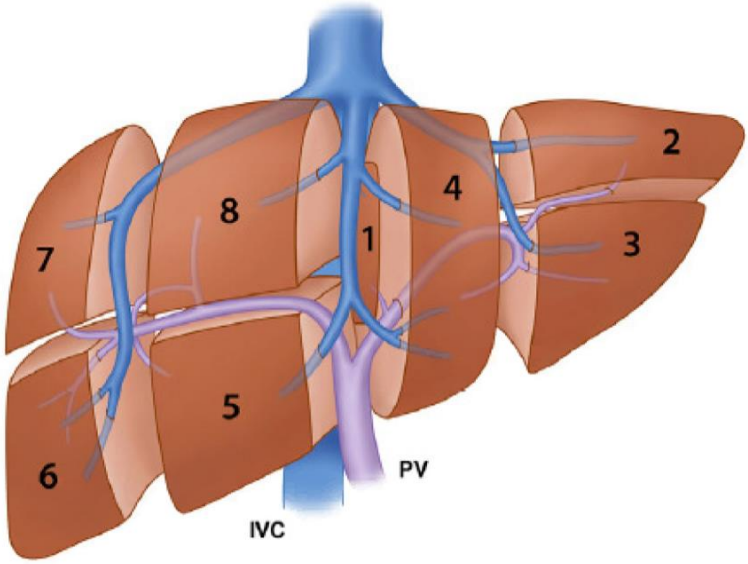


Fig.2. The segmental anatomy of the liver based on the portal vein and the hepatic vein branching (IVC: inferior vena cava and PV: portal vein) (12).

Starting from scratch, the liver features a dual vascular supply, where the portal vein provides approximately 70-75% of the nutritive blood supply. The latter arises as the confluence of the splenic vein and the superior mesenteric vein. The cystic vein, left gastric vein and branches of pancreaticoduodenal and right gastric veins are supplementary veins which drain in the portal vein. It is a low pressure system with pressures between 3 and 5 mm Hg. The remainder of

blood supply is provided from the hepatic artery and is about 30%. This dual blood inflow makes the organ even within limits tolerable for occlusion of the hepatic artery, where this is more restricted for the portal vein.
Interesting to add is the possible quick evaluation by the deep burgundy color of the liver, when normal functioning. Which is directly related with its rich vascularization, as described above (14).

The anatomy of the hepatic veins was thoroughly analyzed by professor Couinaud. As regards the right liver he identified 3 sets of veins draining into the right side of the inferior vena cava: the right superior, right middle and right inferior hepatic veins. Concerning the left liver he catalogued the middle/ left hepatic vein and the caudate veins draining into the left side of the inferior vena cava (12).

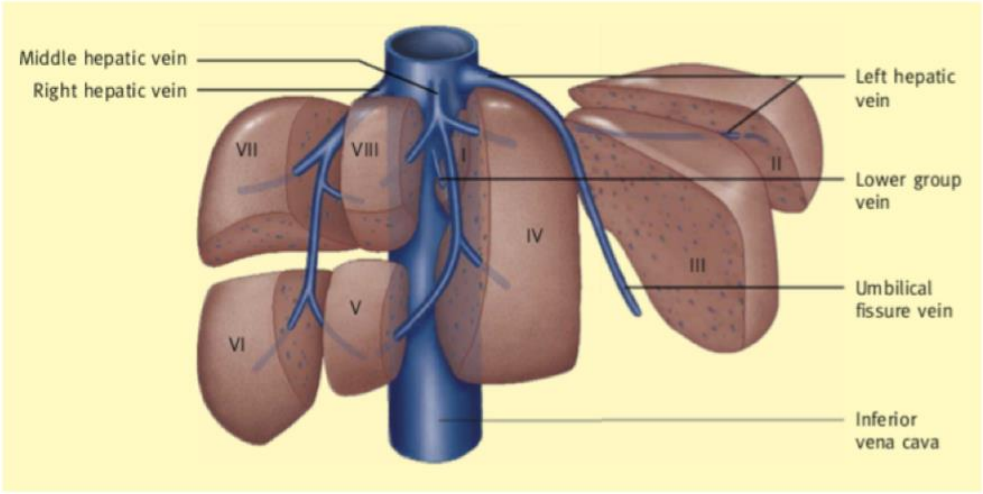


Fig.3. The location of the principal hepatic veins and the relationship of the hepatic veins to the segmental anatomy of the liver (13).

The arterial vasculature of the liver is variable. In the most common constellation the celiac axis give rise to the common hepatic artery that continues laterally and branches into the proper hepatic artery and the gastroduodenal artery. Through the hepatoduodenal ligament the proper hepatic artery along with the portal vein and the common bile duct proceed towards the liver to split up in left and right hepatic arteries. The artery of the gallbladder, named the cystic artery, usually branches from the right hepatic artery.

Besides its unique anatomic structure there is much more to admire when discussing the liver, most certainly when assessed in its role as a donor organ. The normal liver is known for its regeneration capacity, a fundamental aspect in the hepatobiliary surgery. As a consequence it has the possibility to fully recover in its size and function after the split liver transplantation (13).

4.4 Introducing split liver transplantation

The year 1988 was a fundamental year concerning split liver transplantations. In that year, Rudolf Pichlmayr[3] performed the first split liver transplantation. The German surgeon succeeded to divide and transplant one donor liver into two recipients. The 'graft receiving' patients were an adult and a pediatric liver patient. During the same year, Henri Bismuth[4] pioneered in the full right/ full left split[5] procedure treating two adult recipients. Looking at these 'split liver' procedures in the pre-MELD era, the patient and graft survival rates were inferior, compared to the full liver transplantations. Consequential was the hesitation concerning further spreading of the technique (15, 16).

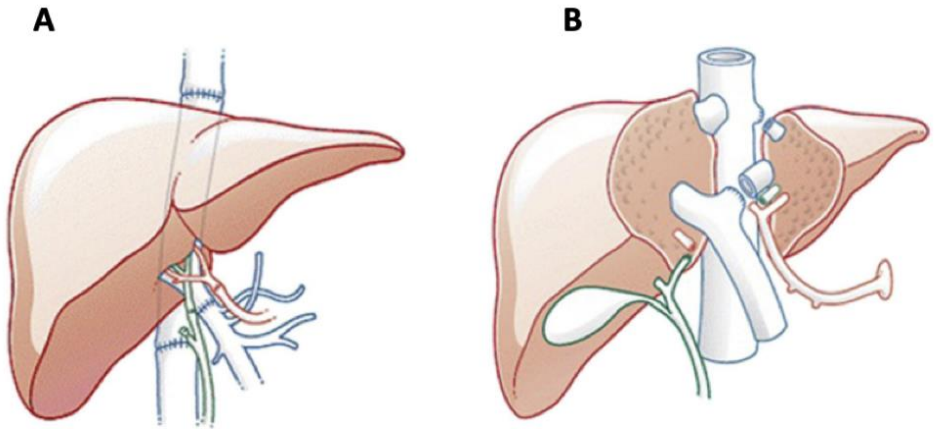


*Fig.4. The comparison between a whole liver transplantation (**A**) and a split liver transplantation (**B**) (17).*

[3] Rudolf Pichlmayr worked as a German professor of transplantation and special surgery at the Hannover Medical School.
[4] Henri Bismuth worked as a Tunisian professor at the Hepatobiliary Center at the Paul Brousse Hospital in Villejuif. He is considered to be a pioneer in the hepatobiliary surgery and was one of the first surgeons to develop a hepatic transplantation program.
[5] Full right and full left are referring to the proportions of the divided liver graft that is transplanted, containing each 4 segments and sharing vessels as well as biliary ducts.

However, due to start of the MELD-era, improvements in surgical procedures, the insight in the concept of size matching between recipients and the donor grafts, the avoidance of high-risk adult recipients and the reducing of the cold ischemia time, the surgeons obtained similar results compared to practitioners of the conventional 'whole graft' technique (16). Even more, SLT performed in experienced transplant centers, has been associated with excellent graft and patient survival both in pediatric and adult recipients (3, 11, 18).
The following observations may corroborate the interest of the procedure.
SLT of selected livers was introduced primarily to reduce the mortality of children on the waiting list. An essential objective if one takes into account that in the eighties 40 % of the pediatric recipients on the waiting list died. As a result of the introduction of SLT and living donor liver transplantation the mortality rate tremendously declined to 10 % in infants and to 5 % in older children. The SLT provided its help by raising the amount of donor organs, as well as solving the size-match problem for children. Not to mention that this solution isn't related with any disproportionate costs for the individual, neither the national health system (15, 16, 19-21).

During the MELD-era the graft failure risk of adult recipients, receiving the right part of a splitted liver, appeared to be not significantly different from the risk of whole-liver recipients when performed by an experienced team and accurate patient selection (10, 15, 18).
Moreover, split liver transplantations show similar results (short- and long-term outcomes) to those obtained in transplantations of whole organ LT (4, 22). Both the short and long-term outcomes can be comparable to whole organ LT, with the condition that evaluations of donor organs and recipients are conducted. Furthermore, it is desirable that logistics of organ allocation and splitting procedures are modified in order to increase the number and the safety of SLT (15). The organ allocation policies have a crucial role in the use of split livers and authorizing the cooperation between transplant centers is vital (10).

Although the achieved success, it remains a technically demanding procedure where, besides the skill and experience, an extensive knowledge concerning the potential anatomic variations is required. Both the donor organs and the recipients have to undergo a thorough evaluation to lower the potential increased perioperative complications.

4.5 Prevalence of split liver transplantation

When assessing the prevalence of SLT in the period between 2007 and 2017, an accurate

representation can be obtained by consulting the yearly statistics of Eurotransplant (ET). Within this reports one can find the yearly frequency of transplantations executed for each type of donor.

These statistics show the amount of transplants performed, however one has to take into account that for each counted transplantation two patients are treated with either a left or a right graft.
In the period of interest a total of 853 deceased donor split liver transplantations were reported in the ET region over the years. Interpretation teaches us the treatment of 1706 patients.

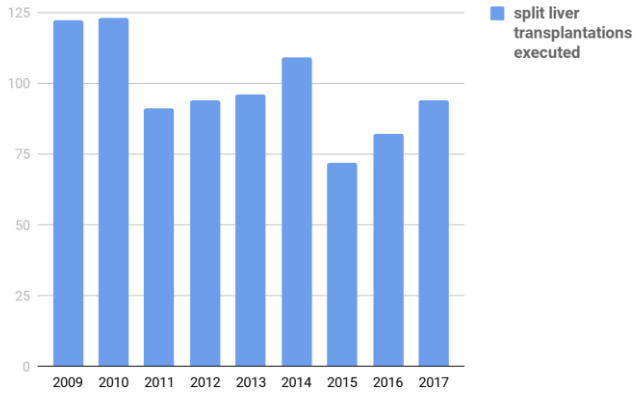


Fig.5. Frequency of SLT on deceased donors in the ET region[6] during the period 2009 - 2017.

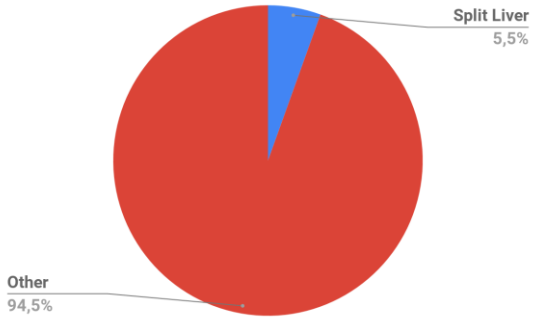


Fig.6. Comparison of the prevalence of SLT towards other LT techniques in the ET region during the period 2009 - 2017.

When omitting the time period of this work and looking at the total amount of splitting deceased donors starting from the first executed SLT until the year 2017 in this ET region, a total of 2534 split liver transplants were reported.
Figure 8 shows the limited practice of SLT (5,5 %) when comparing the technique with the competitive liver transplant interventions (94,5 %). These other techniques include the full liver transplantation and the living donor (split) liver transplantation. Important to note is the fact that the SLT section in this pie chart also exists out of the full left and full right split liver transplantations, which were actually considered as exclusion criteria for our study. The previous information emphasizes the very limited role of the left lateral and extended right grafts in the transplantation society.

[6] The Eurotransplant region represents the total population of the eight Eurotransplant member states (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, The Netherlands and Slovenia).

With the focus on Belgium, mainly three hospitals are involved in the execution of the split liver procedure.Those hospitals are: Ghent University Hospital, University Hospitals Leuven and the Catholic University of Louvain. From the year 2009 to 2017 a total of 48 deceased donor split liver transplantations were executed, as reported in the yearly statistics of Eurotransplant. The following image represents the yearly frequency of fulfilling a split liver transplantation in Belgium.

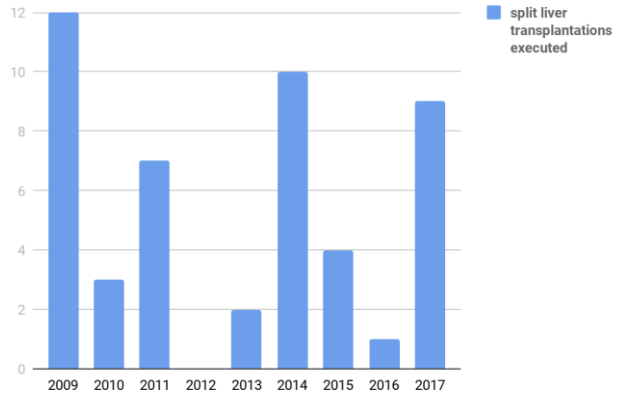


Fig.7. Frequency of SLT on deceased donors in Belgium during the period 2009-2017.

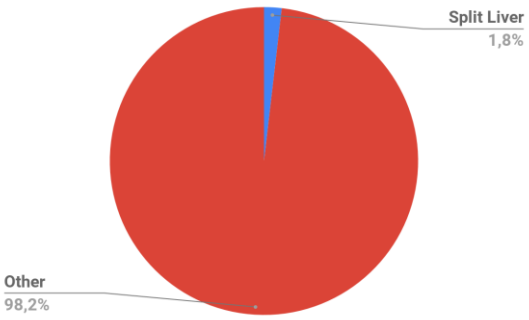


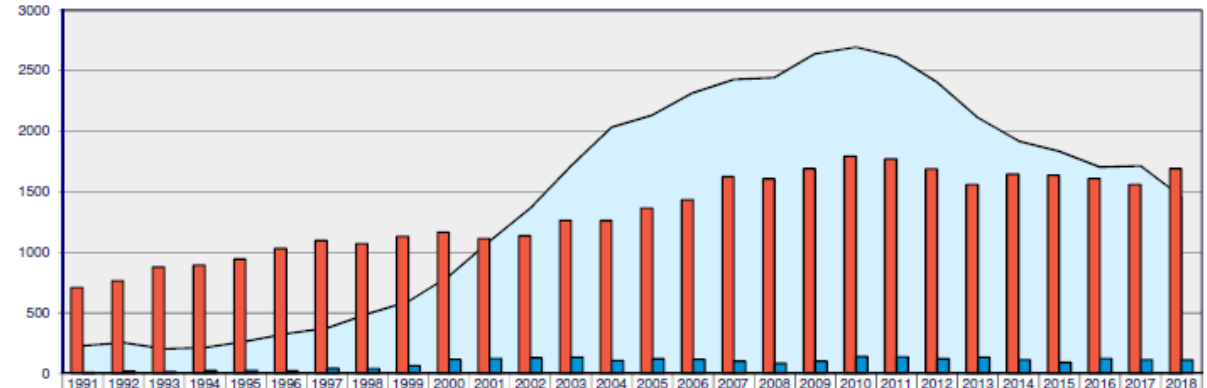
Fig.8. Comparison of the prevalence of SLT towards other LT techniques in Belgium during the period 2009-2017.

Again if one assesses the prevalence of splitting deceased donors starting from the first performed split liver transplantation, the total of transplants performed can be set at 277. This observation clearly proves the minor use of the technique from 2009 until 2017 compared to its larger prevalence during the years prior to 2009 and 'pre-MELD'. The limited use in Belgium gets confirmed by figure 8, where SLT only represents 1,8 % of all liver transplantation techniques.

