KU LEUVEN

FACULTEIT GENEESKUNDE
BIOMEDISCHE WETENSCHAPPEN

Gecombineerde lever-niertransplantaties, resultaten in UZ Leuven

Combined liver-kidney transplantations, outcomes in UZ Leuven

Masterproef voorgedragen tot het behalen van de graad van Master in de biomedische wetenschappen door

Seliene VAN LAER

Promotor: Prof. dr. Ina JOCHMANS
Begeleider: Sofie VETS
Abdominale transplantatiechirurgie en transplantatiecoördinatie

Leuven, 2019-2020

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The preparation and completion of this Master's Thesis partly took place during the period when COVID-19 measures were in effect in Belgium (started on 13 March 2020). Within the framework of the measures taken by KU Leuven, it was not possible to complete the data collection for this Master's Thesis and the processing therefore had to be based on limited results. This aspect needs to be taken into account when consulting this document.

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Preface

A lot of people have supported and assisted me during my thesis year. They deserve a big thank you!

First I would like to thank my promotor Prof. Dr. Ina Jochmans. She believed in me and in my qualities to finish this master thesis. It is a big honor to be part of such an interesting project. She gave me the opportunity and strength to become the scientist I am today.

Next I am pleased to have such a great monitor by my side, Sofie Vets. She was there for me during difficult times and celebrations. With a lot of patience and trust she guided me throughout this year. Even on weekends and late evenings, I could always count on her. She listened to my personal and thesis-related concerns.

Then, the person I shared a desk with this year, my fellow student and friend: Sarah Van Praet. It was a great blessing to experience this journey with her.

From the first day I started at our unit I felt very welcomed by the whole transplant team. I saw and learned a lot of new skills thanks to the enthusiasm and involvement of the team. Everyone was there for me, especially in times when I needed a listening ear. They would always answer my questions with a smile.

Last but not least, I would like to thank my family and friends who supported me during my entire study-period. This year was especially challenging, but via social media I could still feel their warmth and love. In particular my mom and brother deserve a big hug because they took good care of me in these last stressful months.

Seliene Van Laer

Leuven, 2 May 2020.

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List of abbreviations

ACO	Approved combined organ
AKI	Acute kidney injury
ALF	Acute liver failure
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAR	Balance of risk
BMI	Body mass index
CIT	Cold ischemia time
CKD	Chronic kidney disease
CLD	Chronic liver disease
CLKT	Combined liver-kidney transplantation
CVA	Cardiovascular accident
CVVH	Continuous veno-venous hemofiltration
DBD	Donation after brain death
DCD	Donation after circulatory death
DGF	Delayed graft function
DRI	Donor risk index
EAD	Early allograft dysfunction
eGFR	Estimated glomerular filtration rate
FU	Follow-up
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HLA	Human leucocyte antigen
HRS	Hepatorenal syndrome
HU	High urgent
ICU	Intensive care unit
INR	International normalized ratio
IVC	Inferior vena cava
KALT	Kidney after liver transplantation
KDPI	Kidney donor profile index
KDRI	Kidney donor risk index
LAKT	Liver after kidney transplantation
LOS	Length of stay
MEAF	Model for early allograft function
MED	Metabolic / endocrine disease

MELD	Model for end-stage liver disease
M&M	Morbidity & mortality
NASH	Non-alcoholic steatohepatitis
NSE	Non-standard exception
OPTN	Organ Procurement and Transplantation Network
PCLD	Polycystic liver disease
PGD	Primary graft dysfunction
PKD	Polycystic kidney disease
PNF	Primary non function
SE	Standard exception
SVC	Superior vena cava
UNOS	United Network for Organ Sharing
UTI	Urinary tract infection

Abstract

Introduction Combined liver-kidney transplantation (CLKT) is increasingly performed. There is a lack of large CLKT cohorts described in literature and there is no information on the nature of postoperative complications in comparison with liver-only recipients.

Objectives This thesis aims to: (1) describe the UZ Leuven CLKT cohort; (2) compare the post-transplant complication rate and severity of complications of CLKT recipients to liver-only recipients. This was investigated in two studies.

Methods (1) A retrospective study including all adult CLKT patients transplanted in UZ Leuven between 01/01/1997 and 20/12/2019 was conducted. Donor and recipient demographics as well as post-transplant outcomes were summarized for the entire cohort and these were compared for four time eras (1997-2002, 2003-2008, 2009-2014, 2015-2019). (2) A retrospective study of prospectively collected morbidity & mortality (M&M) data of all adult patients receiving a CLKT or a liver-only transplantation between 01/07/2019 and 01/03/2020 was conducted. The existing "M&M tool" to collect complications after a liver-only transplantation was expanded for this purpose. In addition to descriptive analysis of complications in CLKT and liver-only recipients, the incidence and severity (Clavien-Dindo grading) of complications were compared between the two groups.

Results (1) 130 CLKTs were performed in the study period; median follow-up time was five years (2-9). Recipients became older and an increase of transplantations with organs donated after circulatory death (DCD) was observed. Overall patient, liver and kidney graft survival at one, three, five, and ten years were: 92%, 85%, 83% and 67%; 89%, 83%, 81% and 61%; and 91%, 84%, 80% and 55%, respectively. Primary non function rates of liver and kidney were low. Early allograft dysfunction of the liver occurred in 20% of cases, delayed graft function of the kidney in 10%. Kidney function was good with a median estimated glomerular filtration rate at three, six, and 12 months of 58.9 ml/min/1.73m²; 58.2 ml/min/1.73m² and 51.2 ml/min/1.73m², respectively. Liver rejection occurred in 8% of patients, kidney rejection in 21%. Liver cold ischemia time (CIT) decreased in the later time eras, kidney CIT remained stable. Recipients had a significantly longer intensive care unit (ICU) stay in later time eras. (2) Nine CLKT recipients and 36 liver-only recipients were included. CLKT patients suffered from more complications compared to liver-only recipients. The proportion of severe complications and graft-related complications were similar between groups, though CLKT recipients experienced more general and minor complications compared to liver-only recipients. ICU and hospital stay were significantly longer in the CLKT group.

Discussion UZ Leuven patient and graft survival for CLKT is good and comparable to reported outcomes. Short-term organ dysfunction is low to acceptable. These results are obtained despite increasing recipient age and use of DCD donors. In comparison to a temporary cohort of liver-only recipients, CLKT recipients experience more postoperative complications but these are not more serious and not more graft-specific complications. The CLKT population had a considerably longer ICU and hospital stay and needs to be readmitted to ICU and hospital more often than liver-only recipients. Larger datasets are needed to further examine these findings and identify potential areas of improvement.

1. Introduction

Combined liver-kidney transplantation (CLKT) is a life-saving treatment for patients with a combination of end-stage liver and end-stage kidney disease (1). However, there are patients where the indication for CLKT is less clear. This is mostly the case when a pre-emptive transplant of kidney or liver is advised to avoid potential life-threatening complications in the post-transplant period. With the ever-sicker patient population, these types of indications are becoming more frequent. As organ waiting lists are long, the decision to combine multiple organs in one transplantation should be well considered, avoiding transplantations that are unnecessary or futile (1,2). Currently, little is known about the outcomes, morbidity, and mortality of CLKTs in the changing landscape of organ transplantation that is confronted with increasingly older donors with more co-morbidities.

The few studies that have been published in the last 20 years about CLKT, are summarized below and in **Table 1**. According to two single-center retrospective studies the long-term patient and graft survival are comparable between CLKT and liver-only transplantation (1,3). Furthermore, CLKT is a good treatment for patients with both liver and kidney disease (1,3).

In a retrospective study based on United Network for Organ Sharing (UNOS) data, a better patient and graft survival for CLKT than for kidney after liver transplantation (KALT) and liver after kidney transplantation (LAKT) was observed (4). A study on CLKTs for polycystic liver and kidney disease (PCLD/PKD) showed improved outcomes compared to patients with PCLD undergoing liver-only transplantations and to patients undergoing CLKTs due to other indications (5).

The first CLKT in UZ Leuven was performed in 1997. Since then, over 120 patients received a liver and a kidney from the same deceased donor in UZ Leuven. CLKTs represents a substantial part of the liver transplant activity in UZ Leuven. Indeed, in 2018, 8% of all liver transplant patients in UZ Leuven received a CLKT (6). The number of CLKTs has increased over the years and is expected to increase even more in the future. This is due to changing liver transplant indications where patients with concomitant kidney dysfunction are given priority on the waiting list, as their risk of dying is increased (objectified by the model for end-stage liver disease (MELD) score) (7,8). This is illustrated by the fact that today 32% of actively waitlisted liver transplant candidates need a CLKT (UZ Leuven liver transplant waitlist, 09/12/2019).

In order to assess the quality of the CLKT program in UZ Leuven, this master thesis will chart the UZ Leuven CLKT cohort and analyze indications for transplantation as well as morbidity, mortality and graft outcomes. These results will be compared with published data in the literature.

Table 1: *Patient, liver and kidney survival after different types of transplantation and for different indications.*

	Busuttil R. (3)	**Ruiz R.** (1)	**Martin E.** (4)				**Coquillard C.** (5)		
Study period	1984-2001	1988-2004	1988-2007				1988-2013		
Procedure	LTx	CLKT	CLKT	KALT	LAKT	LTx	CLKT: PCLD / PKD	LTx: PCLD	CLKT: other
Number of patients	3200	98	2327	1738	242	66026	107	195	5056
Patient survival (%)									
1 year	81	76	82	33	71	84	91	87	82
3 years	-	72	72	25	61	75	90	82	73
5 years	72	70	64	22	54	68	90	77	67
10 years	68	-	47	15	40	51	-	-	-
15 years	64	-	-	-	-	-	-	-	-
Liver graft survival (%)									
1 year	73	70	80	36	68	80	85	83	80
3 years	-	65	71	31	59	72	84	78	70
5 years	64	65	65	28	53	65	84	73	65
10 years	59	-	50	18	38	51	-	-	-
15 years	55	-	-	-	-	-	-	-	-
Kidney graft survival (%)									
1 year	-	76	-	-	-	-	-	-	-
3 years	-	72	-	-	-	-	-	-	-
5 years	-	70	-	-	-	-	-	-	-

CLKT = combined liver-kidney transplantation, KALT = kidney after liver transplantation, LAKT = liver after kidney transplantation, LTx = liver-only transplantation, PCLD = polycystic liver disease, PKD = polycystic kidney disease, - = not available.

Below a short overview of the anatomy of the liver and the kidney is given, followed by indications for CLKT and allocation methods for these organs, the surgical technique for CLKT as well as several frequent or important complications that may occur after CLKT.