Summarized, in Europe SLT still represents a minor source of additional liver grafts, especially in the adult population. Factors preventing the more frequent use of this groundbreaking surgery are the lack of knowledge regarding the technical aspects, adequate national splitting policy or paucity of splitting surgeons. Other non-minor factors are represented by the learning curve of the transplant surgeon and the fear of complications (i.e. biliary). The regional/national MELD system is also hindering the SLT approach since the grafts are allocated to the sickest patients at risk for a more complicated early postoperative period. Finally, and as a result of a lack of an 'ad hoc' policy, the lack of collaboration between the operating transplantation centers and the

possibility of turning an ideal graft into two marginal ones if the procedure is executed in suboptimal conditions, are definitely hindering the implementation of the procedure.
Few efforts have been made to stimulate the use of the procedure, such as the fifty-fifty rule adopted by Eurotransplant as an example. This includes that every liver obtained from a postmortem donor with an age under fifty years and a weight above 50 kilograms, is eligible for potential split liver transplantation. Nevertheless the decision is left to the transplant center which can eventually agree in good circumstances to undergo SLT, especially if the center is assisted by pediatric transplant activity (23).

Despite this overall underuse, an analysis of SLT and WLT in adults and children together shows an overall net gain in life years and a larger number of successfully transplanted livers by using split liver grafts (3, 10). Justifying this debate is the observation that both in UNOS[7] and in Europa, the present activity in the splitting of livers is too low in comparison with the calculated potential. It has been estimated that if only even half of the potentially donors appropriate for split liver transplantation were made available for this intervention, the pediatric waiting list could possibly be eliminated (18).
As an illustration the dynamic evolution of the ET liver waiting list over the years is shown below.



	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Liver waiting list	229	253	203	212	263	327	374	492	593	803	1093	1366	1714	2035	2134	2319	2429	2442	2641	2695	2614	2406	2111	1918	1835	1704	1714	1459
Deceased donor transplants	710	765	878	892	944	1032	1097	1071	1132	1168	1112	1136	1264	1262	1364	1436	1625	1606	1692	1793	1770	1689	1562	1646	1638	1610	1562	1692
Living donor transplants*	5	15	14	24	25	22	41	38	64	116	124	129	133	106	121	116	101	82	99	138	135	120	133	112	91	122	112	110

Fig.9. Dynamics of the Eurotransplant liver waiting list and liver transplants between 1991 and 2018 .

[7] United Network for Organ Sharing (UNOS) is the private, non-profit institution that administers the nation's organ transplant system in the United States of America.

The initial increase can be explained by the rising knowledge and experience, resulting in wider indications for a place on the waiting list. After a short stable period, the amount of patients on the waiting list descended starting from 2010. This descent can be mainly explained by the organ transplant scandal in Germany. The allocation system has been manipulated by German doctors in order to get donor livers more quickly for their patients. The doctors falsified their patient's medical records. Another explanation is the successful treatment of hepatitis C-virus and the consequently lower prevalence of end-stage liver cirrhosis induced by hepatitis C.

4.6 Impact of sharing grafts

The sharing of grafts implicates the allocation of the two obtained grafts to two different transplantation centers. After surgical intervention the two grafts are ready for transplantation.

When executing a split liver transplantation, the MELD allocation system interferes with making the best use of both the available organs. After the split procedure took place and the first graft is assigned, consequently the corresponding part of the liver needs a reallocation to a compatible receptor. This prolonged reallocation has greater chances to result in lower graft outcomes, caused by reduced rates of the 'in situ splitting' technique[8], prolonged 'cold ischemia time[9]', surgery by not initially involved surgeons and potential higher complication rates. This hypothesis got significantly confirmed by ELSABBAGH ET AL. emphasizing the crucial role of allocation and collaboration between centers concerning the sharing of grafts. Secondary this 'rescue allocation' of the second graft has been described as a reflection of the transplant surgeon's opinion of the available transplant centers. The discussed problem might be resolvable by utilization of a center specific allocation, outside the MELD terms. Important to add is the possible centralization of transplant surgery as a consequence of the foregoing strategy, which is why the suggestion of a nation- or transplant program-wide focus of organ allocation has been submitted. This program would rely more on the number of lives saved, instead of the sickest first policy represented by the MELD score (9, 10, 15, 24, 25).

[8] The liver is split in a hemodynamically stable cadaveric donor.
[9] The Cold Ischemia Time is considered to be an independent risk factor due to the development of delayed function and 'primary nonfunction' of the allograft.

4.7 Donor criteria

The donor selection is essential in SLT. A careful selection reflects the split graft quality. The donor age limit is between 40 and 50 years. An increase of the donor age is seen since the life expectancy of the average human being has been rising over the years. Therefore almost 50% of the donors are aged above 55 years. When including the changes in causes of death there can be established that contemporary donors are associated with advanced cardiovascular and metabolic morbidity (24). A prolonged stay on the intensive care unit, before the organ recovery, is considered to be unfavorable. Other adverse effects on the graft quality are: donor obesity, donor alcohol abuse, the presence of graft steatosis and fibrosis and the use of vasopressors to stabilize the donor hemodynamics.

4.7.1 Extended criteria

An important part of our work goes out to the extension of the donor criteria, which is why a short introduction of the extended criteria, yet applied, is given below. Since the following characteristics have been associated with additional risk factors when performing SLT, they can be seen as extended criteria. As mentioned they increase the risk associated with SLT but do not necessarily result in worse outcomes (2, 26)

Table 1. Extended donor criteria.

Extended donor criteria
macrovesicular hepatic steatosis: > 50%
age: > 65 years
hemodynamic instability
serum sodium: > 165 meq/L
ICU stay: > 7 days
use of vasopressor: > 1

4.8 Technique

To start this topic off one must consider the conditions required for an excellent execution of the split liver technique. Both the knowledge of the potential anatomic variations and the technical

skills are indispensable to bring the transplantation to a successful conclusion (3). For the particular aim of this work, a specific declaration of the surgical procedure would let us deviate too far from the point of interest. Which is why the partim about the technique is rather restricted and focused on a couple important terms.

Generally there are two ways to approach the donor organ. In medical terms one speaks of the **'in situ'** technique whenever the graft is procured inside a hemodynamically stable heart beating (brain-death) cadaveric donor, before cold perfusion. This techniques is characterized by a longer operation but provides a beneficial limitation of the 'cold ischemia time' (CIT) with a perfect evaluation of the vascular and biliary anatomy in vivo[10]. Besides the risk of graft failure seems to increase with every additional hour of CIT. This is why it is preferred by numerous surgeons. The **'ex situ'** technique describes accessing the liver after it has been removed from the donor, providing a shortening of both the operation- and the 'warm ischemia time' (WIT). This last method is also classified as 'back table SLT' because of accessing the organ outside the donor body, after washing and cooling, straight on the operation table. When looking at the different advantages of both techniques, one can imagine the difficulties in electing one of these two above the other. Which is why the choice is mostly correlated with the surgeon's experience towards both techniques and local donor hospital resources (4, 19, 27).
In order to separate the liver for adult/pediatric SLT procedure, two transection lines are used: the trans-hilar or the trans-umbilical division[11]. The difference in these two techniques is the location of separating the liver. Among different transplant teams the choice differs. It depends on the surgeon's experience and the personal preference. Currently the 'ideal splitting technique' is not specified. Although different observations concerning certain parameters, both techniques seem equal in terms of safety and efficiency. However, the trans-hilar approach seems to be more workable for changing the division to anatomical variations, to the diversity of recipient's weight and needs and for re-operations. Briefly there can be concluded that the surgical expertise is more relevant than the technique itself (3, 28).

[10] Referring to the anatomic evaluation of the graft while the donor is still 'alive'.
[11] The liver can be split through segment IV approximately 2 cm on the right of the falciform ligament (trans-hilar) or through the umbilical fissure (trans-umbilical).

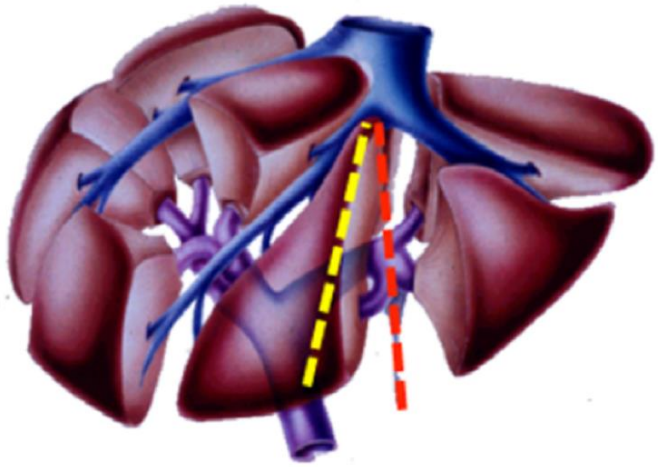


Fig.10. Comparison between a trans-hilar (yellow line) and a trans-umbilical (red line) approach (28).

4.9 Indications and outcomes

4.9.1 Indications

A liver transplantation is indicated when the risk of mortality, correlated with the liver disease the patient is suffering from, is higher than the overall risk associated with the procedure. The main indications for SLT are chronic liver disease, acute liver failure, metabolic disorders and primary liver malignancy. Since we are talking about the split liver transplantation, a distinction in indications between infants (LLG) and adults (ERG) is essential here.

4.9.1.1 Left lateral split

For the pediatric population the following indications are observed the most often: cholestatic liver diseases (extra- and intrahepatic cholestasis), metabolic disorders, acute liver failure and the primary liver malignancies (hepatoblastoma is the most frequent pediatric primary liver tumor). Important to note are the contraindications to pediatric LT which are the unresectable extrahepatic uncontrolled diseases or infections, the untreatable end-stage organ failure and the presentation of irreversible neurologic injuries. In these cases the patient would not benefit from the transplantation.
The children suffering from fulminant hepatic failure (FHF) are in dire need for a transplantation, resulting in potentially higher pretransplant mortality when not transplanted. However in case the FHF patient undergoes a successful SLT, it is still associated with significantly less fortunate posttransplant survival (29, 30).

Next to these contraindications, there are indications where SLT results in optimal patient outcome. As an example research has shown the primary sclerosing cholangitis forms the best indication for SLT, since these young patients mostly receive high-quality liver parenchyma from young donors. This process is also positively influenced by the reduced waiting times (22).

4.9.1.2 Extended right split

Split liver transplantation should be considered for adult patients with any kind of end-stage liver diseases including acute liver failure and primary hepatic malignancy (hepatocellular carcinoma is the most frequent primary liver tumor in the adult population).
For this population an extension of the indications has yet been described. In that way performance of the transplantation can be done under emergency or urgent care circumstances. These conditions do not result in unfavorable outcomes, they are even associated with acceptable morbidity and adequate long-term survival rates (20).

Worthwhile to add is the fact that transplantations for patients with low MELD-scores allow fast and efficient interventions, compared to higher MELD scores.

4.9.2 Outcome

Talking about the patient's outcome, broadly three main influencing factors can be described. These are both donor and patient selection, as well as the technical features applied (22).

An inferior outcome was observed in acute liver failure as an indication for SLT and also adult recipients who received a split graft for the treatment of hepatocellular carcinoma (HCC) experienced greater risk of graft failure compared to those who received a whole graft (4, 18). The risk factors for early graft failure are dissimilar to those for long-term outcomes in young recipients. In other words, the risk factors are time-dependent. Prolonged cold ischemia time (CIT), low recipient weight, donor age younger than 10 years and older than 50 years are documented to have a negative influence on the early complications whereas urgent transplantation is encountered to be related to both short- and long-term complications (4). In addition the use of the in situ or ex situ splitting technique[12] appears to play a part in the graft survival. The ex situ

[12] The liver can be split on the back table (ex-situ) or in a hemodynamically stable cadaveric donor (in-situ).

splitting technique is found to be associated with inferior graft survival by cause of the prolonged CIT and by exposing the graft to supplementary warm ischemia via manipulation. On the other hand the in situ splitting technique provides a more precise anatomical section and enhance the quality of the graft through reducing the CIT (4, 31). At the beginning, studies analyzing the ex situ technique suggested to achieve worse outcomes than the in situ technique. After all the growing experience encountered the difference (10).

An important factor contributing to the patient's clinical outcome is the formation of a multidisciplinary team. Combining knowledge from various disciplines contributes to a better treatment of the patient. The core members of the multidisciplinary team include liver transplant/hepatobiliary surgeons, hepatologists/gastroenterologists, oncologists, radiologists, interventional radiologists, pathologists, and primary care physicians.

Since the short- and long-term outcomes after living donor related transplantation and SLT did not differ significantly, it makes sense that the possibility to harm a healthy person by performing living donor transplantation, should be avoided where possible. Especially when there may be an equivalent alternative.

Choosing and matching an appropriate recipient is an important act in the selection procedure. The risk of size mismatch is always a potential risk factor of graft failure. Recipients with high MELD scores or severe portal hypertension are considered to be high-risk recipients.

5. Objectives

The study targets to evaluate the entire process associated with adult and pediatric recipients undergoing SLT, respectively with extended right grafts (segments I- IV- VIII) and left lateral segments (segments II and III) from standard brain death deceased donors during the last decade when the MELD allocation has been implemented in Eurotransplant.

Extensive analyses will be performed both for the left lateral grafts as the extended right grafts observed in this study, permitting their separate evaluation.
Contributing to the process of defining an operable 'donor-recipient match', it is obligated to perform an extensive analysis of both the donor and recipient variables, the graft function, post-transplant biliary/vascular complications and their role in graft loss or dysfunction. In an attempt to contribute to the identification of a new profile of an ideal donor, an evaluation of the recipient and graft survival after transplantation, linked with potential predictors of graft failure, is necessary.

Furthermore we will attempt to estimate the current risk of graft failure for the procedure and to determine if any potential risk could be mitigated by additionally optimizing recipient selection. Within this section we will evaluate the possible pediatric advantage with SLT at the expense of the adult transplants. Matter of course the impact of sharing split grafts on the results after transplantation will be concluded in the analysis.

6. Patients and methods

6.1 Basis for selection

This retrospective multicentric study includes all adult and pediatric recipients who received a split liver transplantation performed from January 1st 2007 until December 31 2017, matching the selection criteria. This concerns all recipients who were treated with SLT in Belgium in the last 11 years, either with the 'in situ' or 'ex situ' technique. Exclusion criteria included the following: SLT performed with 'full left/ full right' split grafts and donors after circulatory death (DCD).

To acquire a decent amount of retrospective data, a multicentric approach was indicated. Three different university hospitals participated in the study. In consequence the three different research ethics committees needed to approve the design of the study to ensure that the research is in accordance with the ethical standards.
To obtain data from Ghent University Hospital, the hospital where the study finds its origin, the opting-in method was used. It means that the patient's signature, by which an informed consent is given, is indispensable before starting to collect the patient's data.
An anonymous database was given by the University Hospitals Leuven which means an informed consent was not required in order to start the data processing.
Patients treated at the Catholic University of Louvain signed an informed consent before being transplanted.
After approval from the research ethics committees the patient's medical files were analyzed and the information was evaluated for its relevance.
This entire process was executed with respect to the new General Data Protection Regulation (GDPR) legislation. It resulted in 42 patients, subdivided in 26 extended right grafts (ERG) and 16 left lateral grafts (LLG). Within the 42 patients 11 coupled receivers (same donor) could be determined. The included patients were all eligible for extensive analysis.

6.2 statistical analysis

As a next step in the research process, after completing the collecting process, data cleaning has been executed in an extensive way. The "cleaning" process resulted in the disregard of a number of variables because of the presence of too many missing variables. This was mainly due to the

incomplete operative reports or difficulties in interpretation. Notwithstanding we maintained the original study population of 42 patients.

For both the left lateral grafts and the extended right grafts statistical analyses were executed. The categorical covariates were evaluated by the Fisher's exact test whereas the continuous covariates were compared by the parametric unpaired Student's t-test. The normality was assessed by both a graphical representation and the Shapiro-Wilk test. For variables that do not meet the criteria for normal distribution the non-parametric Mann-Whitney U test was used. SPSS 26 was used for statistical analysis. Results were expressed as median with a range. A p-value of <0.05 was considered statistically significant.