1.1 Liver anatomy, function and indications for transplantation

1.1.1 Anatomy

The liver is located in the right upper abdominal quadrant (right hypochondria) under the rib cage. The liver weighs around 1.5 kg, which makes it the largest internal organ in our body. It consists of four lobes: a right and a left lobe and two smaller central lobes (quadrate and caudate) **(Figure 1)** (9,10). The liver is a very vascular organ, it receives about a quarter of the total cardiac output. The liver has a dual blood supply divided between the hepatic artery and the portal vein. The hepatic artery originates from the aorta and brings oxygenated blood to the liver. It splits into a right and a left artery to deliver blood to both lobes. The portal vein passes first through the intestines, pancreas and spleen, so this blood is less oxygenated but contains mainly nutrition (9,10).

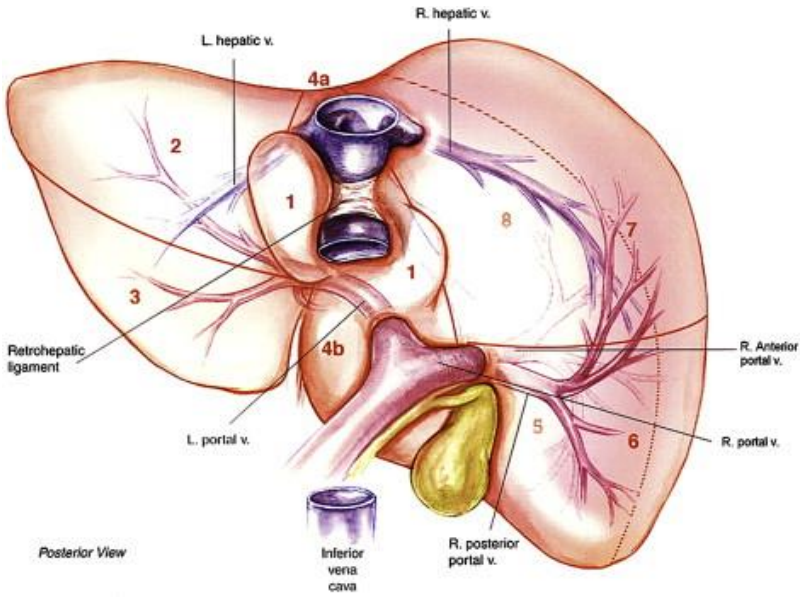


Figure 1: *Anatomy of the liver.*
L. = left, R. = right, v. = vein.
Reproduced with permission from Abdel-Misih and Bloomston 2010, Surgical Clinics of North America, 90(4): 643-53 (9)

The lobule is the structural unit of the liver. Here, the hepatocytes (the most common cells in the liver) are arranged on top of each other in the form of a hexagonal plate. The hepatocytes radiate outwards from a central vein. Going to the periphery, the hepatocytes lay in strips with in between the hepatic sinusoids (a type of capillary bed). At each corner of the lobule a portal canal, hepatic artery and bile duct is located **(Figure 2A)** (11,12).

Besides the hepatocytes, the liver consists of Kupffer cells, hepatic stellate cells, biliary epithelial cells (cholangiocytes) and liver sinusoidal endothelial cells **(Figure 2B)**. Whereas the hepatocytes accomplish many of the metabolic, secretory and endocrine liver functions, the other cells have another important role. Kupffer cells are the macrophage cells from the liver and are essential for the immune defense in the liver. Stellate cells are present in an inactive or in an activated state. In the inactive state they store vitamin A in lipid droplets. When the liver is damaged, the stellate cells are activated, proliferate and lose vitamin A. Stellate cells will accumulate and organize collagen which can develop in fibrosis or cirrhosis. Cholangiocytes have an epithelial function, they surround the lumen of the bile ducts (12,13). They modify the bile produced by the liver and transport it via the bile ducts to the gallbladder. The gallbladder stores and further concentrates bile. This bile is important for the digestion of food (14). Liver sinusoidal endothelial cells form fenestrae at the sinusoidal lumen, which is important for the exchange of proteins and particles and to create a barrier between plasma and the cells of the liver (12,13).

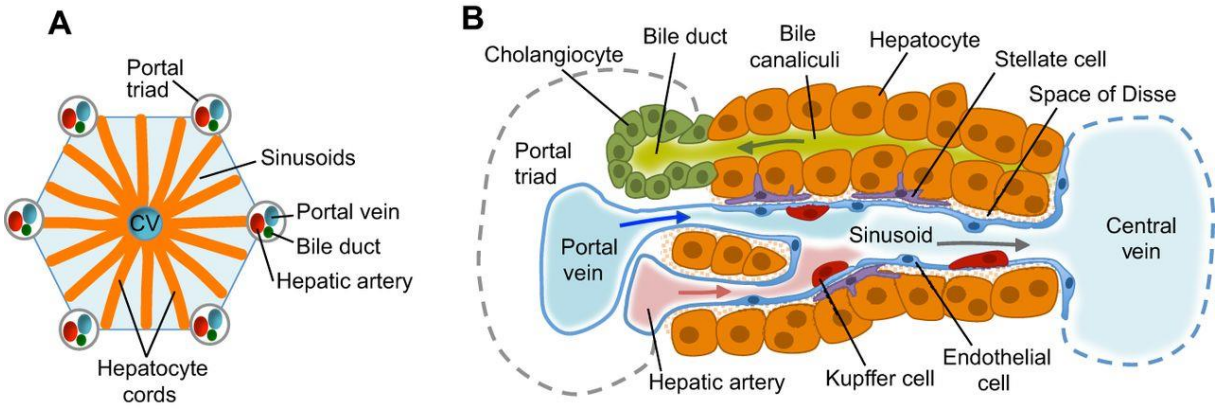


Figure 2: *Organization of the liver. (A) Lobule in the form of a hexagonal plate around a central vein, with at each corner a hepatic artery, portal vein and bile duct. (B) Representation of a sinusoid.*
CV = central vein
Reproduced with permission from Gordillo, Evans and Gouon-Evans 2015, Development, 142(12): 2094-108 (15)

1.1.2 Function and indications for transplantation

The function of the liver is multifactorial. The liver metabolizes macronutrients (glucose, lipids, cholesterol and amino acids) which provides energy for the regulation of blood volume, for the support of the immune system, control of growth signaling pathways and breakdown of xenobiotic compounds.

- The capacity to store **glucose** in the form of glycogen or release glucose while fasting is important for metabolic transitions. The glucose output is dynamic and dependent on the energy-need in the body.

- The liver is important for the uptake, synthesis, packaging and secretion of **lipids** and lipoproteins. The fatty acids can be used as an internal (for the liver) or external (for other organs) energy source. This is important while fasting. During feeding the lipid substrates are stored in adipose tissue or the skeletal muscle will use the substrates as energy source. Due to the lipid homeostasis of the liver it can absorb lipid-soluble vitamins.
- The liver has an important role in **cholesterol** homeostasis. It can absorb cholesterol from the intestines or can synthesize it. Cholesterol is important for the cellular membranes and the membrane fluidity.
- The liver metabolizes proteins and **amino acids**. The liver synthesizes and secretes proteins in the blood for example albumin, growth factors and acute-phase proteins. Albumin is a very common protein in the blood and is important for the transport of molecules and for the regulation of the blood volume. The liver can also process amino acids for energy and degrade waste proteins (12).

In end-stage liver disease these functions fail, and a liver transplantation is the only option to save the patient's life. For patients with end-stage liver disease, acute liver failure (ALF) or hepatocellular carcinoma (HCC) (within certain limits) a liver transplantation is advisable. Cirrhosis is the most common form of end-stage liver disease. ALF can occur due to viruses (hepatitis A and B), drugs and toxic agents. Other indications for liver transplantation are metabolic disease, cholestatic disease or polycystic diseases (16).

1.2 Kidney anatomy, function and indications for transplantation

1.2.1 Anatomy

The kidneys are the filtration organs of the body and are present in duplicates, one on each side of the vertebral column, where they are located on the posterior abdominal wall. One adult kidney weighs 125-170 g in men and 115-155 g in women (17,18). A kidney consists of 11-14 lobes with a central pyramid, the medulla, surrounded by cortex. The pyramid is attached to a minor calyx, then follows a major calyx which lead to the renal pelvis and finally to the ureter **(Figure 3)**. Together they form the collecting system (17).

Together the kidneys receive around 20% of the total cardiac output, supplied to each kidney by a renal artery (18). The renal artery divides into an anterior and posterior branch. The anterior middle portion and the anterior and posterior poles are supplied by the anterior branch. The middle posterior portion of the kidney is equipped by the posterior branch. The renal veins follow the renal arteries (17).

The medulla is supplied by the efferent arterioles and the spiral arterial branches. The efferent arterioles, originating from the juxtamedullary glomeruli, provides the outer medulla in contrast to the spiral arterial branches, which provides the inner medulla (17).

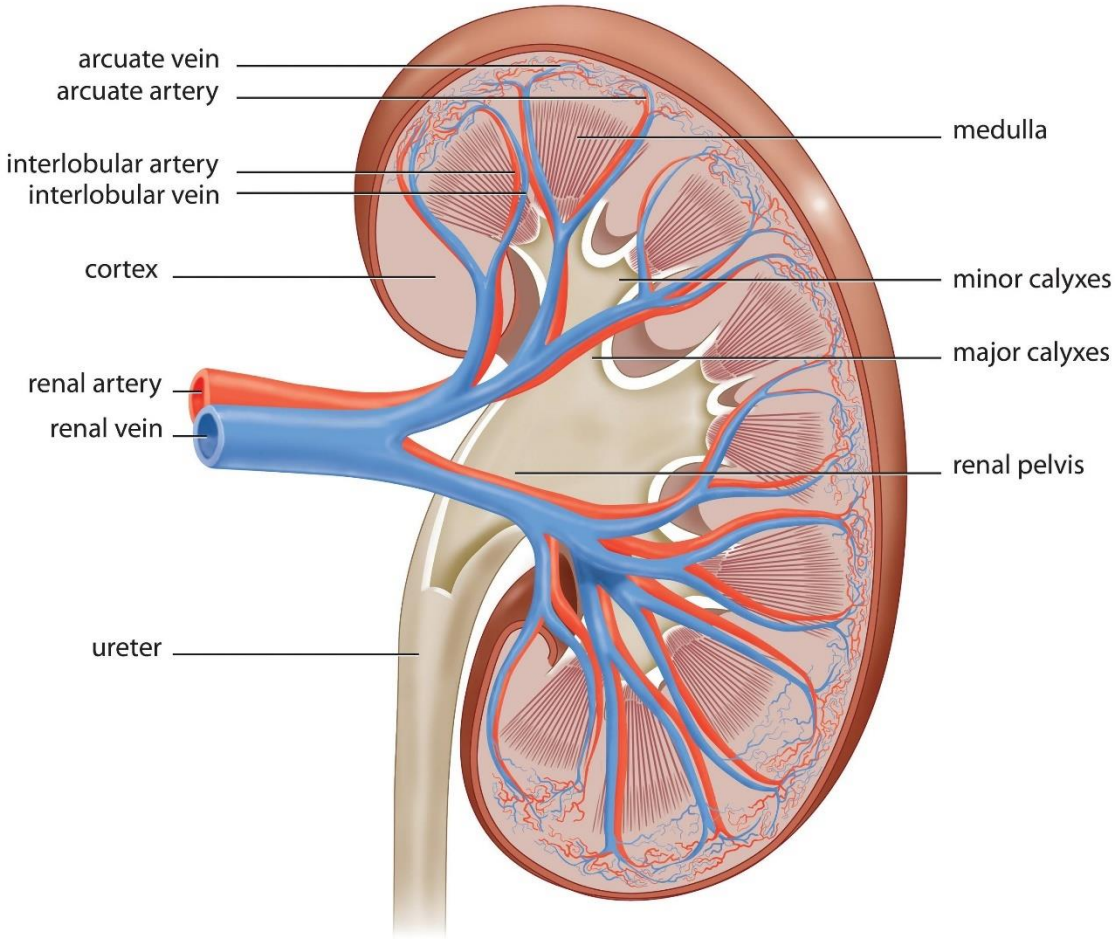


Figure 3: *Anatomy of the left kidney.*
Reproduced with permission from http://www.interactive-biology.com/3254/the-anatomy-of-the-kidney/ (19)