The reason for omitting the aspect of correlation, regarding the paired population, is because of the negligible impact of donor related parameters, once a donor qualifies for a split, on the overall survival of both of the donated grafts. The two grafts are, as described above, mainly influenced by the technique and the patient's parameters. Statistical significant results confirming this theory were obtained by MOUSSAOUI ET AL. (32).
On the other hand, the paired patients provide the possibility of evaluating the graft outcome of two patients coming from the same donor, which is why its involvement is relevant to our work. With the aim to describe the outcome of the paired patients, regarding their connection, the function 'select cases' was used in the excel dataset. Since the end result amounts two different liver grafts, analysis in between the two groups won't be very representative. Therefore the analysis of the paired population will only be descriptive.

Both the patient and the graft survival were considered as the outcomes of the survival analysis. To estimate the survival rates the Kaplan-Meier method was used. The comparison of patient and graft survival in different groups was achieved through the log-rank test.

The cox regression was used to evaluate the effect of both donor and recipient variables on the patient and graft survival. Due to the limited number of data, the preference has been given to the forward method.

7. Results

A total of 42 patients meeting the inclusion criteria of the study were subjected to an extensive analysis. Both the left lateral and extended right graft receivers are part of the 42 patients. Respectively 16 infants and 26 adults are included. Important to note are the 22 patients that can be assumed as 11 couples where each couple shares an organ from the same donor.

7.1 Overall patient and graft survival

Statistical analysis of patient and graft survival was performed using the Kaplan-Meier estimator for both the LLG and ERG study population. The follow-up period was defined as the number of years from the time of transplantation until the last consultation at the hospital.

During the time of follow-up 3 pediatric patients who received a left lateral graft were lost to follow-up. As a result, 13 patients of the LLG population were involved in the survival analysis. The median follow-up of the patients who received a left lateral graft was 10.42 years (125 months). The overall 10-year patient survival was 92.3 %. The overall 10-year graft survival was 76.9 %.

During the time of follow-up 2 adults who received an extended right graft were lost to follow-up. As a result, 24 patients of the ERG population were involved in the survival analysis. The median follow-up of the patients who received an extended right graft was 7.75 years (93 months). The overall 10-year patient survival was 83.3 %. The overall 10-year graft survival was 66.7%.

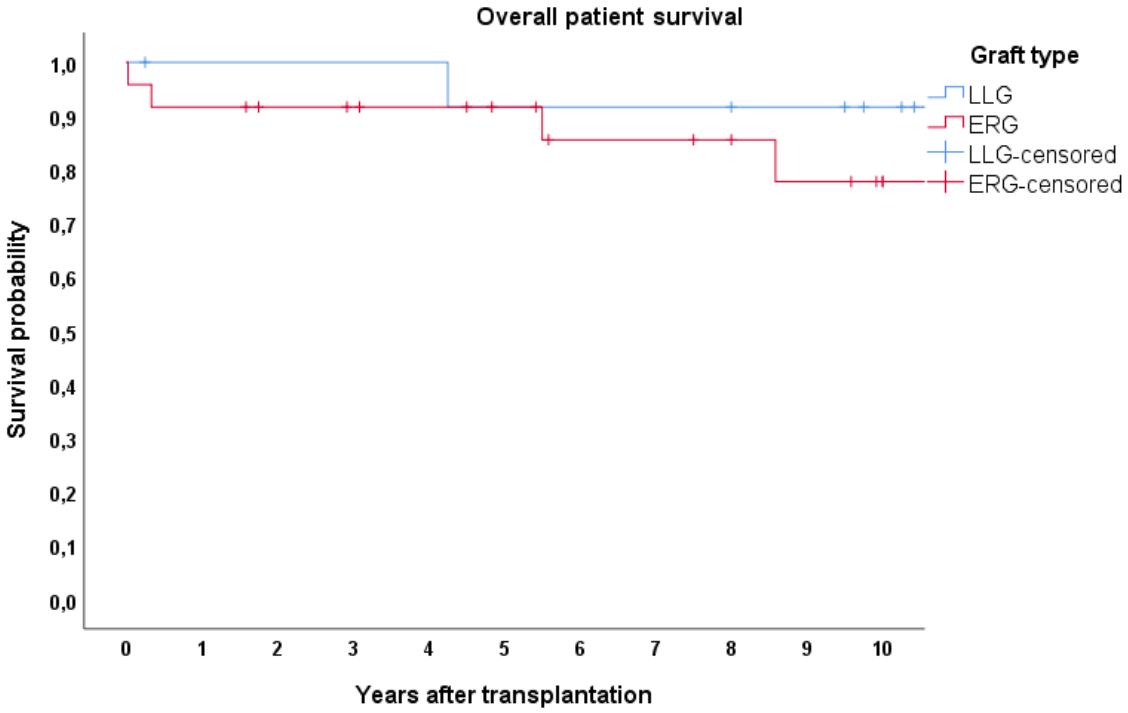


Fig.11. Overall patient survival of the left and right split grafts.

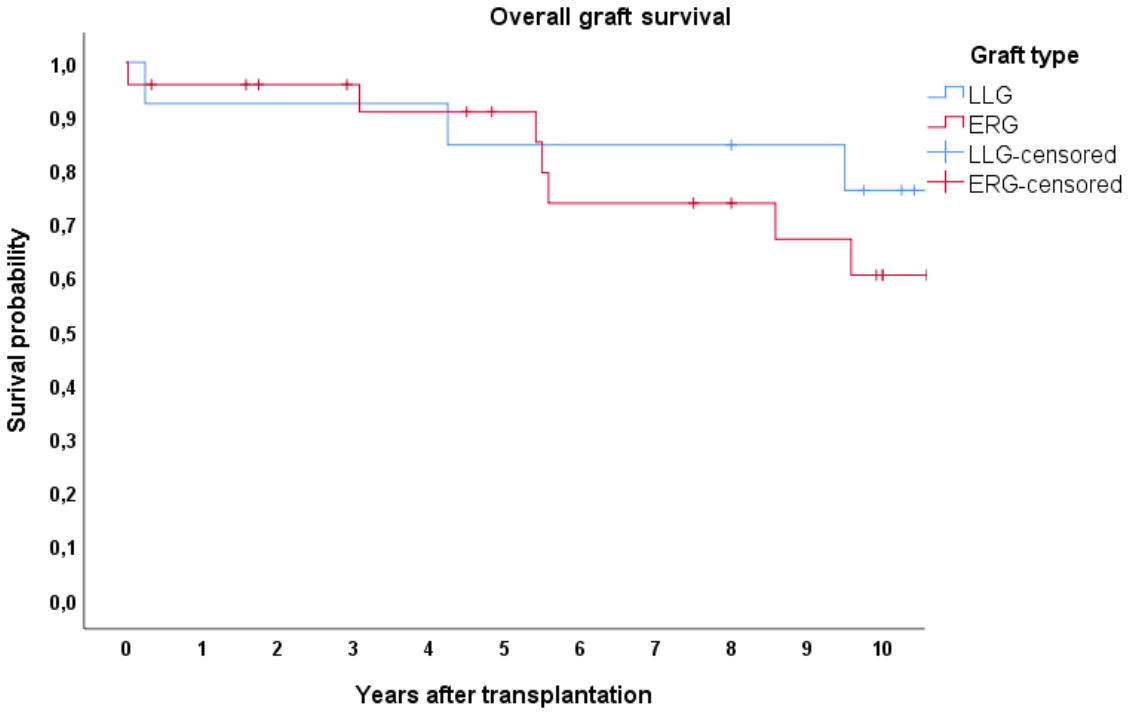


Fig.12. Overall graft survival of the left and right split grafts.

7. 2 Results of the LLG study population

7.2.1 Demographics

The table 2.0 shows the donor, recipient, graft and surgical characteristics for each of the 16 pediatric patients. The categorical variables were given as total number (n) while the continuous variables were assessed by use of the median and the interquartile range (IQR). The reason for choosing the median and IQR can be declared by the skewed distribution of the continuous covariates.

7.2.1.1 Donor variables

The donor's cause of death was mainly traumatic. The median donor age was 21.5 years (IQR, 15.75-44.25). The median donor weight was 70 kg (IQR, 49.5-90). The median donor BMI was 22.05 (IQR, 21.45-25.675) for the patients who receives a left lateral graft. The median CIT was 594.50 minutes (IQR, 382.25-857). As organ preservation fluid the University of Wisconsin (UW) solution was used the most. Since the median of the ET-DRI of the LLG group was lower (1.75) comparing to the ET-DRI of the ERG group (1.87) and higher MELD-scores were found for the LLG group, compared to the ERG group, an interesting relation between the two covariates could possibly be found. This evaluation, permitting us to link donor and recipient variables, will be considered further in this manuscript.

7.2.1.2 Recipient variables

The main indication to initiate SLT was chronic liver disease. Regarding the LLG population, it is important to mention that the disease 'biliary atresia' was subcategorized under the chronic indications because most infants undergo other interventions preparatory to an indicated SLT. The median recipient age was 4 years (IQR, 0.8-8.3). The median recipient weight was 13 kg (IQR, 5.1-30). The median recipient BMI was 17.4 (IQR, 13.4-19.2) for the patients who received a left lateral graft. The median MELD at liver transplantation was 25 (IQR, 16-29).

7.2.1.3 Graft variables

The left lateral grafts were characterized by a median CIT of 594 minutes (IQR, 382.25-857) and a median WIT of 50 minutes (IQR, 32.75-65). The majority of the grafts were found shipped (13) from one center to another and executed with the ex situ technique (12).

7.2.1.4 Outcome variables

As described in the overall patient and graft survival one can find the survival rates once more in the demographic table. For the LLG population the reasons for graft loss of 3 patients were primary non function, post-ischemic biliopathy and death with loss of the graft. Two patients were in need of a retransplantation because of the primary non function and post-ischemic biliopathy described above. The frequency of complications is also displayed in the table, mainly represented by biliary complications.

Table 2. Characteristics of the LLG study population (n=16).

	Median (n)	**Q1-3**
Donor Variables		
Gender		
- male	(10)	
- female	(5)	
Age (years)	21.5	15.75 - 44.25
Height (cm)	177.5	155.25 - 182.5
Weight (kilo)	70	49.5 - 90
Cause of death		
- trauma	(8)	
- CVA	(4)	
- anoxia	(3)	
- missing	(1)	
ICU (days)	2	1 - 5
AST (u/l)	72.5	32.5 - 107
ALT (u/l)	38	28.25 - 59
GGT (u/l)	24.5	15 - 49.75
Sodium (mmol/l)	146.5	142 - 150

ETDRI	1.75	1.62 - 2.08
BMI	22.05	21.45 - 25.68

Recipient variables

Gender		
- male	(10)	
- female	(6)	
Age (years)	4	0.8 - 8.3
Height (cm)	104	56 - 125
Weight (kilo)	13	5.1 - 30
Indication to SLT		
- acute	(5)	
- chronic	(10)	
- tumour	(0)	
- metabolic	(1)	
MELD lab at LTx	25	16 - 29
PT (sec)	35	16 - 68
Bilir. Tot (mg/dl)	9.46	2.4 - 22.7
Sodium (mmol/l)	140	137 - 143
Creatinine (mg/dl)	0.32	0.15 - 0.47
Ascites		
- yes	(3)	
- no	(13)	

Infections before		
- yes	(2)	
- no	(14)	
INR	2.16	1.31 - 2.7
Time on waiting list (days)	131	24 - 274
Center		
- UZ Gent	(11)	
- KUL	(2)	
- UCL	(3)	
BMI	17.4	13.4 - 19.2
Graft		
CIT	594.50	382.25 - 857
WIT	50	32.75 - 65
Shipped		
- yes	(13)	
- no	(2)	
- missing	(1)	
Technique		
- ex situ	(12)	
- in situ	(2)	
- missing	(2)	
Outcome		
Follow up period (months)	129	117 - 138

Complications
- arterial (1)
- portal vein (0)
- biliary (7)
- missing (2)

Graft loss
- yes (3)
  - PNF (1)
  - post-ischemic biliopathy (1)
  - death (1)
- no (11)
- missing (2)

Retransplantation
- yes (2)
  - PNF (1)
  - post-ischemic biliopathy (1)
- no (12)
- missing (2)

Status
- alive (13)
- dead (1)
- missing (2)

7.2.1.5 Relation between the MELD score and ET-DRI

In figure 13 a descriptive bar chart describes the relationship between the MELD score and the ET-DRI.

The highest observed MELD scores (25-34) occurred proportionally more frequent in the LLG group. The lowest observed ET-DRI (green bar: ET-DRI 1.4-1.59) is rather associated with the higher MELD scores, within the LLG group.

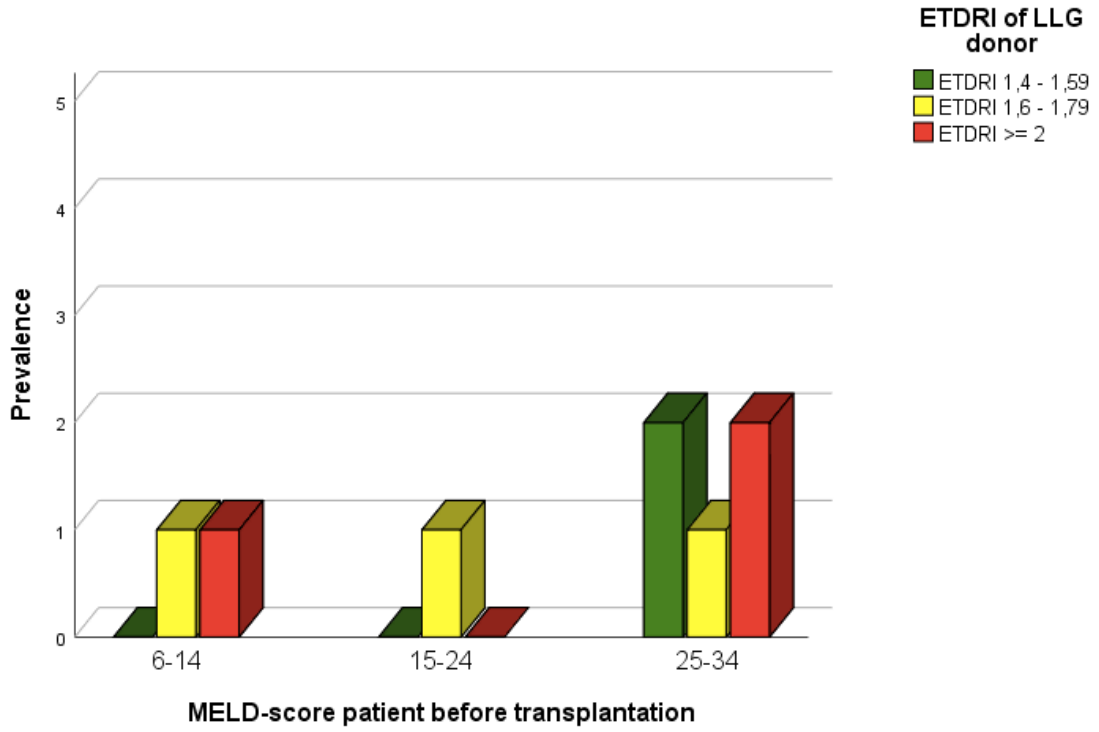


Fig.13. Relation between the MELD score and ET-DRI for the LLG study population.

7.2.2 Statistical analyses

7.2.2.1 Determinants Graft loss

Primarily an extensive analysis, applied to the LLG study population, took place for the variable ‘graft loss’. With this statistical efforts potential related factors were attempt to establish.

No significant associations with the variable ‘graft loss’ were found for the following subjected variables: ‘ascites before transplantation’, ‘infections before transplantation’, ‘donor age’, ‘donor cause of death’, ‘shipping of the graft’, ‘splitting technique’, ‘complications biliary’, ‘complications portal vein’, ‘complications infections’, ‘complications cholangitis’, ‘complications rejection’, ‘complications segment IV’, ‘primary disease: acute liver failure (ALF)’.

Neither any differences for the mean have been observed, between the patients with and without ‘graft loss’, for the following LLG variables: ‘age‘, ‘graft cold ischemia time’, ‘graft warm ischemia time’, ‘donor ETDRI’, ‘donor sodium’, ‘donor GGT’, ‘donor ALT’, ‘donor AST’, ‘donor intensive care unit (days)’, ‘donor BMI’, ‘donor age’, ‘MELD at LT’ and ‘time on waiting list (months)’.

Finally in the terms of graft loss, one can also focus on variables as rejection and retransplantation. In this section we focused on significances described in the consulted literature. The variable 'complications rejection' showed no significant association with the variable 'donor age'. As well as for the variables 'arterial complications' and 'retransplantation' no significant association between the two was reported.

7.2.2.2 Determinants Status

No significant associations with the variable 'status' were found for the following subjected variables: 'donor age' and 'primary disease: ALF'.

7.2.2.3 Determinants complications

No significant associations with the variable 'complications arterial' were found for the following subjected variables: 'donor age'

7.2.3 Analyses of risk factors affecting patient and graft survival

7.2.3.1 Survival distributions compared by log-rank tests

Statistical analysis of patient and graft survival was performed using the Kaplan-Meier estimator. The continuous variables used for the analysis (donor age, donor ET-DRI , MELD lab and cold ischemia time) were converted to categorical variables by determining cut-off values by using the receiver operating characteristic curves (ROC curves). The most appropriate cut-off values have been selected by maximizing both sensitivity and specificity. This corresponds to the point on the ROC curve where both sensitivity and specificity are chosen to be equal.
Kaplan-Meier curves of both the patient and graft survival were compared between donor age, donor ET-DRI, MELD lab at liver transplantation and cold ischemia time. To compare the survival distributions the log-rank test was indicated. These various graphs are listed in the addendum. At univariate analysis, a significant result of cold ischemia time (CIT) on the risk of graft failure was detected (p= 0.034). CIT >660 minutes is associated with an increased risk of graft failure.

Table 3. Cut-off values of the continuous variables used in the log-rank tests and the probability values (p-values) calculated by the log-rank test.

Continuous variable	Cut-off value	p-values patient survival	p-values graft survival
Donor age	40 years (≤40 years or >40 years)	0.398	0.157
Donor ET-DRI	1.69 (≤1.69 or >1.69)	0.480	0.728
MELD lab at liver transplantation	27 (≤27 or >27)	0.317	0.528
Cold ischemia time	660 minutes (≤660 min. or >660 min.)	0.157	**0.034**

7.2.3.2 Cox regression

The cox's model was used to evaluate the effect of both donor and patient variables on the patient and graft survival by using the forward method, represented by respectively table 4. and table 5. Increasing risk of graft failure was associated with CIT >660 min (HR= 1.67).

Table 4. Predictors of patient survival in the fitted Cox model (HR: hazard ratio and CI:confidence interval).

Variable	HR (95 % CI)	p-value
Donor age (≤40 years vs. >40 years)	0.78 (0.30, 1.65)	0.480
Donor ET-DRI (≤1.69 vs. >1.69)	0.83 (0.41, 2.23)	0.482
MELD lab at liver transplantation (≤27 vs. >27)	1.18 (0.76, 2.22)	0.371
Cold ischemia time (≤660 min. vs. >660 min.)	1.39 (0.76, 1.85)	0.157
Donor BMI (≤25 vs. >25)	1.02 (0.62, 2.30)	0.593

Table 5. Predictors of graft survival in the fitted Cox model (HR: hazard ratio and CI:confidence interval).

Variable	HR (95 % CI)	p-value

Donor age (≤40 years vs. >40 years)	1.16 (0.62, 2.14)	0.343
Donor ET-DRI (≤1.89 vs. >1.89)	0.75 (0.32, 2.29)	0.728
MELD lab at liver transplantation (≤25 vs. >25)	1.23 (0.82, 1.96)	0.213
Cold ischemia time (≤660 min. vs. >660 min.)	1.67 (1.39, 1.72)	**0.034**
Donor BMI (≤25 vs. >25)	0.81 (0.33, 2.34)	0.502

7.3 Results of the ERG study population

7.3.1 Demographics

The table 5.0 shows the donor, recipient, graft and surgical characteristics for each of the 26 adult patients. The categorical variables were given as total number (n) while the continuous variables were assessed by use of the median and the interquartile range (IQR). The reason for choosing the median and IQR can be declared by the skewed distribution of the continuous covariates.

7.3.1.1 Donor variables

The donor's cause of death was mainly traumatic. The median donor age was 29 years (IQR, 18.5-41). The median donor weight was 72 kg (IQR, 60-80). The median donor BMI was 22.1 (IQR, 20.65-25) for the patients who received an extended right graft. The median CIT was 600 minutes (IQR, 512-730). As organ preservation fluid the University of Wisconsin (UW) solution was used the most.

7.3.1.2 Recipient variables

The main indication to initiate SLT was chronic liver disease. The median recipient age was 54.45 years (IQR, 38.775-61.550). The median recipient weight was 68.600 kg (IQR, 54.275-80.500). The median recipient BMI was 24.395 (IQR, 21.400-28.325) for the patients who received an extended right graft. The median MELD at liver transplantation was 18 (IQR, 12.5-27).

7.3.1.3 Graft variables

The extended right grafts were characterized by a median CIT of 600 minutes (IQR, 512-730) and a median WIT of 40 minutes (IQR, 32-60). The majority of the grafts were found shipped (21) from one center to another and executed with the ex situ technique (18).

7.3.1.4 Outcome variables

Once again the overall patient and graft survival can be find in the demographic table below. For the ERG population the reasons for the graft loss of 10 patients were primary non function, autoimmune hepatitis, liver abscesses, subacute hepatic failure, failure of the transplant liver, cholangitis and death with loss of the graft. Two patients were in need of a retransplantation because of the primary non function and post-ischemic biliopathy described above. The frequency of complications is also displayed in the table, mainly represented again by the biliary complications.

Table 6. *Characteristics of the ERG study population (n=26).*

	Median (n)	**Q1-3**
Donor Variables		
Gender		
- male	(16)	
- female	(10)	
Age (years)	29	18.5 - 41
Height (cm)	180	170 - 182.5
Weight (kilo)	72	60 - 80
Cause of death		
- trauma	(15)	
- CVA	(8)	
- anoxia	(3)	
ICU (days)	2	1 - 5
AST (u/l)	45	24.5 - 76.5

ALT (u/l)	34	18 - 44
GGT (u/l)	20	14.5 - 44.5
Sodium (mmol/l)	147	142 - 154
ETDRI	1.87	1.69 - 2
BMI	22.1	20.65 - 25

Recipient variables

Gender		
- male	(9)	
- female	(17)	
Age (years)	54.45	38.78 - 61.55
Height (cm)	168	157.5 - 172.25
Weight (kilo)	69.6	54.28 - 80.5
Indication to SLT		
- acute	(3)	
- chronic	(22)	
- tumour	(1)	
- metabolic	(0)	
MELD lab at LTx	18	12.5 - 27
PT (sec)	49	33.83 - 61.75
Bilir. Tot (mg/dl)	2.86	1.45 - 8.31
Sodium (mmol/l)	140	136.75 - 142

Creatinine (mg/dl)	0.9		0.70 - 1.1
Ascites			
- yes		(16)	
- no		(8)	
- missing		(2)	
Infections before			
- yes		(6)	
- no		(20)	
INR	1.63		1.30 - 1.90
Time on waiting list (days)	97.5		45 - 264.25
Center			
- UZ Gent		(19)	
- KUL		(2)	
- UCL		(5)	
BMI	24.40		21.4 - 28.33
Follow up period (months)	93		45.5 - 123.5
Status			
- alive		(20)	
- dead		(6)	

Graft

CIT	600	512 - 730
WIT	40	32 - 60

Shipped
- yes (21)
- no (5)

Technique
- ex situ (18)
- in situ (6)
- missing (2)

Outcome

Follow up period (months)	93	45.5 - 123.5

Complications
- arterial (4)
- portal vein (3)
- biliary (7)
- missing (5)

Graft loss
- yes (10)
  - PNF (2)
  - autoimmune hepatitis (1)
  - liver abscesses (1)
  - subacute hepatic failure (1)
  - failure of transplant liver (1)
  - cholangitis (1)
  - death (3)
- no (16)

Retransplantation
- yes (6)
  - PNF (2)
  - autoimmune hepatitis (1)
  - liver abscesses (1)
  - missing (2)
- no (20)

Status
- alive (20)
- dead (6)

7.3.1.5 Relation between the MELD score and ET-DRI

In figure 22 a descriptive bar chart describes the relationship between the MELD score and the ET-DRI.

In the demographics section the ERG population was characterized by a lower median MELD score and higher median ET-DRI compared to the LLG population. This observation gets confirmed by the figures. For the ERG population it is noticeable that the participants show well spreaded MELD scores, whilst the ET-DRI values are more situated in the central categories. Consequently the more marginal ET-DRI values, in terms of highest and lowest categories, are less frequent.

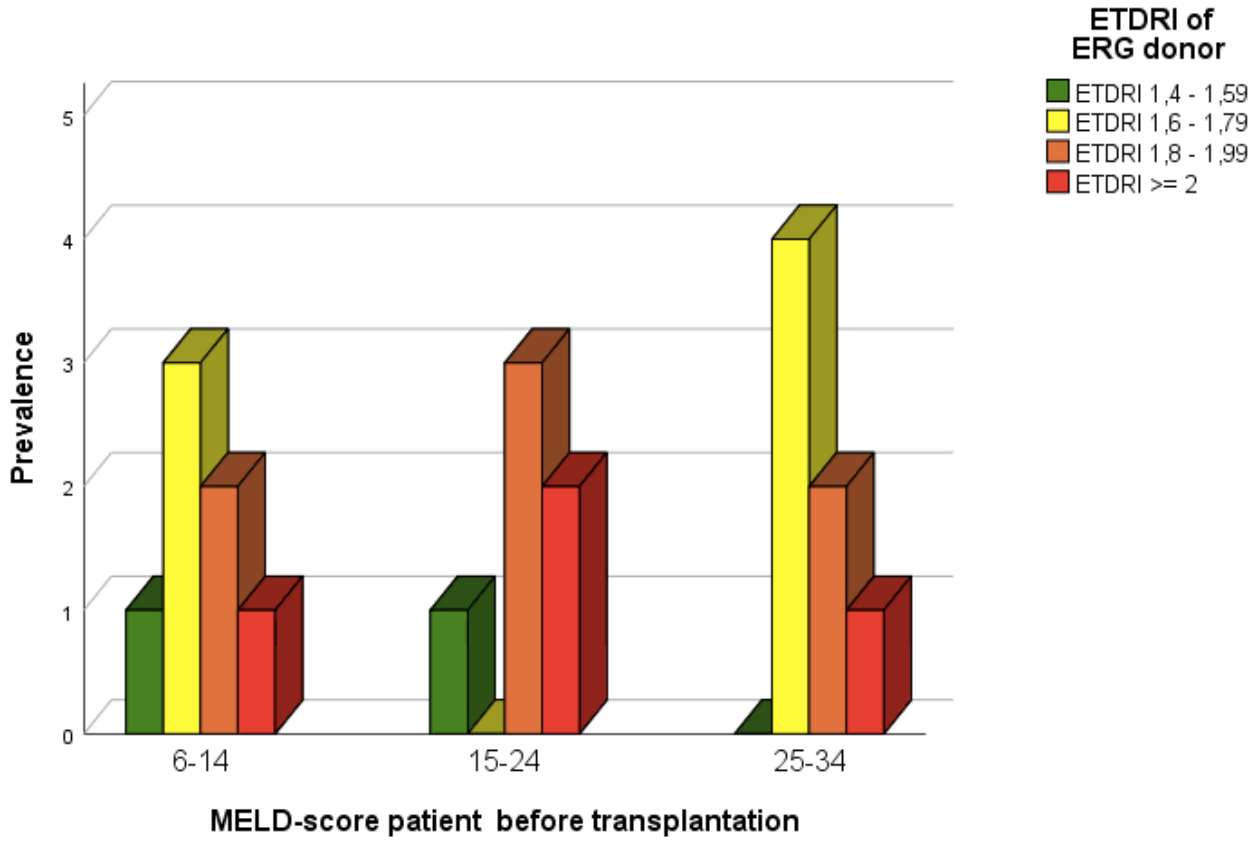


Fig.22. Relation between the MELD score and ET-DRI for the ERG study population.

7.3.2 Statistical Analyses

7.3.2.1 Determinants graft loss

Subsequently an extensive analysis, applied to the ERG study population, took place once more for the variable ‘graft loss’. Again with these statistical efforts, potential related factors were attempted to establish.

No significant associations with the variable ‘graft loss’ were found for the following subjected variables: ‘ascites’, ‘donor cause of death’, ‘donor age’, ‘shipping of the graft’, ‘splitting technique’, ‘complications portal vein’, ‘complications infections’, ‘complications rejection’, ‘recode segment IV’, ‘primary disease: acute liver failure[13]’.

In contrary to the previous variables, significant associations with the variable ‘graft loss’ were certainly reported. In this way the variable ‘infections before transplantation’ showed a significant association with ‘graft loss’, established by a p-value of 0,014. This was also the case for the variable ‘complications biliary’ which demonstrated its association by a p-value of 0,013 and for the variable ‘complications cholangitis’ with a p-value of 0,026. To end off the analysis with the variable ‘graft loss’, another significant association was found for the variable ‘alive’, where the p-value amounted to 0,047.

Besides possible significant associations, another way of assessing the variables is by their difference for the mean between the patients with and without ‘graft loss’. In between this last subdivision, no significant difference for the mean has been documented for the following ERG variables: ‘age‘, ‘donor ETDRI’, ‘BMI’, ‘donor sodium’, ‘donor ALT’, ‘donor AST’, ‘donor intensive care unit’, ‘donor BMI’, ‘donor age’ and ‘MELD at transplantation’.
Significant difference for the mean has been discovered for the variable ‘graft warm ischemia time’ between the patients with and without graft loss. The latter was statistically proven through its associated p-value of 0,002 and featured warm ischemia times twice as long for the patients with graft loss compared to the patients without.

[13] Acute Liver Failure

In terms of graft loss once more the rejection and retransplantation can be assessed. However no significant association could be determined between the variables ‘donor age’ and ‘complications rejection’. Also the variables ‘arterial complications’ and ‘retransplantation’ did not show any significant association what so ever.

Table 7. p-values calculated by statistical analyses

Significances	**p-value**
Graft loss	
Infections before transplantation	**0,018**
Complications: biliary	**0,004**
Complications: cholangitis	**0,026**
Status: alive	**0,018**
Warm ischemia time	**0,009**

7.3.2.2 Determinants Status

No significant associations with the variable ‘status’ were found for the following subjected variables: ‘donor age’ and ‘primary disease: Acute Liver Failure’.

7.3.2.3 Determinants complications

No significant associations with the variable ‘complications arterial’ were found for the following subjected variables: ‘donor age’.

7.3.3 Analyses of risk factors affecting patient and graft survival

7.3.3.1 Survival distributions compared by log-rank tests

Statistical analysis of patient and graft survival was performed using the Kaplan-Meier estimator. The continuous variables used for the analysis (donor age, donor ET-DRI , MELD lab and cold ischemia time) were converted to categorical variables by determining cut-off values by using the receiver operating characteristic curves (ROC curves). The most appropriate cut-off values have been selected by maximizing both sensitivity and specificity. This corresponds to the point on the

ROC curve where both sensitivity and specificity are chosen to be equal. Kaplan-Meier curves of both the patient and graft survival were compared between donor age, donor ET-DRI, MELD lab at liver transplantation and cold ischemia time. To compare the survival distributions the log-rank test was indicated. At univariate analysis, no significant effects of donor age, donor ET-DRI, MELD lab at liver transplantation and cold ischemia time on patient and graft survival was observed.

Table 8. Cut-off values of the continuous variables used in the log-rank tests and the probability values (p-values) calculated by the log-rank test.