1.2.2 Function and indications for transplantation

The functional unit of the kidney is the nephron. The nephron consists of a glomerulus (a cluster of capillaries) and a tubule system. The kidneys are important to maintain the homeostasis in the body. They regulate: (20,21)

- the excretion of fluid and electrolytes
- the calcium homeostasis
- the blood pressure (renin-angiotensin-aldosterone system)
- the filtration and excretion of waste products
- the stimulation of erythrocytes production

The glomerular filtration rate (GFR) is a good parameter to measure the kidney function. It is the volume of fluid filtered by the glomerulus per unit of time. When the kidney is damaged, the renal function declines and potentially heads to acute kidney injury (AKI) or chronic kidney disease (CKD) (22).

AKI is divided into prerenal, renal and postrenal kidney injury. Examples of prerenal insufficiency are low perfusion volume due to cardiac problems and high-volume loss. Renal kidney injury is a structural problem and is caused by acute tubular necrosis, acute glomerulonephritis, renal vasculitis or acute interstitial nephritis. The etiology of postrenal AKI is an obstruction distal to the collecting system like hypertrophy of the prostate, an operative injury or nephrolithiasis (23). When the underlying cause of AKI can be treated, AKI is usually reversible. The tubuli of the kidney can recover from the injury and renal function (partially) recovers. When there is structural or irreversible damage, the injury becomes chronic and AKI can evolve to CKD. There are also different etiologies for CKD, like diabetes, hypertension, renal artery stenosis or renal vein thrombosis, tumors, glomerulonephritis and PKD (24).

A failing kidney can be replaced by dialysis or by a transplant kidney. Usually dialysis is started when the kidneys fail. But transplantation is the preferred choice for CKD because it improves survival and quality of life compared with dialysis. Dialysis has some disadvantages: it provides cardiac stress, it gives a higher risk for kidney and urinary tract cancer and a higher mortality. There is also an increased risk of graft rejection when transplantation occurs after several months of dialysis (25).

1.3 Indications for combined liver-kidney transplantation

A patient with one of the above indications for liver transplantation and one for kidney transplantation, so with both end-stage liver and end-stage kidney disease, will benefit from a CLKT. But for patients with a potentially reversible liver or kidney dysfunction it is more difficult to predict the best treatment (1,26,27). There are different considerations that need to be made. The kidney transplantation waitlist is long, so unnecessary CLKTs needs to be avoided. On the other hand, a failing kidney can threaten the life of a liver only transplant patient (2). The same thoughts arise in the case of a primary kidney and pre-emptive liver transplantation: does the patient need both kidney and liver? Will the hepatic complications be life-threatening after a kidney only transplantation (27)?

In a previous retrospective UZ Leuven study with 62 CLKT recipients, they showed that patients with single organ failure and an advanced liver or kidney disease, that can cause complications when performing a single transplantation, will benefit from CLKT (28).

CLKT candidates can therefore be classified by the 'Leuven classification':

- Patients with primary liver and kidney failure
- Patients with primary liver and pre-emptive kidney failure
- Patients with primary kidney failure and pre-emptive liver failure
- Patients with pre-emptive kidney and liver failure, which is rather theoretical

1.4 Organ allocation in Eurotransplant

Since 1967 the Eurotransplant International Foundation exists (29). It is a non-profit organization for the allocation of organs in eight European countries: Belgium, the Netherlands, Luxembourg, Germany, Austria, Slovenia, Croatia, and Hungary. The organization was started by Professor van Rood because he became aware that the human leucocyte antigen (HLA) matching between donor and recipient is an important predictor of short- and long-term outcomes after kidney transplantation. Until then, kidneys were mainly matched by blood type. The probability of finding a good match between donor and recipient is increased when countries work together and share organs across boarder in this organization. After allocating kidneys, the organization also started allocating livers and other organs (29,30). Unlike for kidneys, HLA-matching seems to have less impact on the success rate of liver transplantation. The benefits of an international system of liver donation lies in increased chances of a suitable organ (blood type, organ quality and size) for patients that urgently need a liver transplant. Unlike for end-stage kidney failure, there is no 'liver dialysis' that can support patients while waiting for a suitable liver offer.

1.4.1 For liver transplantation

Allocation of deceased donor livers is tiered within Eurotransplant, based on urgency and geographical region. International priority is given only to patients with a high urgent (HU) or an approved combined organ (ACO) status. This HU status can only be received in case of ALF or an urgent need for retransplantation (6,30,31). An ACO includes all multi-organ liver transplants, except CLKT patients. An ACO patient gets priority above the transplantable patients on the waiting list and below the HU patients (31). When a liver is used from another Eurotransplant country for a HU or an ACO patient, the receiving country is obliged to offer the next available liver in the same blood group to the offering country (31).

When there are no HU or ACO patients on the waiting list, the donor liver is allocated following a strict process that can differ slightly from country to country.

The following parameters are important in the liver allocation process: blood group and severity of the disease. Severity of the disease, and therefore urgency, is determined by the MELD

score (6,30,31), a combination of creatinine, bilirubin and international normalized ratio (INR) in the blood. The MELD score is calculated with the formula below:

$$MELD = 10 * \left[0.957 * \log\left(creatinine \frac{mg}{dl}\right) + 0.378 * \log\left(bilirubine \frac{mg}{dl}\right) + 1.120 * \log(INR) + 0.643\right]$$

A higher MELD score is associated with a more severe disease and increased mortality risk without transplantation. It was developed by the Organ Procurement and Transplantation Network (OPTN) / UNOS in 2002 and implemented by Eurotransplant in 2003 (31).

In most Eurotransplant countries, the MELD score is now used to drive allocation policy, i.e. patients with a higher MELD score receive priority on the waiting list and therefore have a higher chance of receiving an organ offer (30). This is also called “patient driven allocation”. However, in some cases, the MELD score does not reflect the severity of the disease. This patient can get an exceptional MELD score: a ‘standard exception’ (SE) or a ‘non-standard exception’ (NSE), that artificially increase the MELD score over time so that the patient has an increasing chance of receiving an offer that correlates with their waiting time. Examples of SE are HCC or PCLD (31,32).

In countries where the MELD score is not the driving factor of allocation, so called “center driven allocation”, the transplant team is free to allocate the offered liver to any patient on their waiting list (31).

The liver allocation system is unique, it is a mix of both patient and center driven allocation. In Belgium, livers derived from donation after brain death (DBD) follow the “patient driven allocation” system; livers derived from donation after circulatory death (DCD) are offered by the “center driven allocation” principles if they are not accepted for HU or ACO waitlisted candidates. The reasons for this mix are complex but come down to reducing risk associated with DCD liver transplantation (31).

Since the introduction of the MELD score in the Eurotransplant zone, there is a big increase in CLKTs due to the high serum creatinine in patients with kidney failure. This results in a high MELD score and a higher priority on the ranking (6,7).

1.4.2 For kidney transplantation

The regular kidney allocation is based upon many factors of which blood group compatibility is the first. The ranking is further based on: (33)

- Age

- Medical urgency (determined by inability to dialyze)
- HLA-A, -B and -DR match between donor and receptor. Dependent on the number of mismatches between the HLA-tissue type from donor and receptor, the receptor will receive points on the ranking. The HLA-mismatches are calculated based on the HLA-A and HLA-B broad antigen and on the HLA-DR split antigen.
- Waiting time (time on dialysis): when a patient is registered on the kidney waiting list, the time on maintenance dialysis (dialysis is not interrupted for more than 90 days) is counted. Per year waiting, the patient will receive extra points. When a patient is pre-emptive on the kidney waiting list, so is not yet dialyzed, he or she will not receive points for the waiting time.
- Donor region

1.4.3 For combined liver-kidney transplantation

Organ allocation for combined organs is based on the allocation policy of the organ that is perceived as 'most vital'. For CLKT, liver allocation policy is followed where the liver 'leads' and the kidney 'follows'. An offer is therefore made to the patient with the highest MELD score (for DBD livers), or as a center offer in case of DCD. Although this approach makes sense for patients with a primary liver indication, patients who are listed for a CLKT with a primary kidney indication and are receiving their liver pre-emptively, are disadvantaged as the kidney allocation principles (i.e. time on dialysis) do not result in point accrual on the waiting list. Furthermore, HLA matching is not taken into account and this might potentially lead to a higher risk of kidney rejection in CLKT recipients.

1.5 Surgical techniques for combined liver-kidney transplantation

CLKTs are mostly performed as a two-step procedure, i.e. first the liver is transplanted in a classical fashion followed by a classical kidney transplantation (10,34).

The liver transplantation is usually approached through a bilateral subcostal incision. The native liver is removed (hepatectomy): the bile duct, hepatic artery and portal vein are cleaved close to the liver hilum to leave enough vessel-length for the following anastomoses. For the reduction of blood loss, the portal vein can form a temporary porto-caval shunt by joining the vena cava (35). The native liver can be removed with replacement of the inferior vena cava (IVC) or with preservation of the recipient IVC; this is the piggyback method **(Figure 4)**. The clamping of the IVC has some negative effects on heart and kidneys. To reduce these side effects a veno-venous bypass is used which passages blood from the IVC below to the superior vena cava (SVC) above. The implantation of the new liver is associated with portal vein, hepatic artery and bile duct anastomoses. The bile duct is connected duct-to-

duct or duct-to-small-bowel (choledochojejunostomy). When the IVC is removed during the hepatectomy, the remaining ends of the recipient IVC are ligated to the corresponding parts of the donor liver **(Figure 4C)**. When the recipient IVC is preserved, the new liver can be implanted in two ways. With the classical piggyback method by sewing the donor IVC to the recipient junction **(Figure 4A)** or the cavo-cavostomy by sewing the donor IVC lateral to the recipient IVC **(Figure 4B)** (35,36).

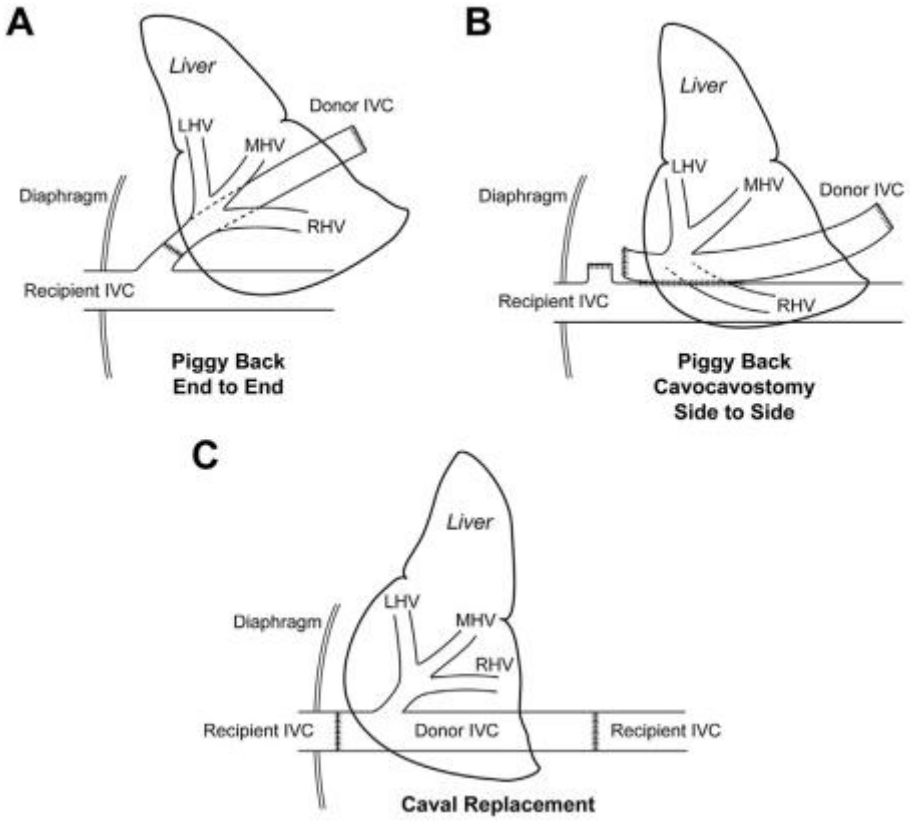


Figure 4: *Implantation of donor IVC. (A) Piggyback technique. (B) Piggyback technique with side-to-side cavocavostomy. (C) Caval replacement.*
IVC = inferior vena cava, LHV = left hepatic vein, MHV = middle hepatic vein, RHV = right hepatic vein.
Reproduced with permission from Lee and Foley 2016, Surgical Clinics of North America, 96(2): 269-281 (37)

After the native hepatectomy, it is sometimes needed to perform a nephrectomy as well. This is mostly the case where PCLD and PKD is the indication for transplantation and either to make space for the organs or to remove any source of infection (34).

When the liver is implanted and the patient is stable, the kidney transplantation can start, i.e. the kidney transplant follows the liver transplant in one procedure. The patient does not leave the operating theatre. The abdomen is fully closed and the wounds are dressed, the drapes are removed and a new set of instruments etc. are used.

Sometimes it can be advantageous to delay the kidney transplantation for a certain period of time (38). The timing of the kidney transplantation will be discussed later.

The kidney is implanted in one of the iliac fossae. The renal artery is implanted to the recipient's common or external iliac artery and the renal vein to the external iliac vein. The kidney is located close to the bladder so the donor ureter can be connected to the bladder. Mostly a double-J stent is placed, and removed after a few weeks, to reduce the chance of urine leakage (35).

Sometimes the liver and kidney are transplanted in one-step. The liver and kidney are prepared as usual. The transplantation is performed through a xiphopubic (midline) laparotomy and a preperitoneal pocket is created for the kidney. First the liver graft is implanted followed by the kidney graft. This technique can be used when liver and kidney are voluminous due to PCLD or PKD and when simultaneous native nephrectomy is suggested (34).

1.6 Simultaneous versus delayed combined liver-kidney transplantation

Generally, CLKT is performed as one procedure where the kidney is transplanted immediately after the liver (simultaneously), as described above. There are a few considerations with regard to simultaneous procedures. Not only is the CLKT procedure a complex operation but also the conditions for the kidney to be transplanted in, are not ideal. For example, liver function is optimized with low central venous pressure and after a liver transplantation vasopressors are often needed to maintain blood pressure. Whereas the kidney functions best in opposite conditions. Furthermore, the kidney allograft is damaged by hepatic reperfusion injury and increased bilirubin leading to a higher chance on acute tubular necrosis and delayed graft function (DGF) (7,38).

Another procedure, so called delayed kidney transplantation, is to transplant the liver first and the kidney hours – to sometimes days – later. One center reported that this can be done safely if the kidney is preserved by hypothermic pulsatile perfusion (7,38).

The first of such delayed procedures was performed in June 2007 at Indiana University, Indianapolis, USA. This center studied 130 CLKTs between 2002 and 2015 in an observational cohort study (38).

The delayed procedure, with cold ischemia time (CIT) for the kidney up to 81 hours, was associated with different benefits:

- Improved patient and graft survival
- The patient is hemodynamically stable
- Less blood loss during kidney transplantation by permitting decompression of varices
- Better renal allograft outcome and less DGF of the kidney
- The vasopressors can be weaned before kidney transplantation which reduces the risk on DGF

- The delayed closure of the abdomen will lower the abdominal pressure
- Better operative conditions like a new incision, a fresh surgeon and a separate procedure
- The post-liver reperfusion debris after the liver transplantation is cleared
- The maintenance of continuous veno-venous hemofiltration (CVVH) aims a lower risk of DGF (7,38)

1.7 Postoperative liver complications

Liver transplantation is a major and invasive surgical procedure and despite major advances in all kind of domains, there is still considerable morbidity and mortality (M&M) associated with the procedure. The postoperative complications can be divided in different categories: liver dysfunction, surgical complications, biliary complications and immunological complications (10,35,39).

1.7.1 Liver dysfunction

Primary graft dysfunction (PGD) is a liver complication due to ischemia (40). Two types of PGD exist: early allograft dysfunction (EAD) and primary non function (PNF) which reflect different stages of the same syndrome (40).

According to the Olthoff criteria, published in 2010, EAD can be defined as a change in one of the following postoperative laboratory results: bilirubin ≥ 10 mg/dL on day seven, INR ≥ 1.6 on day seven and alanine or aspartate aminotransferase (ALT or AST) > 2000 IU/L within the first seven days (41). EAD occurs in 40% of liver transplants (10).

PNF is irreversible graft failure, in contrast to EAD, which is reversible (10). Incidences of PNF range from 4% to 8% (42). High potassium concentration, increased serum lactate levels, hemodynamic instability, renal failure, encephalopathy and metabolic acidosis are some presentations of PNF (40). An urgent retransplantation is needed to save the patient's life (10).

1.7.2 Surgical complications

Some examples of surgical complications are bleeding, wound infection, wound breakdown and vascular complications (35). The vascular complications, with an incidence of 8-15%, can be divided into arterial (5-10%), portal (1-3%) and venous (<2%) complications (43). These complications occur due to stenosis or thrombosis. The most common are hepatic artery and portal vein thrombosis (10,43).

1.7.3 Biliary complications

Bile complications are the most common after liver transplantation (35). They occur in 23% of all liver transplantations (44). These include biliary strictures (anastomotic or non-anastomotic) (15%) and biliary leaks (9%) (44). Most of them take place in the first three months after liver transplantation (10,44).

1.7.4 Immunological complications

Acute cellular rejection is a common immunological complication. It occurs in 25-30% of liver transplantations (39). There are no specific symptoms of acute rejection. It can present asymptomatic or with non-specific symptoms like fever and abdominal pain. Acute cellular rejection is mostly identified by abnormal blood results. A liver biopsy proves the rejection and can define the type and the severity of the rejection (39).

1.8 Postoperative kidney complications

The postoperative complications after a kidney transplantation are divided into different categories: kidney dysfunction, surgical complications, ureteral complications and immunological complications (35).

1.8.1 Kidney dysfunction

DGF is defined as the need of dialysis in the first seven days after transplantation. It is the most common complication after a kidney transplantation, occurring in 30% and >50% of respectively DBD and DCD kidneys (35). DGF might increase the risk of rejection and result in a shorter graft survival (35,45).

1.8.2 Surgical complications

Surgical complications include renal artery thrombosis, renal vein thrombosis and renal artery stenosis (35). Renal artery and renal vein thrombosis occur in less than 5% of kidney transplants (35). Renal artery stenosis is more common than renal artery or vein thrombosis. It occurs mostly around three to six months post-transplant (35).

1.8.3 Ureteral complications

There are two types of ureteral complications: urine leak and ureter obstruction. Their incidence is between 3% and 9% (46). Due to poor surgical technique or to ureteral necrosis,

a urine leak can emerge. It occurs mostly when the urinary catheter is pulled out in the first week post-transplantation. The place of the leak is usually situated at the site of anastomosis between donor ureter and bladder. Ureter obstruction can occur early post-transplant by anastomotic strictures, a blood clot or extrinsic compression by a lymphocele. When the obstruction occurs later than three months post-transplant, it is due to an ureteral stricture, infection or rejection (35).

1.8.4 Immunological complications

Acute cellular rejection occurs in 20-25% of kidney transplants, mostly in the first six months after transplantation (35).

2. Aim

The aim of this master thesis is to investigate the CLKT patient population in UZ Leuven and to situate UZ Leuven in the field of other transplant centers. Right now little is known about the outcomes, morbidity and mortality of CLKTs in the changing landscape of organ transplantation which is confronted with sicker patients and ever older donors with more co-morbidities.

We hypothesize that

1) UZ Leuven achieves good outcomes after CLKT despite the expected increase in risk factor of both donor and recipient.
2) Compared to liver-only transplants, CLKT recipients experience more and more severe complications as after a CLKT, patients are at risk of complications from both liver and kidney. No data on this topic are published, so by studying this we will clarify the severity of this operation and we hope to provide improved information to our patients.

3. Methodology

To investigate these hypotheses, two studies were carried out:

1) The first study charted the UZ Leuven CLKT cohort and critically analyzed indications, demographics, outcomes and the evolution over time.
2) The second study compared complications and the complication rate observed in CLKT patients with those of liver-only transplants.