Continuous variable	Cut-off value	p-values patient survival	p-values graft survival
Donor age	40 years (≤40 years vs. >40 years)	0.825	0.823
Donor ET-DRI	1,89 (≤1,89 vs. >1,89)	0.860	0.852
MELD lab at liver transplantation ccc	25 (≤25 vs. >25)	0.804	0.821
Cold ischemia time	600 minutes (≤600 min. vs. >600 min.)	0.663	0.473

7.3.3.2 Cox regression

The cox's model was used to evaluate the effect of both donor and patient variables on the patient and graft survival by using the forward method. Increasing risk of mortality was associated with donor BMI >25 (HR= 1.42).

Table 9. Predictors of patient survival in the fitted Cox model (HR: hazard ratio and CI:confidence interval).

Variable	HR (95 % CI)	p-value
Donor age (≤40 years vs. >40 years)	1.13 (0.59, 2.09)	0.351
Donor ET-DRI (≤1,89 vs. >1,89)	0.63 (0.23, 1.96)	0.830

MELD lab at liver transplantation (≤25 vs. >25)	1.07 (0.42, 2.21)	0.355
Cold ischemia time (≤600 min. vs. >600 min.)	0.71 (0.32, 2.03)	0.824
Donor BMI (≤25 vs. >25)	1.42 (1.13, 1.57)	**0.046**

Table 10. Predictors of graft survival in the fitted Cox model (HR: hazard ratio and CI:confidence interval).

Variable	**HR (95 % CI)**	**p-value**
Donor age (≤40 years vs. >40 years)	0.55 (0.17, 1.91)	0.868
Donor ET-DRI (≤1,89 vs. >1,89)	0.71 (0.21, 2.06)	0.784
MELD lab at liver transplantation (≤25 vs. >25)	0.61 (0.13, 1.84)	0.881
Cold ischemia time (≤600 min. vs. >600 min.)	0.67 (0.20, 2.12)	0.827
Donor BMI (≤25 vs. >25)	0.94 (0.38,1.95)	0.433

7.4 Outcome of the coupled patients

This section debates the 22 patients, assumed as 11 paired recipients in which each couple shares an organ from the same donor. This population provides the possibility to look at the outcome of two different transplants originated from one donor graft.

In this way both the outcomes of the paired patients will be assessed as one result, dividing the paired patients study population in 4 groups accessible for descriptive analysis. Each group gets characterized by the graft outcome for each patient, which can either be success (S) or failure (F). Descriptive evaluation of the characteristic variables for each different group may reflect the the outcome of the groups. In the tables below an illustration of the implemented descriptive analysis, with focus on the most interesting variables, is given for each of the 4 created groups. Because of the missing outcome of 1 patient, one couple was disregarded and the final amount of participating couples was set on ten.

This analysis resulted in the observation that at first glance more graft loss occurred when the donor presents with a young age or a high GGT value.

Table 11. characteristic variables for the different groups.

Outcome respectively for LLG and ERG	SS	SF	FS	FF
Number of corresponding couples	4	4	2	0
Donor				
Age median (Q1-3)	36 (21,3-42,5)	24 (20,3-36,8)	19 (9-missing)	
BMI median (Q1-3)	23 (21,7-26,8)	22 (20,3-26,6)	21,2 (15,3-missing)	
Intensive Care Unit[14] median (Q1- 3)	3,5 (2-7,3)	1,5 (1 - 2,75)	4,5 (1-missing)	
GGT median (Q1-3)	54,5 (22,5- 98,5)	20,5 (14,5-43,3)	118 (12-missing)	
ET-DRI median (Q1-3)	1,86 (1,8-2)	1,7 (1,5-miss)	1,7 (missing)	

8. Discussion

The procedure of split liver transplantation encounters much resistance. In practically every article we analyzed, there's a restrained questioning of the procedure with certain skepticism, especially around the use of the extended right graft. Every innovative intervention should undergo a process in which it is evaluated in a critical way. Nevertheless the potential groundbreaking intervention should not be obstructed from a decent chance of showing its capacity. Although its relevance, only few major clinical studies were conducted to evaluate the outcome. Therefore the knowledge and conclusions are often based on the analysis of small populations within single centers (10, 15, 16).

[14] The 'intensive care unit' variable addresses the number of days a donor stayed in intensive care

During the introduction an extensive description of SLT found place in which information was substantiated by multiple charts, open for discussion.
Assessing the frequency of splitting, observations show a widely adopted technique across Europe. However percentages of SLT are still limited and show noticeable regional variations. Evaluating the prevalence as well in the ET region as in Belgium, the numbers teach us a trend, which can't be described as positive. Especially in Belgium we observe a rather irregular pattern with not even a single SLT in the year 2012.
Looking at the period starting from the first ever executed SLT in 1988 until the year 2017, a proportional higher yearly splitting frequency was reported. This period includes the 'pre-MELD era' which was known for its higher splitting prevalence, partly explained by the absence of a policy of highest priority allocation (MELD). The reason for the negative impact of the MELD score on the prevalence is the situation in which the reallocation of an unused split graft arises, after focusing on the highest priority patient only. This resulted in a lower motivation to perform SLT during the MELD era. The previous observation gets confirmed by multiple study results where they describe even a greater reluctance for executing SLT under the MELD era (3, 4, 15, 18).
The restricted use of the technique was also displayed by the pie chart, showing the minor proportion of SLT towards other liver transplant techniques.

Once more it has to be said that the limited study population, because of the 'opting-in' GDPR legislation as well as the frequently missing data, did not favor the potential statistical significant findings.

Both the patient and graft survival are lower in the ERG study population compared to the patient and graft survival of the LLG study population. More graft failure occured in the adult population. The retransplantation rate of the ERG population is 23.07 % whereas the retransplantation rate of the LLG population is 16.67 %.Therefore the hypothesis of saving children at the expense of adults cannot be excluded. Moreover, the split liver transplantation is a technically demanding procedure characterized by the potentially increased risk of complications. Those are arguments in which the procedure of splitting a liver should be centralized in one transplantation center using a well-defined allocation policy. Centralization of the expertise seems necessary to promote and optimize the technique (3, 20, 31-33).

The relation between the MELD score and the ET-DRI was presented by the bar charts. These charts reflected the observations we made in the demographic tables. Interesting in the LLG group

was the majority of high MELD scores (25-34) corresponding with the lowest observed ET-DRI. These high MELD scores for the pediatric participants possibly reflect the urgency of a pediatric procedure and declares the rather low associated ET-DRI representing grafts primarily allocated to children in need. This emphasizes once more the hypothesis of the treatment of the pediatric population at the expense of the adults.
Apart from the descriptive comments, no significant relation has been observed. The latter can possibly be attributed to the limited participants due to missing values concerning the MELD scores and/or the ET-DRI.

An extensive analysis has been carried out for each of the qualified LLG variables in order to investigate the possible relation with one of the outcome variables. Starting with assessing the potential 'graft loss' associations, it was not possible to determine significant results. This observation can be explained by the amount of participants, since multiple participants would increase the probability of correct statistical interpretations. Although the small amount of participants one should not minimize the fantastic outcomes of the pediatric study population, which forms another reason why it was hard to find significant associations between risk factors and outcome (4, 25).
In proportion to the amount of participants in both investigated groups, the LLG study population was characterized by patients corresponding with the highest MELD scores (25 - 34) associated with low ET-DRI values (1,4 - 1,59). This observation gets confirmed by several articles describing the ET-DRI decreases as MELD at transplant increases, citing an important section of the donor-recipient match (11).

Important improvements in the splitting procedure have been achieved by excluding the recipients with high MELD scores and by keeping the CIT's low. Furthermore the introduction of the in situ splitting technique led to major improvements. Hereby the best outcome is achieved by reducing the ischemia time and by developing a careful selection procedure both for donors and recipients (10, 23, 33). The importance of the ischemia time was confirmed by our statistical analysis. Comparing the survival distributions using the log-rank tests led to a significant finding of the cold ischemia time (CIT) in the LLG study population. In the fitted COX model a CIT >660 min. was associated with a greater risk of graft failure. To conclude a CIT higher than 660 minutes is associated with a higher risk of graft failure confirmed by both the univariate and multivariate analysis. Besides patients of the ERG population complicated by graft loss were characterized by warm ischemia time (WIT) twice as long compared to patients without the complication of graft

loss. The prolonged WIT may reflect the difficult implantation of the liver graft in the recipient. Regarding this observation, the importance of both the CIT and WIT can't be denied and the shortening should be considered as an important aim in order to provide better outcomes for the patients obtaining a left lateral graft and an extended right graft. At multivariate analysis a donor BMI >25 was associated with an increased risk of mortality in the ERG study population. This finding may reflect the use of steatotic grafts. Because of the growing number of patients on the waiting list and the organ shortage more marginal liver grafts are used. Graft steatosis is seen as an adverse effect on the graft quality (2, 3, 24, 26).
When assessing other outcome variables such as the patient's 'status' and 'complications: arterial', no significant risk factors could be determined. This contrasts the consulted articles since variables as 'donor age' by example, is seen as an important donor risk factor (4, 11, 18, 22-24, 32-34).

Little statistical significances with the variable 'graft loss' could be detected, more specific for the variables 'infections before transplantation', complications biliary' and 'complications cholangitis'. Resulting in the determination of infections before SLT, biliary complications and cholangitis after SLT as recipient risk factors for our study population. These observations are well described in the literature.For the other potential risk factors no significant results were obtained in our study.
The other outcome variables: 'status' and 'complications: arterial' did not show any relevant results with recipient factors this time either.
Our coupled study population provided the determination of possible donor factors related to unfavorable outcomes. The limited corresponding couples for each group made it very difficult to draw conclusions from this analysis, neither did it allow any further analysis for significances.
Despite the foregoing, the descriptive analysis resulted in the observation of two possible donor risk factors, since they were associated with a decreased graft outcome for one of the two grafts. These donor factors are the determination of a young donor age and an elevated GGT value, both confirmed by the literature (4, 9). This restricted analysis was added to show the attempt we made to pursue an extensive analysis and to show the potential of such analysis. A larger study population, characterized by numerous participants for each of the 4 groups, may give innovative insights in the donor risk profile.

9. Shortcomes

One of the obstacles during our study was dealing with the new General Data Protection Regulation (GDPR) legislation. The protection of the patients data is a duty of the government and its medical institutions. Nevertheless the strict interpretation of the new legislation by the UZ Gent has a strong impact on the course of experimental research. Every patient fulfilling the inclusion criteria must explicitly give their consent in order to get access to their medical related data. Through the use of this 'opting-in procedure', we were unable to include all patients in the study. As a result, we only obtained a limited study population of 42 patients while at first the aim was to include over a hundred participants. In this way obtaining significant findings became more difficult in the statistical analysis.

When processing the scientific literature, concerning the outcome of split liver transplantations, it became clear that a limited amount of studies assessing the outcome of extended right and left lateral grafts has been conducted yet. Most of the literature makes a comparison between whole liver transplantation and split liver transplantation, causing rather limited sources to compare our study results. Within our attempt to carry out the desired study model, lots of interesting variables were disregarded because of their widespread answer possibilities, making it even after compression impossible to perform statistical analyses on the collected data. As a matter of fact this is a reflection of our limited study population.

10. Conclusion

Split liver transplantation has known an important evolution over the years. Starting from an experimental intervention the procedure evolved to a widely accepted treatment for both adults and children, suffering from end-stage liver disease. Not only it provided a possibility to reduce the mortality rate on the waiting list significantly for pediatric patients, also it has served as a driving force to develop alternative treatments, in order to encounter the treatment gap. Equal outcomes for SLT, compared to conservative interventions, can be seen when respecting the procedure's conditions. These conditions can be summarized by the strict donor selection criteria, the donor-recipient match, the sufficient technical expertise and adequate logistics to shorten the cold ischemia time. Only if the latter conditions are met, equal outcomes for SLT, compared to conservative interventions, can be seen.
Nevertheless the split procedure only represents a minor part of the liver transplant techniques during the years 2007-2017. In this 10-years period the split activities have proportionally contributed in a very limited way when compared to the SLT prevalence of the past, permitting us to describe a negative trend in SLT prevalence. These current numbers can be seen as a reflection of the MELD policy introduction, since the highest priority allocation results in a lower motivation to perform SLT .

The goal of this work was to create a representative sample of the population, providing the execution of an extensive multicentric analysis resulting in the procurement of reliable results. Even though we were not able to include all the desired participants, some interesting results have been observed and compared towards the literature.

Both the patient and graft survival are lower in the ERG study population compared to the patient and graft survival of the LLG study population. More graft failure occured in the adult population.
For the LLG study population a CIT >660 minutes was significant associated with an increased risk of graft failure confirmed by both the univariate and multivariate analysis. The ERG study population was characterized by significant higher recurrences of graft loss for participants with infections before the transplantation, patients confronted with biliary and/or cholangitis related complications and for grafts featuring a prolonged WIT. These warm ischemia times were twice as long for the patients with graft loss, reflecting a difficult implantation of the graft, compared to the patients without graft loss. Concerning the patient survival a significant effect of the donor's

BMI was perceived. A donor BMI >25 was associated with an increased risk of mortality in the ERG study population.
The described risk factors, associated with potential unfavorable outcomes, form a great addition and confirmation to the exclusion criteria which are described yet. This takes us closer towards an ideal donor-recipient model. Study models of this kind should be encouraged on bigger scale study population.

Split liver transplantation has proved to yield comparable results to whole liver transplantation when respecting the splitting conditions. Therefore this procedure should be encouraged whenever possible since it provides the treatment of two patients in need for an organ.
Although the very limited respond to the attempts made to stimulate the use of the procedure, it is indispensable to keep promoting SLT, as it forms a more than helpful therapy in times of increasing patients on the waiting list.

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12. Appendix

12.1 Abbreviations used in the work

Abbreviation	**Meaning**
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CIT	Cold ischemia time

DRM	Donor-recipient model
ECD	Extended criteria donor
ERG	Extended right graft
ET	Eurotransplant
ET-DRI	Eurotransplant donor risk index
FHF	Fulminant hepatic failure
Fig.	Figure
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyltransferase
HCC	Hepatocellular carcinoma
ICU	Intensive care unit
LLG	Left lateral graft
LT	Liver transplantation
MELD	Model for End-Stage Liver Disease
OSO	Organ sharing organization
PNF	Primary non function
SE MELD	Standard exceptional MELD
SLT	Split liver transplantation

sRRI	Simplified recipient risk index
UNOS	United Network for Organ Sharing
WIT	Warm ischemia time
WLT	Whole liver transplantation

12.2 List of diseases in which the standard exceptional MELD is applied

The standard exceptional MELD is used in the following diseases:

1. Biliary atresia
2. Hepatocellular carcinoma (HCC)
3. Non-metastatic hepatoblastoma
4. Cystic fibrosis
5. Familial amyloidotic polyneuropathy
6. Primary hyperoxaluria type 1
7. Polycystic liver disease
8. Urea-cycle disorder/organic acidemia
9. Hepatopulmonary syndrome
10. Portopulmonary hypertension
11. Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber-Syndrome)
12. Hepatic hemangioendothelioma
13. Persistent hepatic dysfunction (including small for size syndrome) with indication for retransplantation. This SE replaces the current SE “small for size syndrome”.