3.1 Part 1: UZ Leuven experience with combined liver-kidney transplantation

This retrospective study included all adult (≥ 18 years old) CLKT patients transplanted in UZ Leuven between 1 January 1997 and 20 December 2019. Data were retrieved until 20 March 2020 to allow at least a three month follow-up (FU) for all patients. The only exclusion criterion were patients who received a liver and a kidney graft in the context of a multivisceral transplantation.

Donor and recipient demographics as well as outcomes after transplantation were summarized for the entire cohort and evolutions or changes over time were investigated.

Four time eras were arbitrarily defined to allow comparison of results over time:

- 01/01/1997 – 31/12/2002
- 01/01/2003 – 31/12/2008
- 01/01/2009 – 31/12/2014
- 01/01/2015 – 20/12/2019

Definitions that were used:

The ‘Leuven classification’ reflects the primary reason for organ transplantation:

- Primary liver and primary kidney failure
- Primary liver and pre-emptive kidney failure
- Primary kidney and pre-emptive liver failure
- Pre-emptive liver and pre-emptive kidney failure

For the donor population the type of donation (DBD or DCD) and the cause of death were identified, the latter one was divided in four subcategories: trauma, cardiovascular accident, anoxia and other.

The liver donor risk index (DRI) takes, according to Feng et al. (47), into account donor age, African-American race, DCD donors, cause of death, height, donor procedure performed by UZ Leuven or by another team and CIT.

With regard to surgical technique, we noted:

- Type of incision (one midline incision where liver and kidney are transplanted in 'one-step' versus two separate incisions, i.e. a 'two-step' procedure).
- Timing of kidney transplant (immediately after the liver transplantation or a "delayed" kidney transplantation. Here the patient goes to the intensive care unit (ICU) after the liver transplantation for any period of time before returning to the operating theatre for the kidney transplantation).

Primary outcomes were patient survival after CLKT, liver and kidney graft survival. Patient survival, liver graft survival and kidney graft survival were followed until five years after transplantation.

- Liver graft loss was defined as relisting for transplantation or death with functioning graft.
- Kidney graft loss was defined as return to chronic dialysis, removal of the kidney graft or death with functioning graft. When the kidney graft was still functioning, the estimated glomerular filtration rate (eGFR) was measured at three months, six months and one year after transplantation to evaluate the kidney function.

Secondary outcomes include:

- Liver PNF: at day three post-transplantation: AST ≥ 3000 U/L and one of the following: INR ≥ 2.5 and/or total bilirubin ≥ 10 mg/dL
- Liver EAD: bilirubin ≥ 10 mg/dL on day seven, INR ≥ 1.6 on day seven and ALT or AST > 2000 IU/L within the first seven days (41)
- Liver model for early allograft function (MEAF) scoring: this is a score from zero to ten with higher scores reflecting higher risk on patient mortality at three month (48)
- Kidney DGF: the need for dialysis in the first seven days after transplantation
- Kidney PNF: chronic dialysis starting from transplantation until at least three months after transplantation
- Biopsy-proven acute liver and kidney rejection
- Biliary leaks or biloma's, diagnosed by means of radiological examination
- Biliary strictures, diagnosed by means of radiological examination

3.2 Part 2: Comparing complications after combined liver-kidney transplantation versus liver-only transplantation

Complications and the complication rate of adult patients (≥ 18 years old) receiving a CLKT or a liver-only transplant were compared for patients transplanted between 1 July 2019 and 1 March 2020, with a minimum FU period of 2 weeks. The only exclusion criterion were patients who received a liver and a kidney graft in the context of a multivisceral transplantation.

Complications were prospectively registered using the “M&M tool” which was developed by Beatrijs Steelandt (master thesis student 2018-2019) (10). The existing “M&M tool” was expanded with the option to indicate combined transplantations and the most important complications after kidney transplantation. The updated “M&M tool” can be found in **Appendix I**.

In addition to descriptive analysis of complications in CLKT and liver-only transplant recipients, the incidence and severity of complications were compared between the two groups.

We provided both the overall number of complications per patient and the proportion of patients with at least one complication.

We divided the complications in these subcategories: general complications, specific liver complications and specific kidney complications.

The following general complications were analyzed:

- Medical complications
- Infections
- Thromboembolic complications
- Cardiovascular complications
- Cerebrovascular complications
- Malignancies

The following liver complications were analyzed:

- Surgical complications
- Biliary complications
- Immunological complications
- Malignancies

The following kidney complications were analyzed:

- Surgical complications
- Urinary complications
- Immunological complications

Definitions that were used:

All definitions defined in Part 1, were used in this study as well.

In addition, the severity of the registered complications was defined by the Clavien-Dindo grading system (49) **(Figure 5)**. Complications with a Clavien-Dindo grade III or higher were considered severe complications.

Table I. Classification of surgical complications (Clavien-Dindo)

Grade	*Definition*
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: Drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIA	Intervention not under general anesthesia
Grade IIIB	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring intermediate care/ICU-management
Grade IVA	Single organ dysfunction (including dialysis)
Grade IVB	Multi organ dysfunction
Grade V	Death

*Including brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.

Figure 5: *Clavien-Dindo classification of surgical complications.*
CNS = central nervous system, ICU = intensive care unit.
Reproduced with permission from Herrera-Cabezón, Sánchez-Acedo, Zazpe-Ripa, et al. 2015, Revista Espanola de Enfermedades Digestivas, 107(3): 143-151 (50)

3.3 Statistics

Descriptive statistics were presented as median (interquartile range) for continuous variables or as number (percentage) for categorical variables. For the comparison of two groups, continuous variables were compared by the nonparametric Mann Whitney U-test test. When there were more than two groups, data were compared with the nonparametric Kruskal Wallis test. For categorical variables, the Chi-square test or the Fisher exact test was used depending on the distribution of the data. Kaplan-Meier curves were constructed for patient and graft survival analysis. $P < 0.05$ was considered statistically significant. When multiple groups were compared, Bonferroni corrections for multiple testing were performed where needed. The statistical program SPSS version 26 was used for these analyses.

4. Results

4.1 Part 1: UZ Leuven experience with combined liver-kidney transplantation

4.1.1 Indications

Between 1 January 1997 and 20 December 2019, 130 CLKTs were performed in UZ Leuven. The number of CLKTs increased over time **(Figure 6)** with 15 procedures between 1997-2002 (Era 1), 23 between 2003-2008 (Era 2), 47 between 2009-2014 (Era 3) and 45 between 2015-2019 (Era 4).

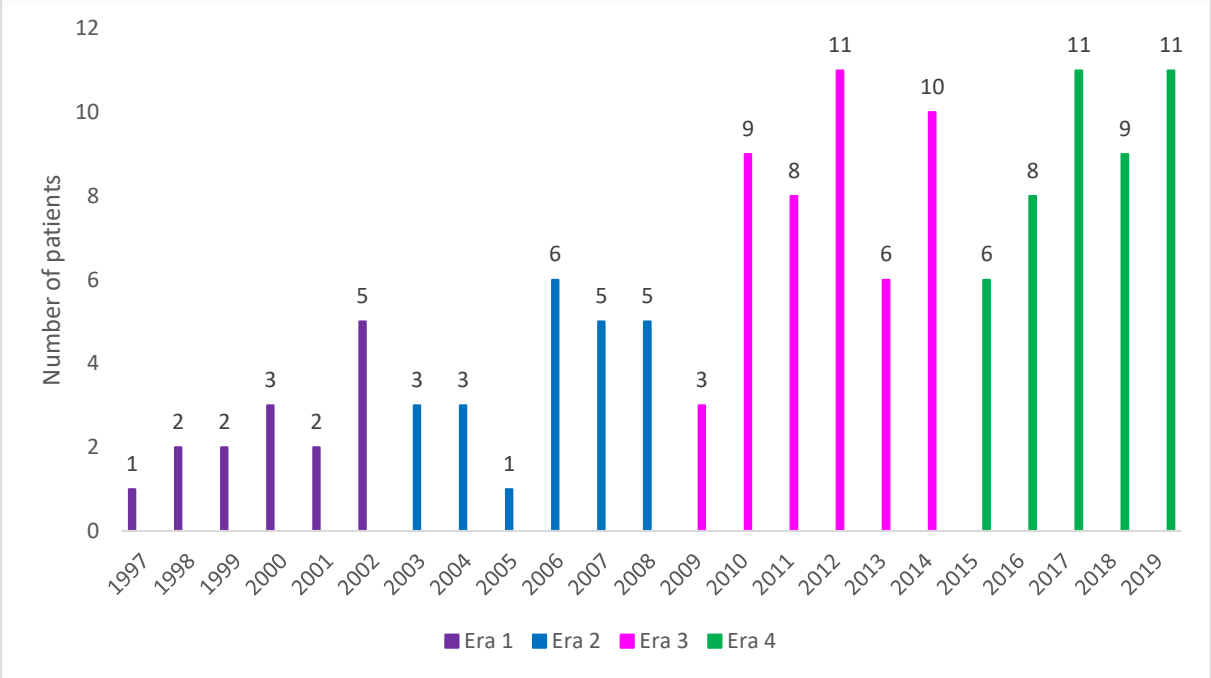


Figure 6: *Number of transplantations per year grouped per era.*

The 'Leuven classification' reflects the primary reason for transplantation. From the 130 CLKT patients, 63 patients (48%) were transplanted for a primary liver and primary kidney indication, 42 patients (32%) for a primary liver and pre-emptive kidney indication and 25 patients (19%) for a primary kidney and pre-emptive liver indication. A pre-emptive liver and pre-emptive kidney indication did not occur **(Figure 7)**. The 'primary liver + kidney' group and the 'primary kidney + pre-emptive liver' group had a similar distribution when comparing the different time eras. For the 'primary liver + pre-emptive kidney' group the distribution is similar from 1997 till 2014 and a slight non-significant increase was observed between 2014-2019 **(Table 2)**.