12.3 Log-rank tests LLG study population

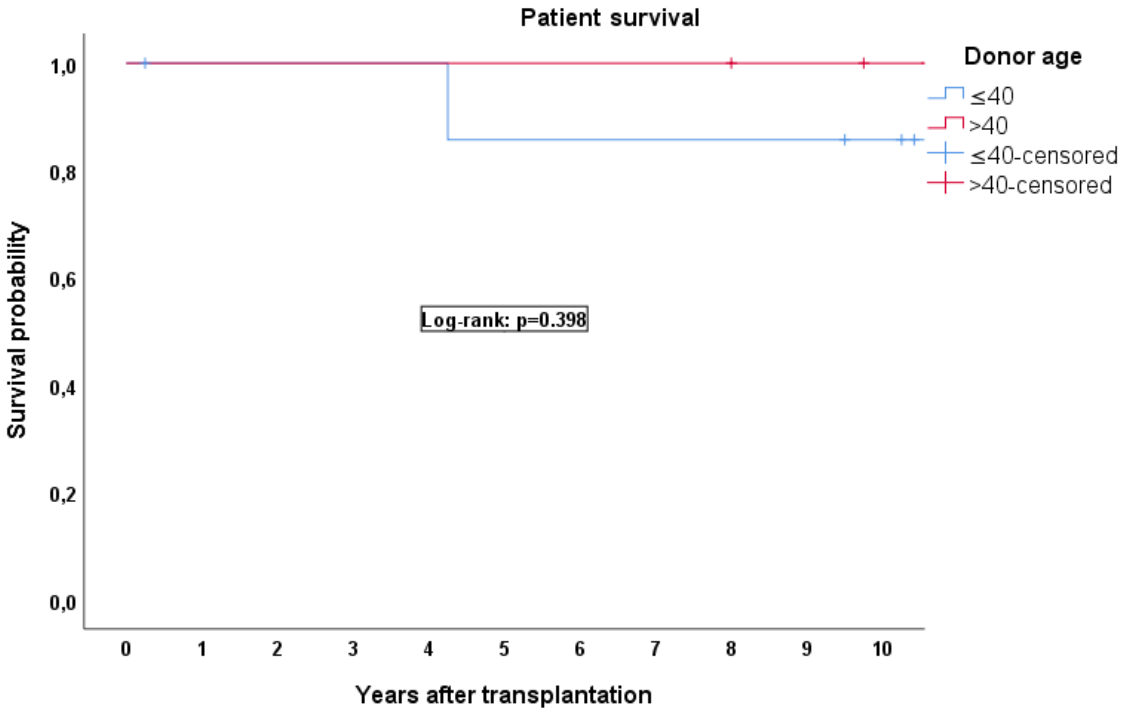

Fig.14. Left split patient survival according to donor age.

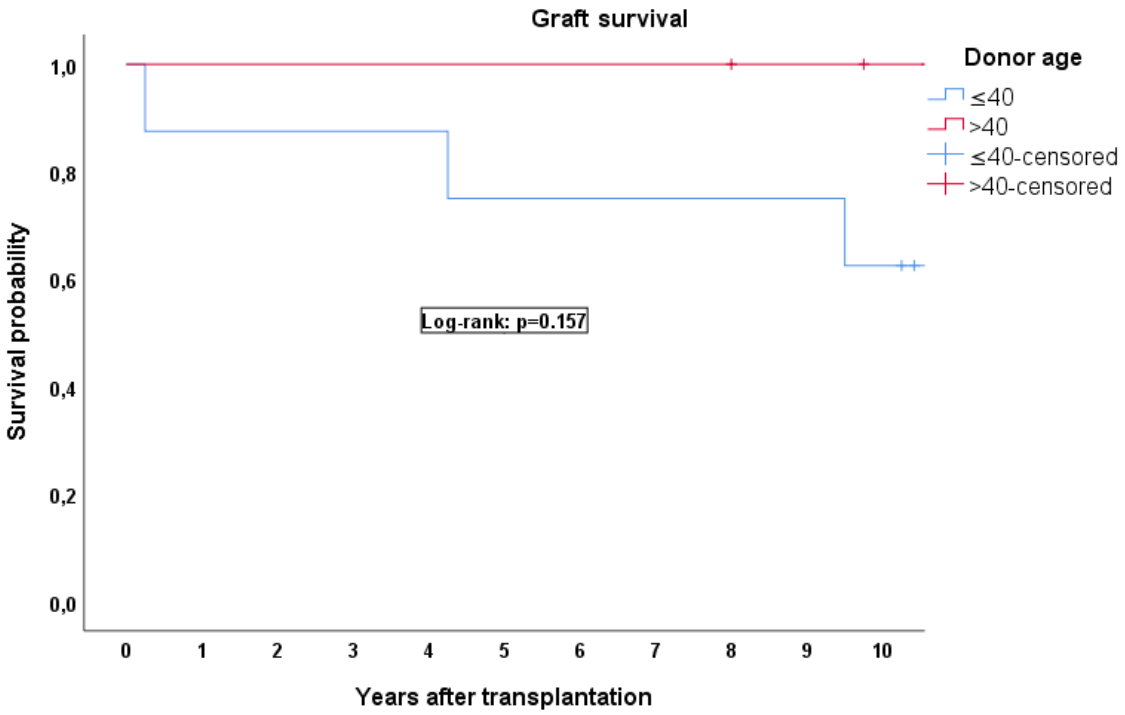

Fig.15. Left split graft survival according to donor age.

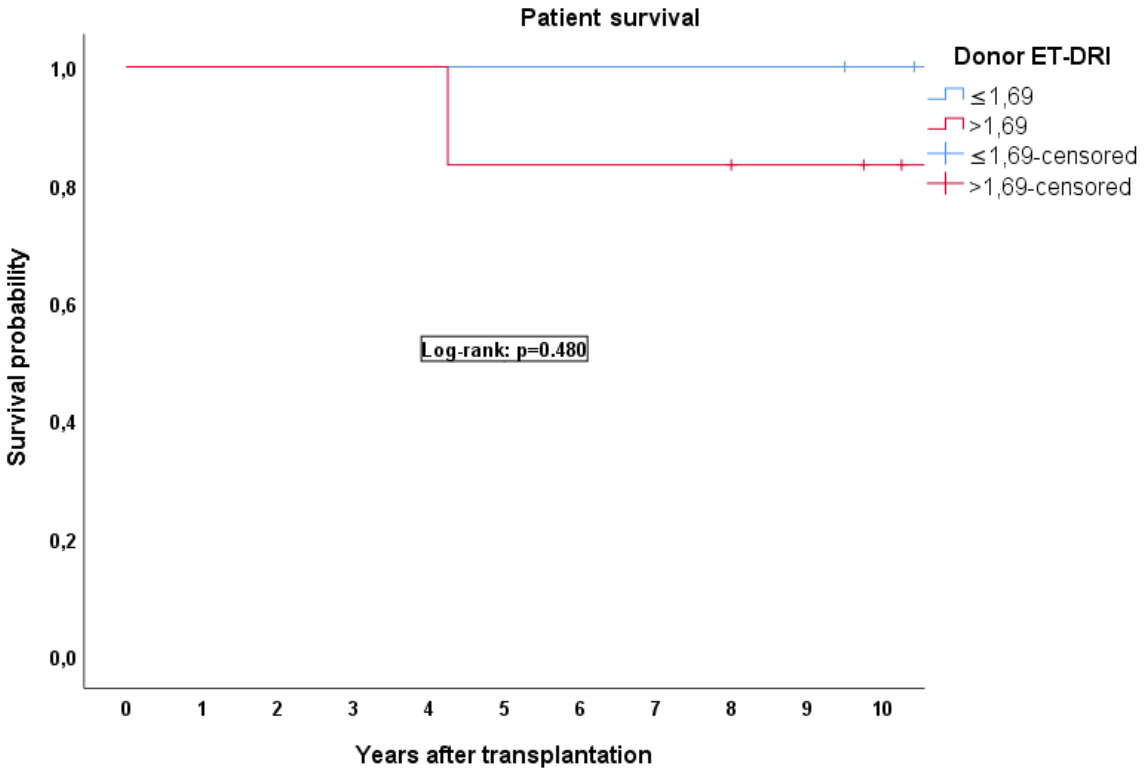

Fig.16. Left split patient survival according to donor ET-DRI.

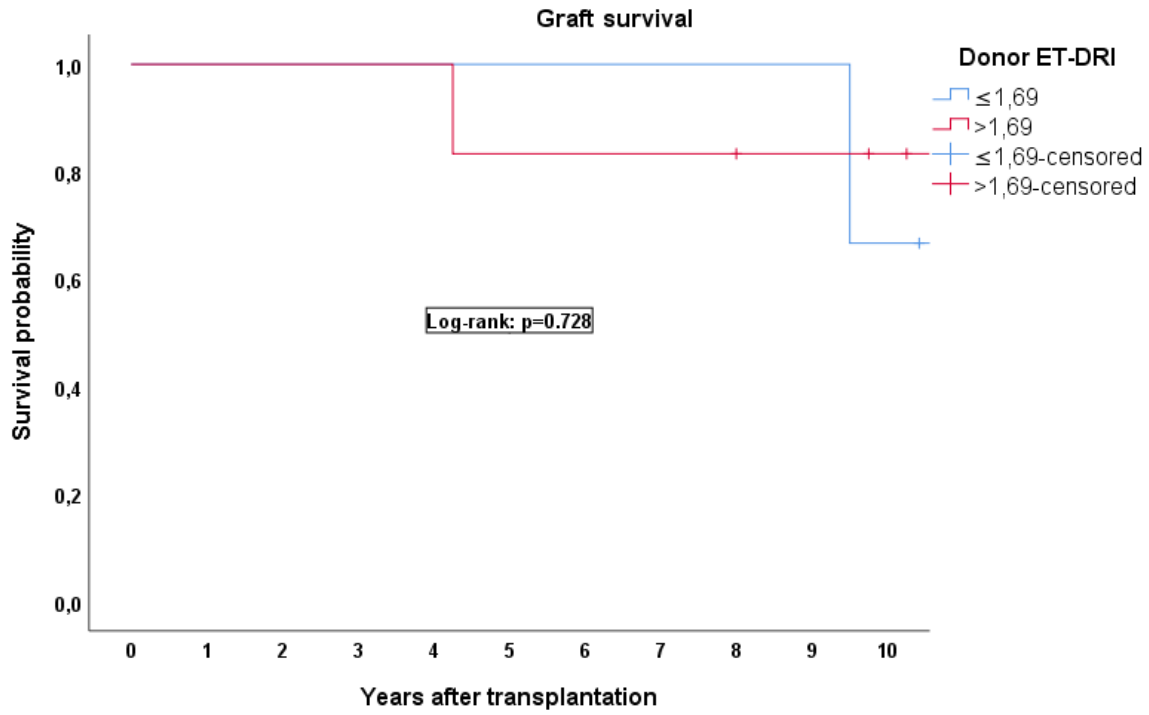

Fig.17. Left split graft survival according to donor ET-DRI.

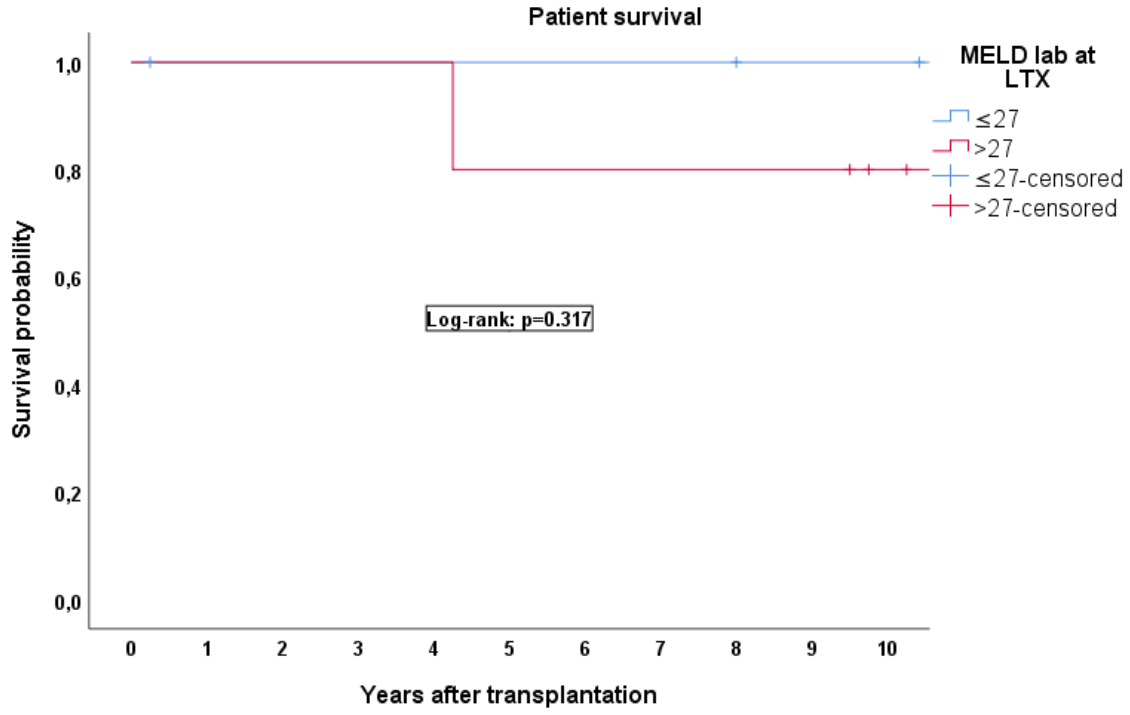

Fig.18. Left split patient survival according to MELD score.

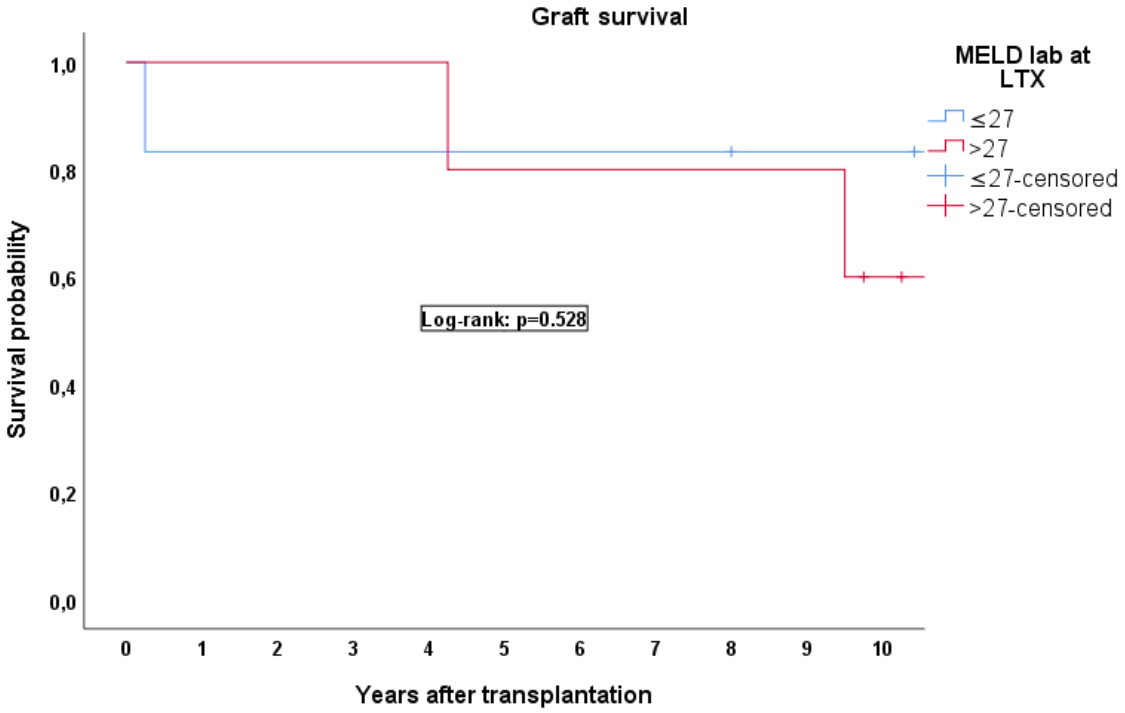

Fig.19. Left split graft survival according to MELD score.

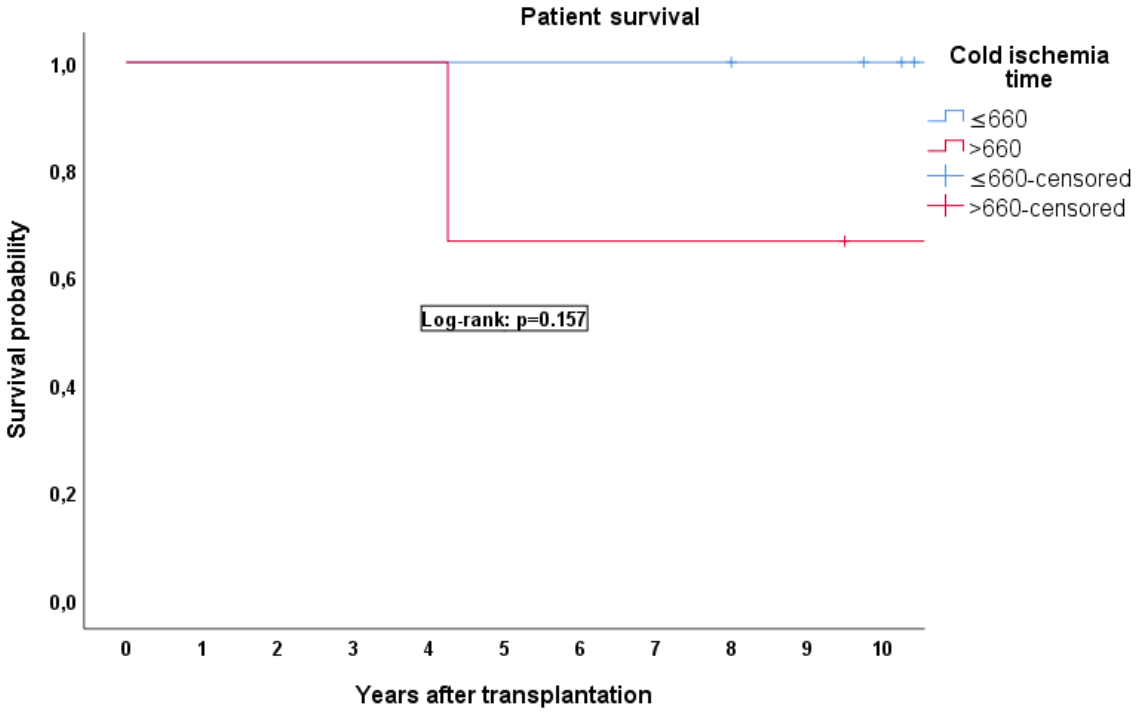

Fig.20. Left split patient survival according to CIT.

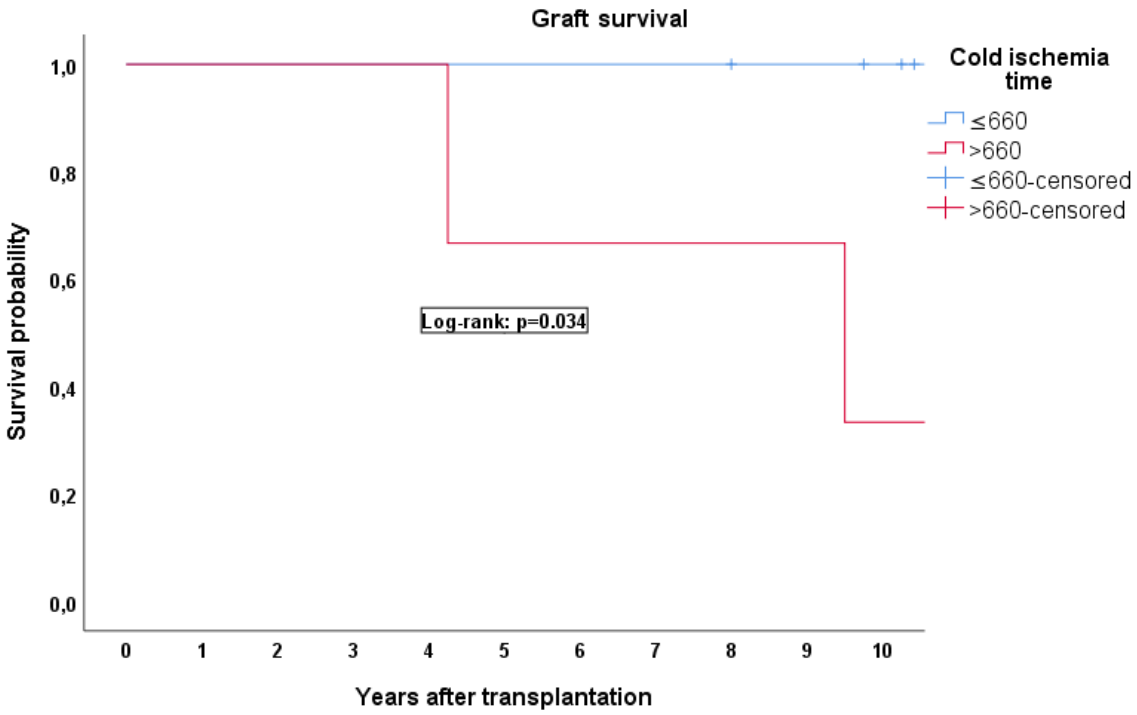

Fig.21. Left split graft survival according to CIT.

12.4 Log-rank tests ERG study population

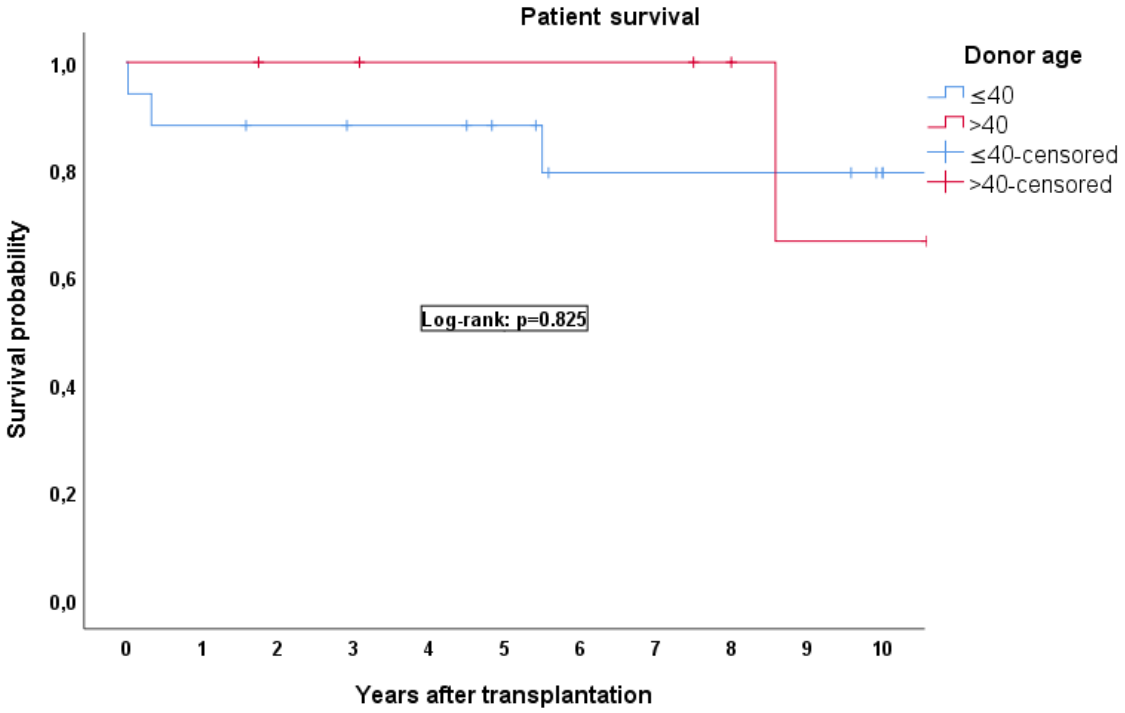

Fig.23. Right split patient survival according to donor age.

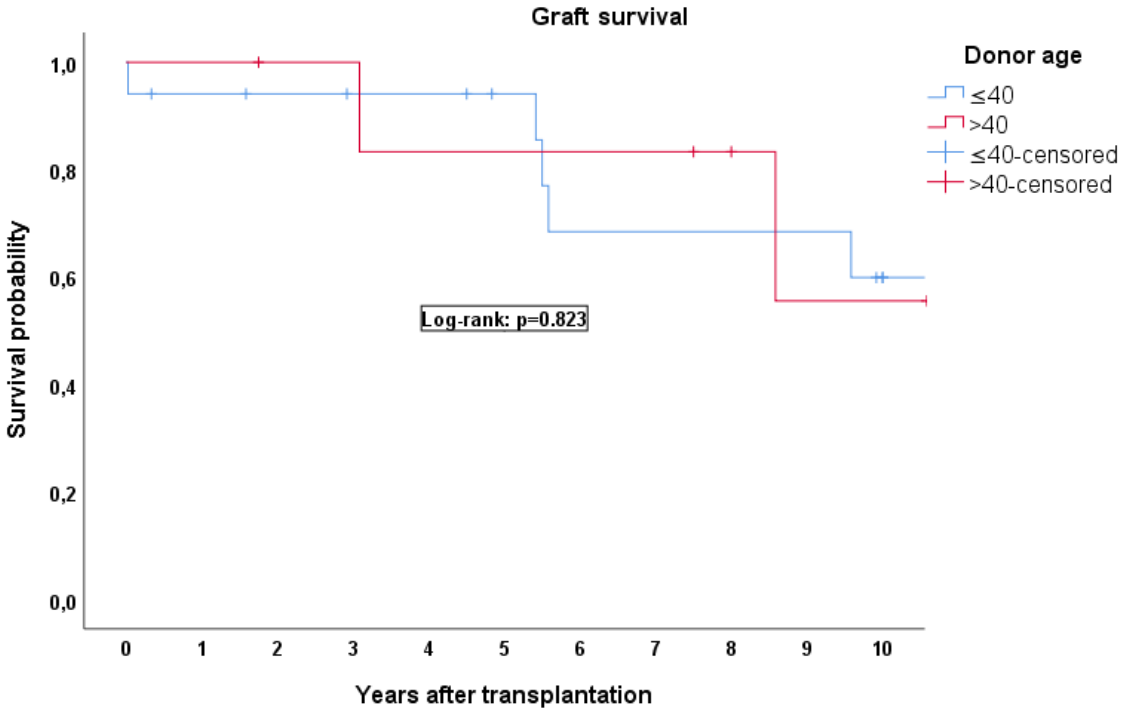

Fig.24. Right split graft survival according to donor age.

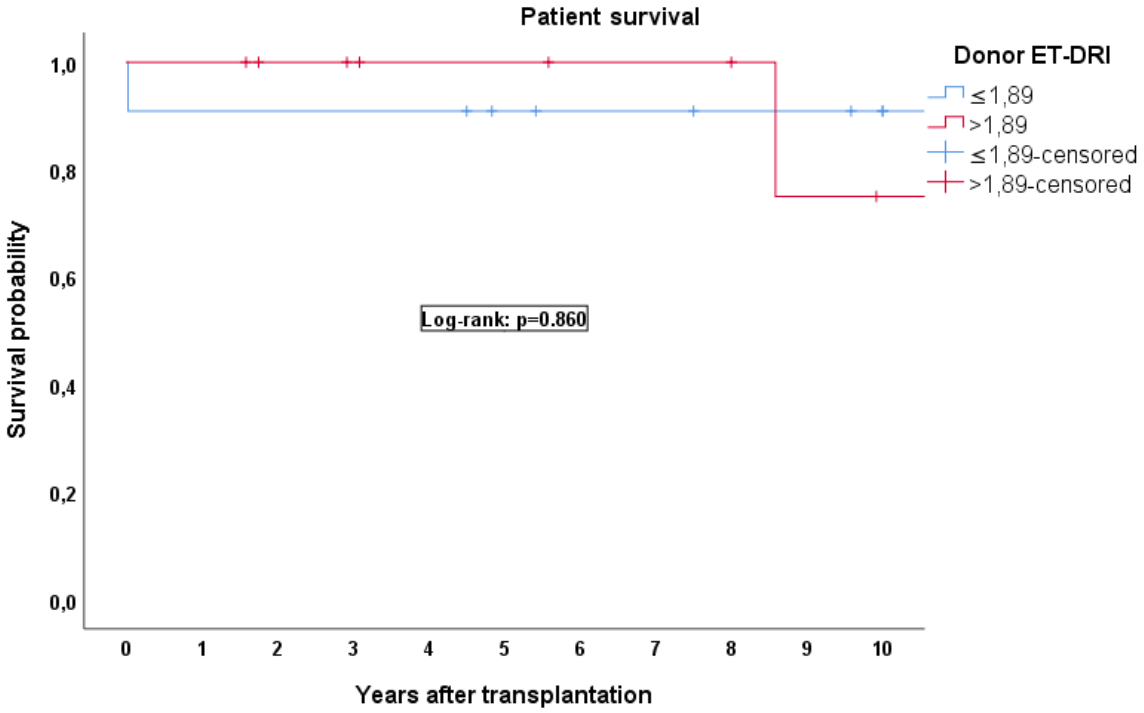

Fig.25. Right split patient survival according to donor ET-DRI.

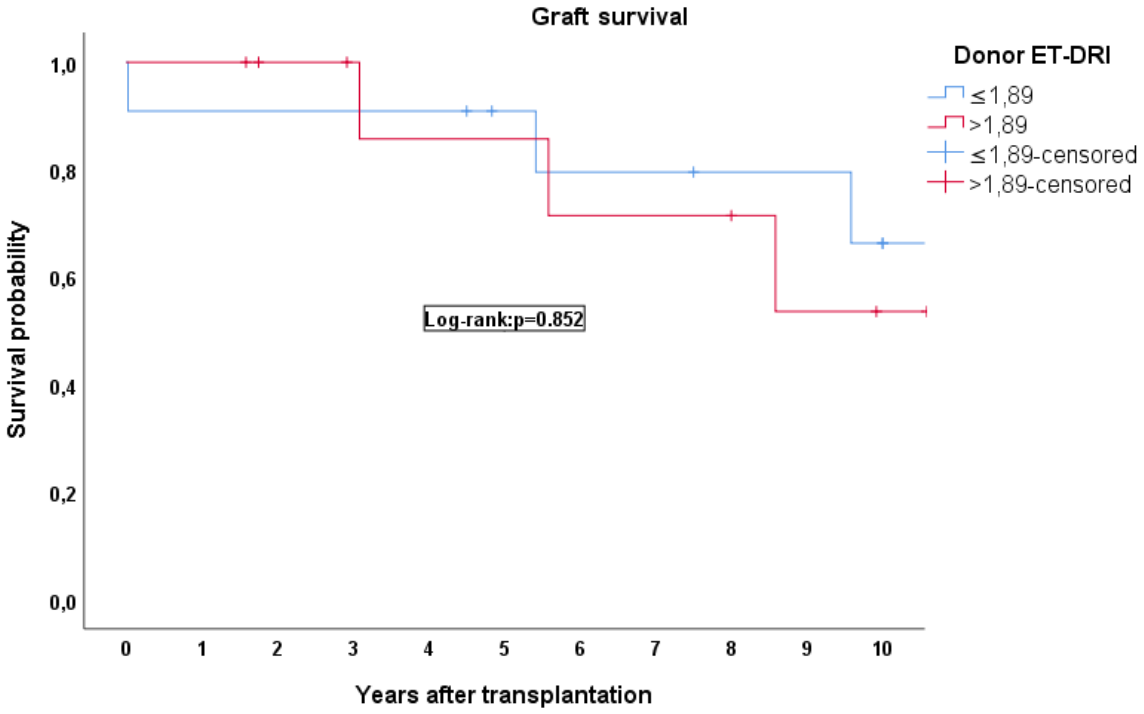

Fig.26. Right split graft survival according to donor ET-DRI.