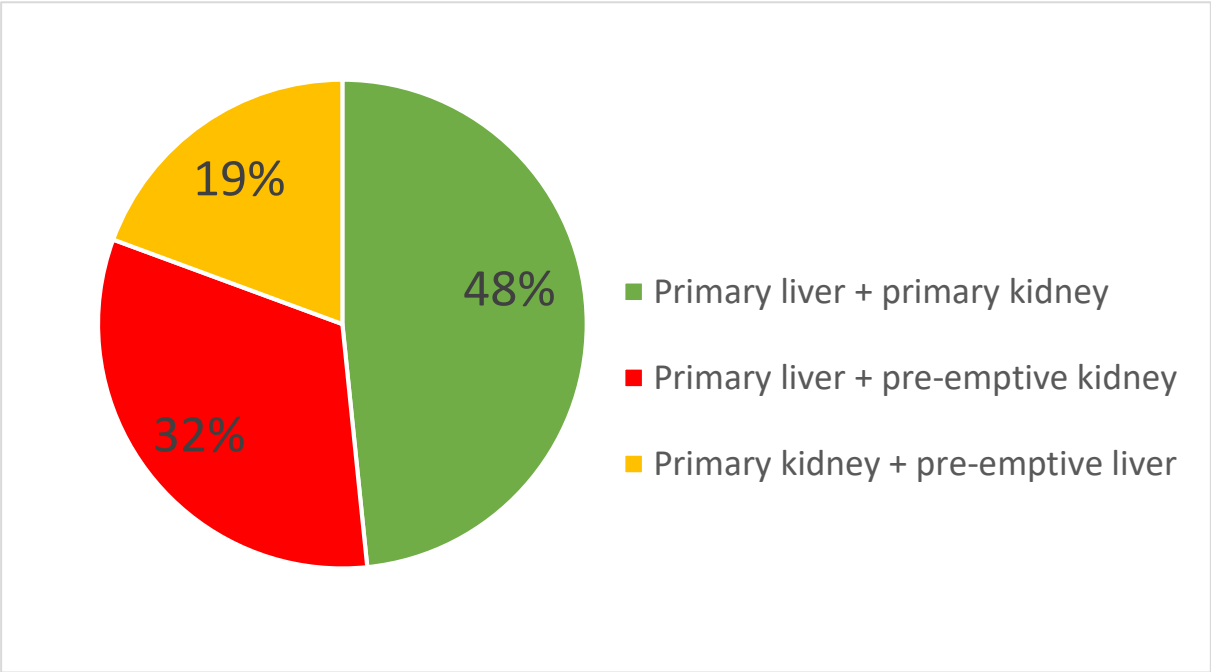


Figure 7: *'Leuven classification' for primary liver and/or kidney indication of the CLKT population between 1997 and 2019.*
CLKT = combined liver-kidney transplantation

The primary liver indications for CLKT are shown in **Figure 8A**. 15% of the patients had a double liver indication, in the other 85% only one indication was documented. The primary indications were PCLD in 56 patients (43%), chronic liver disease (CLD) due to alcohol in 25 patients (19%), cholestatic disease in ten patients (8%), hepatitis B virus (HBV) in seven patients (5%), hepatitis C virus (HCV) in five patients (4%), non-alcoholic steatohepatitis (NASH) in six patients (5%), other chronic liver indications in seven patients (5%), metabolic / endocrine disease (MED) in three patients (2%), ALF in two patients (2%), HCC in one patient (1%), hepatic artery thrombosis in one patient (1%) and other indications in seven patients (5%). The second indications were HCC (n=14, 11%), MED (n=1, 1%), HCV (n=1, 1%), NASH (n=1, 1%) and other indications (n=2, 2%).

When comparing the different time eras, the primary indications: PCLD, NASH and cholestatic disease increased slightly, but the difference was not statistically significant. The primary indication HBV decreased significantly. For the other indications, no changes were observed **(Table 2).**

Table 2: *Pretransplant information of the CLKT population transplanted between 1997 and 2019.*

	Total (n=130)	**Era 1: '97-'02 (n=15)**	**Era 2: '03-'08 (n=23)**	**Era 3: '09-'14 (n=47)**	**Era 4: '15-'19 (n=45)**	**P-value**
Leuven classification, n (%)						0.78
Primary L + K	63 (48)	8 (53)	10 (44)	25 (53)	20 (44)	
Primary L + pre-emptive K	42 (32)	5 (33)	7 (30)	12 (26)	18 (40)	
Primary K + pre-emptive L	25 (19)	2 (13)	6 (26)	10 (21)	7 (16)	
Primary liver indications, n (%)						
Acute liver failure	2 (2)	1 (7)	0	1 (2)	0	0.25
Metabolic / endocrine disease	3 (2)	0	1 (4)	1 (2)	1 (2)	1.00
Hepatocellular carcinoma	1 (1)	0	0	0	1 (2)	0.64
Polycystic liver disease	56 (43)	4 (27)	12 (52)	22 (47)	18 (40)	0.43
CLD						
Post-ethyl cirrhosis	25 (19)	2 (13)	8 (35)	9 (19)	6 (13)	0.22
HCV	5 (4)	1 (7)	1 (4)	1 (2)	2 (4)	0.80
HBV	7 (5)	3 (20)	0	4 (9)	0	**0.01**
Cholestatic disease	10 (8)	1 (7)	1 (4)	1 (2)	7 (16)	0.10
Non-alcoholic steatohepatitis	6 (5)	0	0	1 (2)	5 (11)	0.16
Other	7 (5)	2 (13)	0	4 (9)	1 (2)	0.15
Hepatic artery thrombosis	1 (1)	0	0	1 (2)	0	1.00
Other indications	7 (5)	1 (7)	0	2	4 (9)	0.48
Secondary liver indications, n (%)						
Metabolic / endocrine disease	1 (1)	0	1 (4)	0	0	0.29
Hepatocellular carcinoma	14 (11)	3 (20)	2 (9)	6 (13)	3 (7)	0.46
CLD						
HCV	1 (1)	1 (7)	0	0	0	0.12
Non-alcoholic steatohepatitis	1 (1)	0	0	1 (2)	0	1.00
Other liver indications	2 (2)	0	0	1 (2)	1 (2)	1.00
Kidney indications, n (%)						
CKD						
Diabetic nephropathy	6 (5)	0	0	1 (2)	5 (11)	0.16
Chronic primary glomerulonephritis	15 (12)	3 (20)	6 (26)	5 (11)	1 (2)*	**0.01**
Chronic secondary glomerulonephritis	1 (1)	1 (7)	0	0	0	0.12
Polycystic kidney disease	53 (41)	3 (20)	12 (52)	22 (47)	16 (36)	0.16
Renovascular disease	1 (1)	0	0	0	1 (2)	0.64
Other	32 (25)	5 (33)	4 (17)	11 (23)	12 (27)	0.71
Acute kidney injury	9 (7)	0	0	6 (13)	3 (7)	0.21
Hepatorenal syndrome	6 (5)	2 (13)	0	1 (2)	3 (7)	0.20
Other indications	7 (5)	1 (7)	1 (4)	1 (2)	4 (9)	0.48
Retransplantation liver, n (%)	12 (9)	0	1 (4)	4 (9)	7 (16)	0.30
Retransplantation kidney, n (%)	18 (14)	6 (40)	2 (9)	6 (13)	4 (9)	**0.04**
HU status, n (%)	8 (6)	1 (7)	7 (30)	0*	0*	**<0.001**

*Significant versus Era 2.

CKD = chronic kidney disease chronic, CLD = chronic liver disease, CLKT = combined liver-kidney transplantation, HBV = hepatitis B virus, HCV = hepatitis C, HU = high urgent, K = kidney, L = liver.

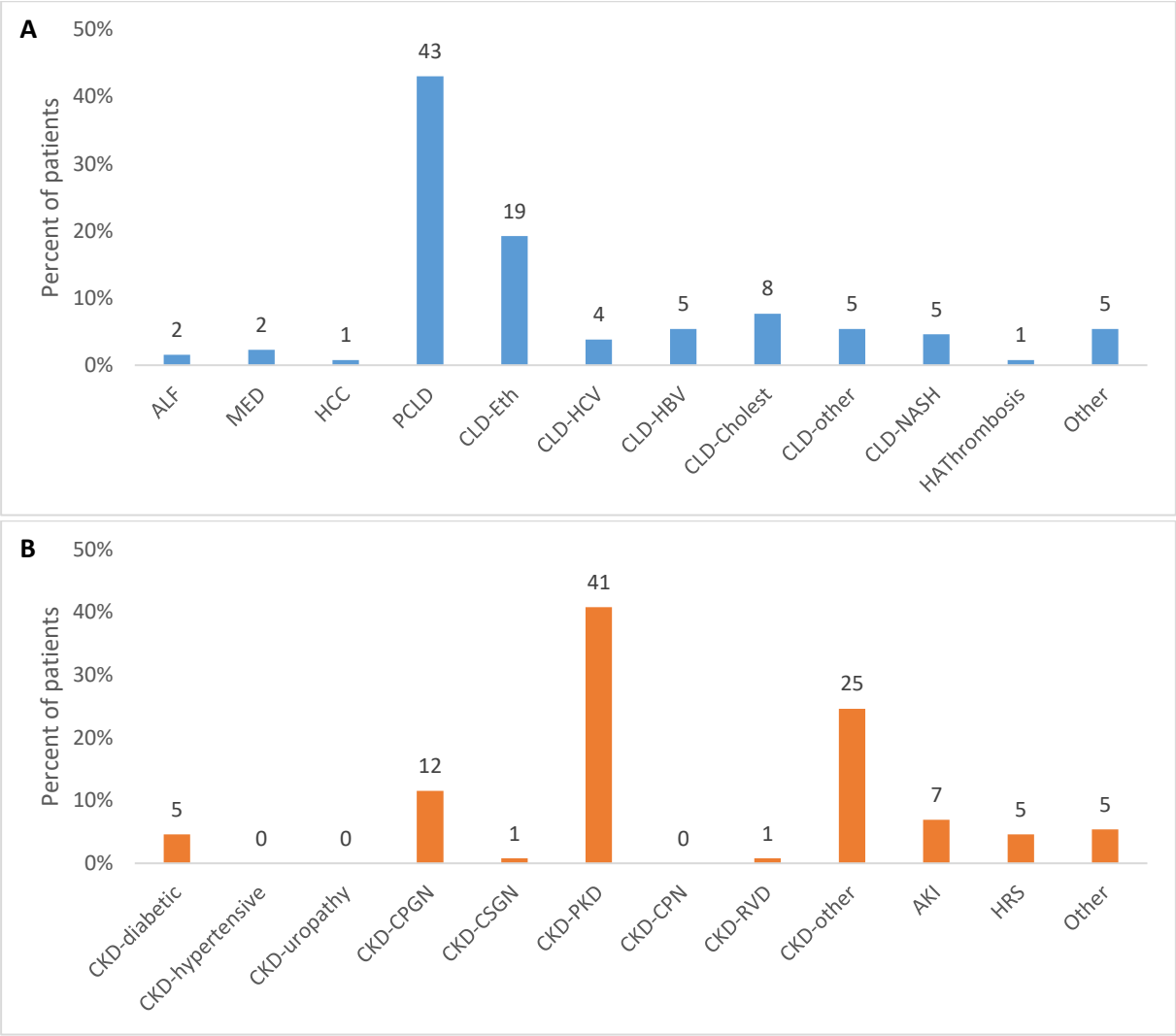


Figure 8: *Indications for CLKT of the population transplanted between 1997 and 2019. (A) Primary liver indications. (B) Kidney indications.*
AKI = acute kidney injury, ALF = acute liver failure, cholest = cholestatic, CKD = chronic kidney disease, CLD = chronic liver disease, CLKT = combined liver-kidney transplantation, CPGN = chronic primary glomerulonephritis, CPN = chronic pyelonephritis, CSGN = chronic secondary glomerulonephritis, diabetic = diabetic nephropathy, Eth = ethanol, HAThrombosis = hepatic artery thrombosis, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HRS = hepatorenal syndrome, hypertensive = hypertensive nephropathy, MED = metabolic / endocrine disease, NASH = non-alcoholic steatohepatitis, PCLD = polycystic liver disease, PKD = polycystic kidney disease, RVD = renovascular disease, uropathy = obstructive uropathy.