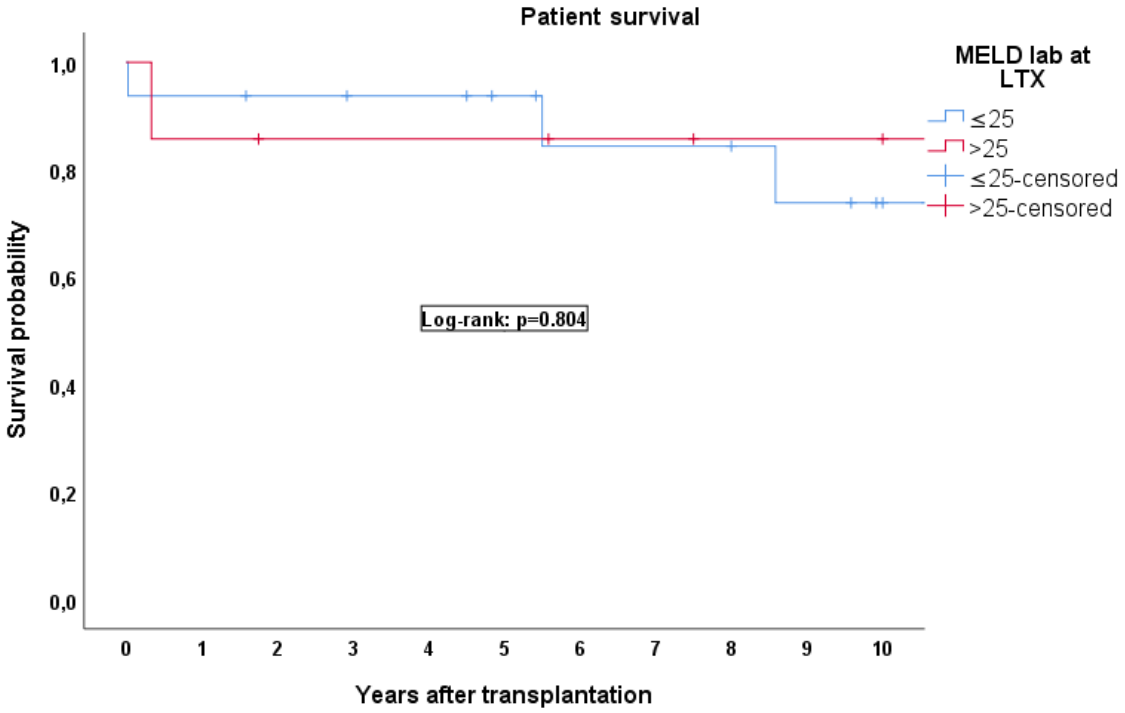

Fig.27. Right split patient survival according to MELD score.

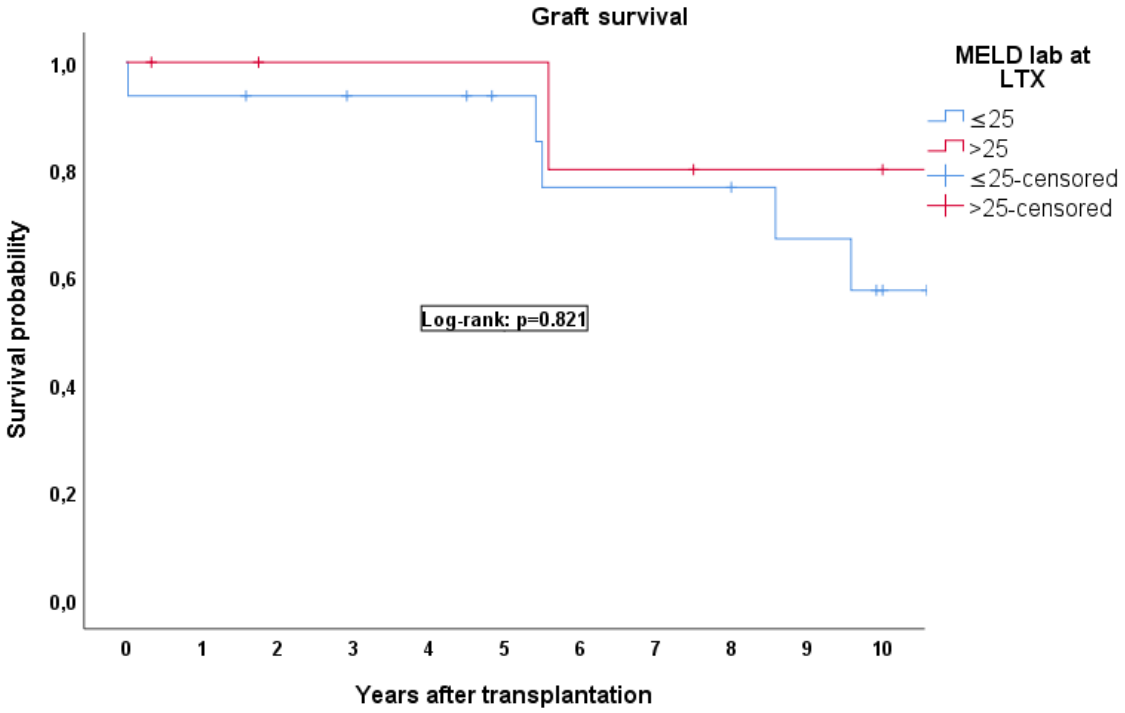

Fig.28. Right split graft survival according to MELD score.

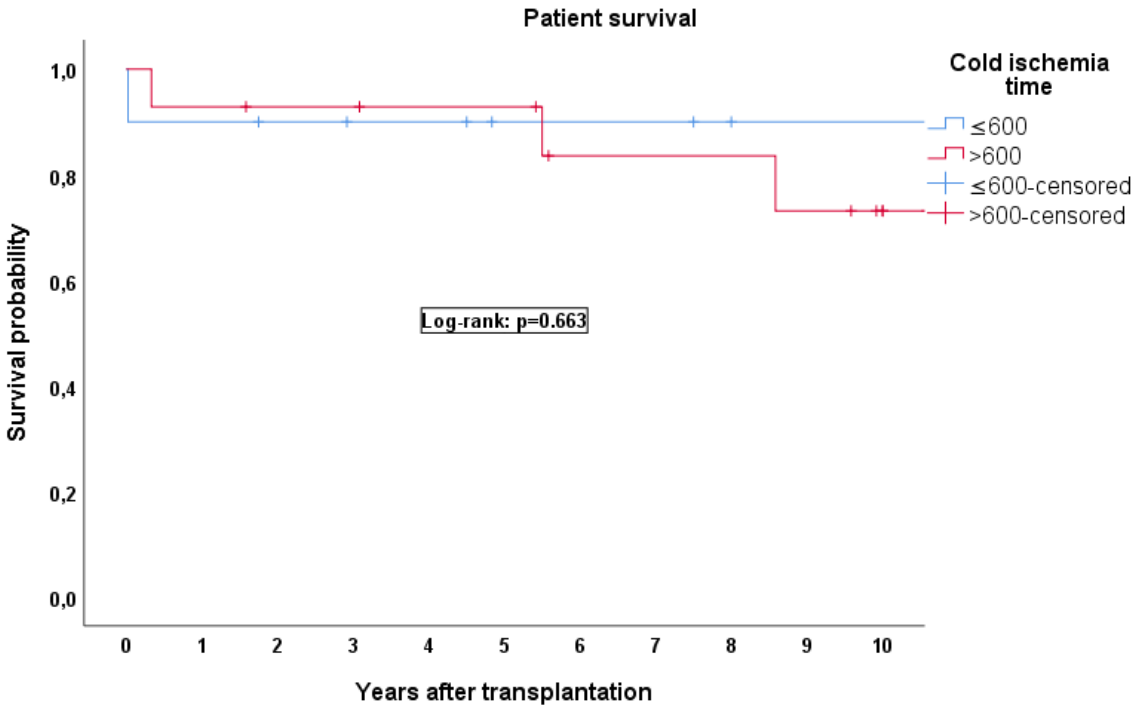

Fig.29. Right split patient survival according to CIT.

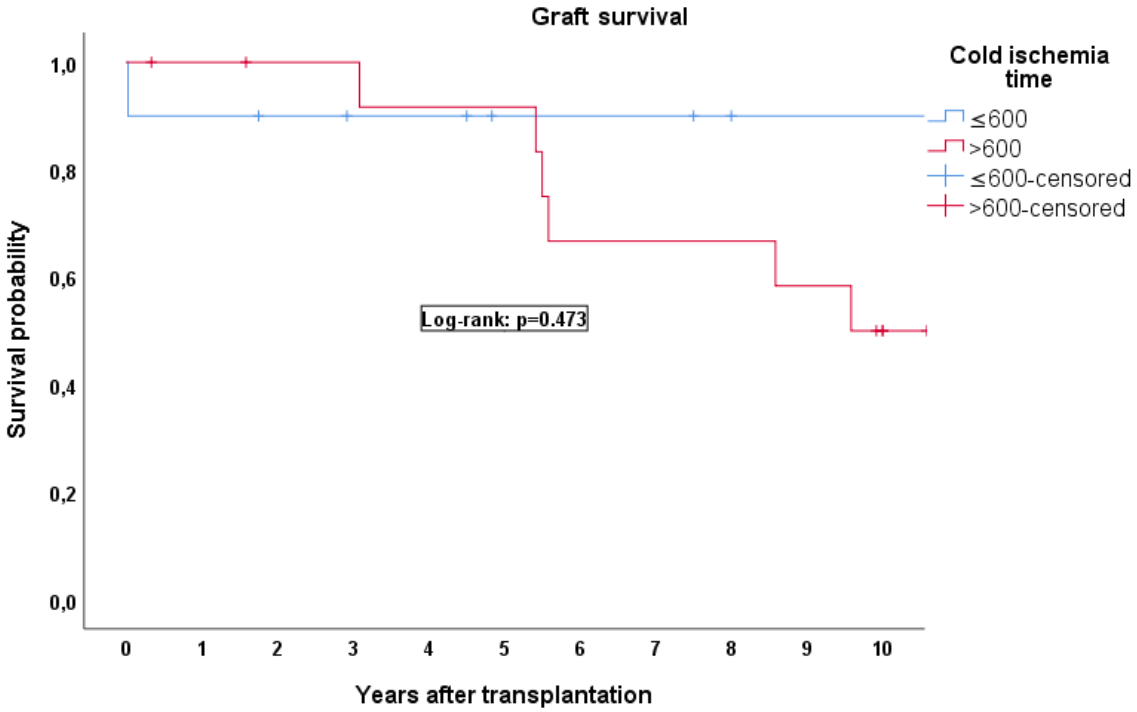

Fig.30. Right split graft survival according to CIT.

12.5 Abstract in Dutch

Achtergrond: Split lever transplantatie maakt het mogelijk om 2 patiënten te behandelen in plaats van 1 patiënt in vergelijking met de conservatieve therapie. Het delen van de lever resulteert in een links lateraal transplantaat (segmenten II en III) en een uitgebreid rechter transplantaat (segmenten I, IV-VIII). Het linker deel wordt getransplanteerd in een kind terwijl het rechter deel getransplanteerd wordt in een volwassen persoon. Deze techniek werd ontwikkeld omwille van de toenemende discrepantie tussen het aantal organen en de vraag naar deze organen. Dit resulteerde in een toename van de wachtlijst en bijgevolg een toename van de mortaliteit. Bijgevolg ontwikkelden de chirurgen innovatieve methoden om op een efficiënte manier om te gaan met de beschikbare organen. Het concept van split lever transplantatie is een interessante topic in tijden waar een tekort aan donororganen en een toename van de mortaliteit op de wachtlijst aanwezig zijn. Bovendien werd meermaals geijverd voor onderzoek, toegepast op uitgebreide databanken omtrent deze techniek. Desalniettemin werd deze procedure onvoldoende onderzocht. Het merendeel van de wetenschappelijke evidentie is gebaseerd op kleinschalige klinische studies.

Doelstellingen: Deze studie tracht het proces geassocieerd met de pediatrische en volwassenen patiënten die een split lever transplantatie ondergingen te onderzoeken. De studie includeert de hersendode donoren gedurende de laatste decade wanneer het MELD allocatie beleid werd ingevoerd in de Eurotranplant regio. Een uitgebreide analyse werd uitgevoerd voor zowel de variabelen geassocieerd met de links laterale transplantaten als met de uitgebreide rechter transplantaten. Met als doel het bijdragen tot het vinden van een betere donor-recipiënt overeenkomst, een uitgebreide analyse op zowel de donor als recipiënt variabelen is obligaat. Ook de functie van het transplantaat, de postoperatieve complicaties (biliair, vasculair,…) en hun rol in het verlies of de dysfunctie van het transplantaat werden geanalyseerd.

Methoden: Deze retrospectieve multicentrische studie includeerde alle volwassenen en pediatrische patiënten die een split lever transplantatie ondergingen in de periode van januari 2007 tot en met december 2017. De geïncludeerde patiënten dienden te voldoen aan de inclusiecriteria. Ze werden behandeld in één van de drie deelnemende ziekenhuizen in België (Universitair Ziekenhuis Gent, Universitair Ziekenhuis Leuven of Université catholique de Louvain) in de periode van 2007 tot 2017 met ofwel de in situ of ex situ techniek. De exclusiecriteria waren de volgende: split lever transplantatie uitgevoerd met het bekomen van een volledig links en volledig rechts transplantaat en donoren na circulatoire dood. Uiteindelijk werden 42 patiënten betrokken bij de studie waarvan respectievelijk 26 patiënten met een

uitgebreid rechter transplantaat en 16 patiënten met een links lateraal transplantaat. Het verkrijgen en verwerken van de data werd uitgevoerd met het naleven van de GDPR wetgeving (General Data Protection Regulation). In de populatie van 42 patiënten waren 11 ‘koppels’ aanwezig. De term koppels duidt op het feit dat binnen 1 koppel een zelfde donor gedeeld werd.
Resultaten: Significante associaties in zowel de graft als patiënt uitkomst werden geobserveerd. De algehele 10-jaars patiënt en graft overleving zijn respectievelijk 92.3 % en 76.9 % voor de patiënten die een links lateraal transplantaat ontvingen. De algehele 10-jaars patiënt en graft overleving zijn respectievelijk 83.3 % en 66.7 % voor de patiënten die een uitgebreid rechter transplantaat ontvingen. De links laterale transplantaten, gekarakteriseerd door een koude ischemie tijd hoger dan 660 minuten werden geassocieerd met een significant hoger risico op graft verlies. Deze bevinding werd bevestigd door zowel de univariate (p=0.034) als multivariate (p=0.034) analyses. De patiënten die een uitgebreid rechter transplantaat ontvingen toonden in hogere mate verlies van het transplantaat wanneer ze geconfronteerd werden met infectie voor de transplantatie (p=0.018), biliaire complicaties (p=0.004) en/of cholangitis (p=0.026) en wanneer een verlengde warme ischemie tijd aanwezig is (p=0.009). Voor wat betreft de patiënten overleving een significante impact van het BMI van de donor werd geobserveerd. De multivariate analyse (p=0.046) toonde een verhoogd risico van mortaliteit bij een donor BMI >25 in de populatie die een uitgebreid rechter transplantaat ontving. De analyse van de 11 ‘koppels’ leverde informatie op met betrekking tot mogelijke donor factoren gerelateerd aan een ongunstige uitkomst. Deze analyse werd enkel beschrijvend uitgevoerd en kan gezien worden als een aanzet tot het streven naar meer uitgebreide analyses met als doel een ideale donor-recipiënt overeenkomst te vinden.
Conclusie: Split lever transplantatie biedt niet alleen de mogelijkheid tot het reduceren van de mortaliteit op de wachtlijst voor pediatrische patiënten maar dient ook als een drijvende kracht voor de verdere ontwikkeling van alternatieve en innovatieve technieken om de behandelingskloof te dichten. Gelijkaardige uitkomsten tussen de split lever transplantatie en de conventionele lever transplantatie worden gezien op voorwaarde dat de gepaste condities voor de splitprocedure worden nagestreefd en nageleefd. Desalniettemin maakt de splitprocedure slecht een klein percentage uit van de het percentage van de mogelijke lever transplantatietechnieken gedurende de periode van 2007 tot en met 2017. Men kan zelfs spreken van een negatieve trend in de prevalentie sinds de implementatie van het MELD systeem. De significante risicofactoren geassocieerd met de potentiële ongunstige uitkomsten, voortvloeiend uit onze studie, vormen een grote meerwaarde en bevestiging van de exclusie criteria die reeds besproken werden. Dit brengt ons dichter bij een ideaal donor-recipiënt model.

Dergelijke studies dienen gestimuleerd te worden op grotere schaal met het verkrijgen van grotere studiepopulaties. Centralisatie van de expertise in één transplantatiecentrum omtrent deze procedure lijkt noodzakelijk om deze techniek te promoten en te optimaliseren.