An overview of the kidney indications for CLKT is presented in **Figure 8B**. 53 patients (41%) were transplanted for PKD, 15 patients (12%) for chronic primary glomerulonephritis and one patient (1%) for chronic secondary glomerulonephritis, six patients (5%) had diabetic nephropathy, one patient (1%) had renovascular disease and 32 patients (25%) were transplanted for other CKD. Nine patients (7%) were transplanted for AKI, six patients (5%) for hepatorenal syndrome (HRS) and seven patients (5%) for other kidney indications.

When comparing the different time eras, chronic primary and secondary glomerulonephritis decreased, while PKD and diabetic nephropathy increased. Only the decrease in chronic primary glomerulonephritis was statistically significant **(Table 2)**.

Some patients received a re-liver or re-kidney transplantation. Overall, the proportion of patients undergoing a kidney retransplantation was significantly different over the time eras. The data suggest that the proportion has decreased in Era 2 (2003-2008), Era 3 (2009-2014), and Era 4 (2015-2019) compared to Era 1 (1997-2002), though these differences were not significant upon posthoc testing **(Table 2)**.

The proportion of patients transplanted with an HU status changed over the time. Significantly more patients with an HU status were transplanted between 2003-2008 compared with transplants between 2009-2014 and 2015-2019 **(Table 2)**.

4.1.2 Recipient and donor demographics

The first patient was transplanted in 1997 with an overall median (interquartile range) FU time of five years (2-9). Patients transplanted between 1997-2002 (Era 1) had a median FU of 13 years (10-18), the median FU between 2003-2008 (Era 2) was 12 years (7-13), between 2009-2014 (Era 3) was six years (3-8) and between 2015-2019 (Era 4) was one year (0-3).

Baseline characteristics of this population are shown in **Table 3**. Overall, more women received a CLKT (70 females (54%) vs 60 males (46%)). Recipients transplanted between 1997-2002 were significantly younger than those transplanted between 2003-2008, 2009-2014, and 2015-2019 ($P<0.05$; $P<0.05$; $P=0.01$; respectively). Overall the CLKT patients had a normal body mass index (BMI) with a median BMI of 23 kg/m^2 for the whole population and no differences were observed between the time eras. No differences were showed regarding the MELD and balance of risk (BAR) score with a median score of 23 and nine, respectively.

The donor baseline demographics are also displayed in **Table 3**. Overall, organs from male donors were more often used (83 males (64%) vs 47 females (36%)) and this distribution was the same in the four eras ($P=0.23$). The donor age seemed to increase towards the last time era, however the difference was not statistically significant ($P=0.07$). Overall, trauma and cardiovascular accident were the most common causes of death (40% and 45%, respectively) which was similar in the four time eras. In all four eras the majority of donors were DBD donors (89%), only 11% of the donors were DCDs. The proportion of DCD donors increased significantly ($P<0.05$), with DCDs being used since Era 3 (2009-2014). The overall DRI was significantly different between the eras. The data suggested a clinically meaningful higher DRI in Era 3 (2009-2014) and Era 4 (2015-2019), though this difference was not significant upon posthoc testing.

***Table 3**: Baseline characteristics of the CLKT patient and donor population transplanted between 1997 and 2019.*

	Total (n=130)	**Era 1: '97-'02 (n=15)**	**Era 2: '03-'08 (n=23)**	**Era 3: '09-'14 (n=47)**	**Era 4: '15-'19 (n=45)**	**P-value**
Recipient						
Age (y)	58 (53 – 64)	49 (38 – 56)	59 (56 – 62)*	58 (53 – 63)*	60 (53 – 68)*	**0.02**
Sex, n (%)						0.38
Male	60 (46)	10 (67)	11 (48)	20 (43)	19 (42)	
Female	70 (54)	5 (33)	12 (52)	27 (57)	26 (58)	
BMI (kg/m^2)	23 (21 – 26)	21 (20 – 24)	24 (19 – 28)	23 (21 – 26)	23 (20 – 26)	0.35
MELD score	23 (19 – 27)	26 (23 – 32)	23 (18 – 27)	23 (19 – 27)	22 (19 – 27)	0.13
Missing		*2*	*0*	*0*	*0*	
BAR score	9 (7 – 12)	12 (8 – 14)	8 (7 – 11)	9 (7 – 12)	9 (7 – 12)	0.52
Missing	*4*	*3*	*0*	*0*	*1*	
FU period (y)	5 (2 – 9)	13 (10 – 18)	12 (7 – 13)	6 (3 – 8)*$^{+}$	1 (0 – 3)*$^{+\$}$	**<0.001**
Donor						
Age (y)	48 (29 – 56)	43 (22 – 54)	38 (20 – 51)	50 (30 – 56)	51 (32 – 61)	0.07
Sex, n (%)						0.23
Male	83 (64)	9 (60)	14 (61)	26 (55)	34 (76)	
Female	47 (36)	6 (40)	9 (39)	21 (45)	11 (24)	
Cause of death, n (%)						0.13
Trauma	52 (40)	8 (53)	9 (39)	15 (32)	20 (44)	
CVA	59 (45)	7 (47)	12 (52)	27 (57)	13 (29)	
Anoxia	12 (9)	0	1 (4)	4 (9)	7 (16)	
Other	7 (5)	0	1 (4)	1 (2)	5 (11)	
Type of donor, n (%)						**<0.05**
DBD	116 (89)	15 (100)	23 (100)	44 (94)	34 (76)	
DCD	14 (11)	0	0	3 (6)	11 (24)	
DRI	1.56 (1.30 – 1.81)	1.36 (1.14 – 1.59)	1.40 (1.20 – 1.68)	1.60 (1.34 – 1.83)	1.57 (1.33 – 2.00)	**0.05**
Missing	*3*	*2*	*0*	*0*	*1*	

Continuous data are presented as median (interquartile range), categorical data as number and percentage.

*Significant versus Era 1. $^{+}$Significant versus Era 2. $^{\$}$Significant versus Era 3.

BAR = balance of risk, BMI = body mass index, CLKT = combined liver-kidney transplantation, CVA = cardiovascular accident, DBD = donation after brain death, DCD = donation after circulatory death, DRI = donor risk index, FU = follow-up, MELD = model for end-stage liver disease.

4.1.3 Transplantation information

We evaluated the timing of the kidney transplantation: immediately after the liver transplantation or delayed, defined as: the patient went to the ICU between the two transplantations. Significantly more delayed kidney transplantations were performed between 2003-2008 and 2015-2019 compared with the era 2009-2014, respectively five (22%) and eight (18%) compared with zero **(Table 4)**.

Most transplantations were performed by a two-step incision (overall 89%). A midline (one-step) incision appeared for the first time in Era 3 (2009-2014) with a significant increase in Era 4 (2015-2019) compared with Era 2 (2003-2008) and Era 3 (2009-2014).

The overall median CIT of the liver was 7h10. The CIT between 2003-2008 was significantly longer than between 2015-2019, respectively 8h15 and 6h17 **(Table 4)**.

The overall median CIT of the kidney was 12h46 which remained stable when comparing the time eras.

Table 4: *Transplantation information of the CLKT population transplanted between 1997 and 2019.*

	Total (n=130)	**Era 1: '97-'02 (n=15)**	**Era 2: '03-'08 (n=23)**	**Era 3: '09-'14 (n=47)**	**Era 4: '15-'19 (n=45)**	**P-value**
Delayed Tx, n (%)	16 (12)	3 (20)	5 (22)[+]	0*	8 (18)	**<0.05**
Incision, n (%)			*	*		**<0.001**
1-step	15 (12)	0	0	2 (4)	13 (29)	
2-step	115 (89)	15 (100)	23 (100)	45 (96)	32 (71)	
CIT liver (h:mm)	7:10 (5:16 – 8:49)	7:15 (6:32 – 9:00)	8:15* (6:18 – 9:13)	7:18 (5:17 – 9:29)	6:17 (4:44 – 7:56)	**0.01**
Missing	*2*	*1*	*0*	*0*	*1*	
CIT kidney (h:mm)	12:46 (10:23 – 14:45)	12:46 (11:59 – 14:54)	13:47 (11:48 – 15:26)	13:08 (9:40 – 15:18)	11:45 (9:17 – 14:13)	0.15
Missing	*9*	*2*	*3*	*1*	*3*	

Continuous data are presented as median (interquartile range), categorical data as number and percentage.
[+]Significant versus Era 3. *Significant versus Era 4.

CIT = cold ischemia time, CLKT = combined liver-kidney transplantation, Tx = transplantation.

4.1.4 Short-term outcomes

The median ICU stay between 1997 and 2019 was five days and the median hospital stay was 24 days. A significant increase in the length of stay (LOS) on the ICU was observed between 2009-2014 and 2015-2019, respectively four and seven days. Also the total LOS in the hospital seems to increase over the different time eras, but the increase was not statistically significant **(Table 5)**.

Liver

Short-term liver outcomes are displayed in **Table 5**. No liver PNF occurred in this patient cohort. One in five patients developed EAD and this proportion was similar between the time eras. MEAF scores were similar between the time eras with a median score of 2.79. In total 16 patients (12%) developed a biliary leak and 21 patients (16%) developed biliary strictures. A non-significant decrease in biliary complications was observed over the time eras. In total ten (8%) cases of liver rejection were described between 1997 and 2019. Liver rejection occurred significantly more between 1997-2002 (n=4, 29%) compared with 2009-2014 (n=0).

Kidney

In total, 3% and 10% of patients suffered respectively from kidney PNF and DGF. Kidney rejection occurred in 21% of patients. The overall eGFR at three months, six months and one year were 58.9 ml/min/1.73m^2; 58.2 ml/min/1.73m^2 and 51.2 ml/min/1.73m^2 respectively. The eGFR at three months, six months and one year post-CLKT were similar between the four eras. No significant differences between the time eras were observed for these kidney parameters **(Table 5)**.

Table 5: *Liver and kidney outcomes of the CLKT population transplanted between 1997 and 2019.*

	Total (n=130)	**Era 1: '97-'02 (n=15)**	**Era 2: '03-'08 (n=23)**	**Era 3: '09-'14 (n=47)**	**Era 4: '15-'19 (n=45)**	**P-value**
LOS ICU (d)	5 (3 – 14)	4 (3 – 14)	5 (3 – 12)	4 (2 – 6)	7 (4 – 19)*	**0.01**
LOS hospital (d)	24 (16 – 48)	23 (16 – 53)	19 (16 – 35)	20 (15 – 43)	35 (20 – 66)	0.07
Liver						
PNF, n (%)	0	0	0	0	0	-
Missing	*6*	*5*	*0*	*0*	*1*	
EAD, n (%)	26 (20)	4 (27)	3 (13)	8 (17)	11 (24)	0.32
Missing	*12*	*5*	*0*	*5*	*2*	
MEAF	2.79 (1.69 – 4.43)	4.31 (2.05 – 6.60)	2.07 (1.43 – 3.66)	2.62 (1.39 – 4.17)	2.99 (2.06 – 4.99)	0.07
Missing	*6*	*5*	*0*	*0*	*1*	
Rejection, n (%)	10 (8)	4 (27)*	2 (9)	0	4 (9)	**<0.05**
Missing	*1*	*1*	*0*	*0*	*0*	
Biliary leak, n (%)	16 (12)	3 (20)	2 (9)	6 (13)	5 (11)	0.73
Missing	*1*	*1*	*0*	*0*	*0*	
Biliary stricture, n (%)	21 (16)	5 (33)	4 (17)	5 (11)	7 (16)	0.18
Missing	*1*	*1*	*0*	*0*	*0*	
Kidney						
DGF, n (%)	13 (10)	1 (7)	3 (13)	4 (9)	5 (11)	0.92
Missing	*1*	*1*	*0*	*0*	*0*	
PNF, n (%)	4 (3)	1 (7)	0	1 (2)	2 (4)	0.45
Missing	*1*	*1*	*0*	*0*	*0*	
Rejection, n (%)	27 (21)	3 (20)	4 (17)	9 (19)	11 (24)	0.92
Missing	*1*	*1*	*0*	*0*	*0*	
eGFR 3m (ml/min/1.73 m²)	58.9 (44.7 – 74.5)	53.5 (43.7 – 67.2)	64.5 (48.8 – 75.6)	59.3 (43.7 – 72.7)	59.3 (40.4 – 77.6)	0.71
Missing	*15*	*3*	*2*	*5*	*5*	
eGFR 6m (ml/min/1.73 m²)	58.2 (43.8 – 73.2)	47.1 (41.3 – 56.3)	65.3 (46.3 – 84.9)	58.8 (46.3 – 69.6)	57.6 (36.8 -77.8)	0.20
Missing	*21*	*3*	*2*	*7*	*9*	
eGFR 1y (ml/min/1.73 m²)	51.2 (40.6 – 66.3)	47.6 (35.6 – 58.4)	58.3 (44.5 – 67.6)	52.2 (42.1 – 65.9)	45.7 (29.1 – 72.0)	0.35
Missing	*23*	*3*	*3*	*5*	*12*	

Continuous data are presented as median (interquartile range), categorical data as number and percentage.
*Significant versus Era 3.

CLKT = combined liver-kidney transplantation, DGF = delayed graft function, EAD = early allograft dysfunction, eGFR = estimated glomerular filtration rate, ICU = intensive care unit, LOS = length of stay, MEAF = model for early allograft function, PNF = primary non function, - = not available.

4.1.5 Liver graft survival

The Kaplan-Meier curve for liver graft survival is shown in **Figure 9**. The survival estimates with their standard error are shown in **Table 6**. The overall liver graft survival at one, three, five and ten years was 89%, 83%, 81% and 61%, respectively. For patients transplanted between 1997-2002 the liver graft survival was 87% at one and five years. Transplantation between 2003-2008 resulted in a liver graft survival of 91% and 87% at one and five years. For patients transplanted between 2009-2014 the one- and five-year graft survival were 92% and 77% respectively. Transplantation in the last time era, between 2015-2019, resulted in a one- and five-year liver graft survival of 83% and 54%. No significant differences were observed between the different time eras till five years after transplantation (P=0.44).

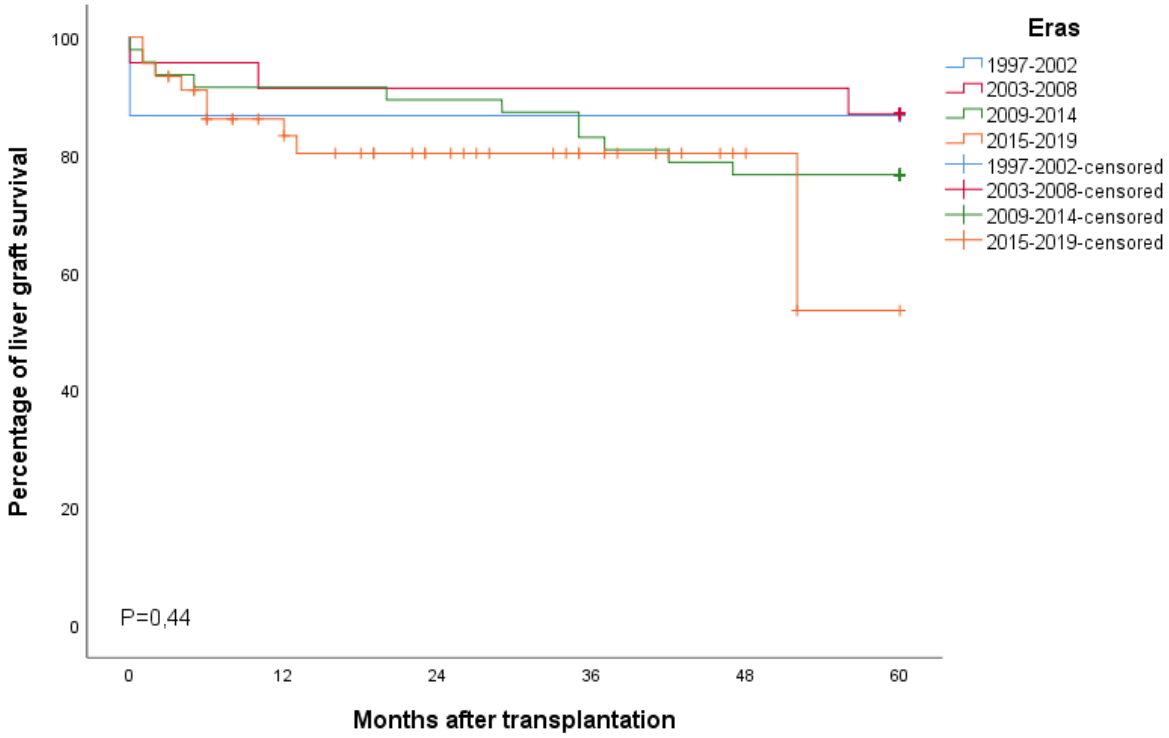


Figure 9: *Kaplan-Meier curve for liver graft survival for the different time eras.*

4.1.6 Kidney graft survival

Figure 10 displays the Kaplan-Meier curve for kidney graft survival. The survival estimates are shown in **Table 6**. The overall kidney graft survival for this patient population from 1997 till 2019 was 91%, 84%, 80% and 55% respectively at one, three, five and ten years. For patients transplanted between 1997-2002 the kidney graft survival was 93% at one and five years. Transplantation in the second time era, between 2003-2008, resulted in a graft survival of 96% and 87% at one and five years. For patients transplanted between 2009-2014 the one- and five-year graft survival were 92% and 77% respectively. Patients transplanted between

2015-2019 showed a one- and five-year kidney survival of 83% and 27%. No significant differences were observed between the four time eras (P=0.12).

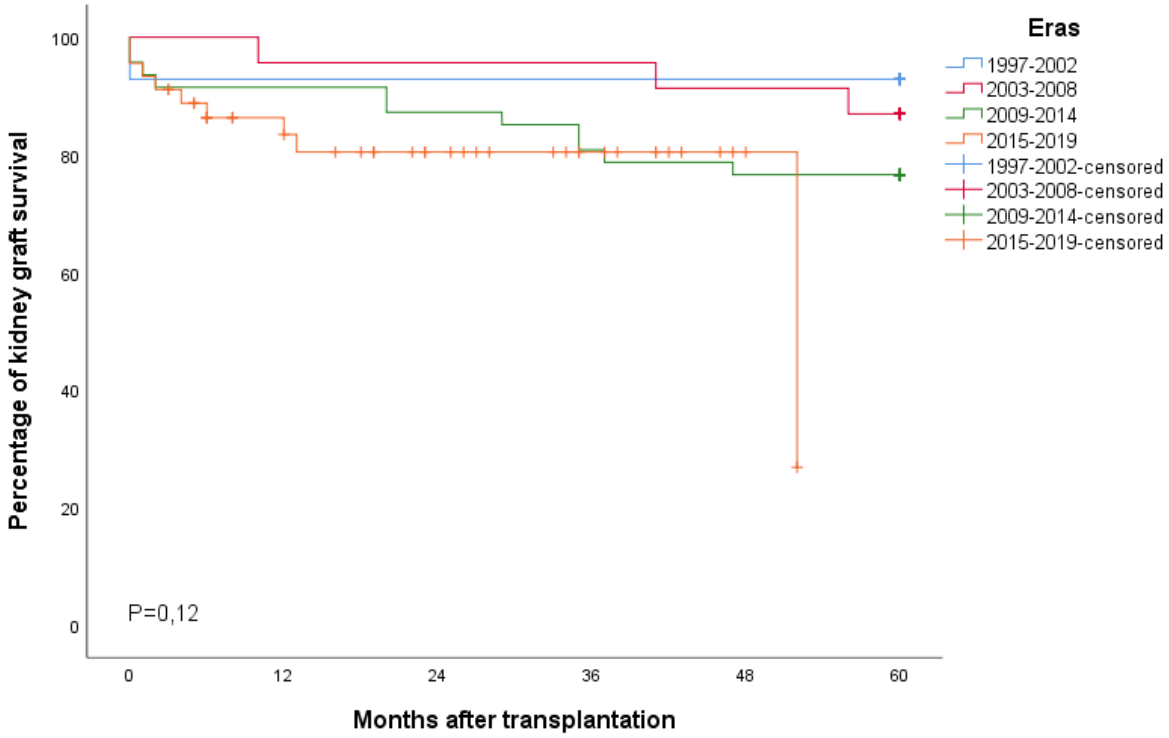


Figure 10: *Kaplan-Meier curve for kidney graft survival for the different time eras.*

4.1.7 Patient survival

The Kaplan-Meier curve for patient survival is shown in **Figure 11**. The survival estimates with their standard error are shown in **Table 6**. The overall patient survival at one, three, five and ten years was respectively 92%, 85%, 83% and 67%. One year after transplantation the curves of time eras 1997-2002, 2003-2008, 2009-2014 were similar with an overall survival of 93%, 96% and 94%, respectively. The overall one-year survival of the most recent era (2015-2019) was slightly, but non-significant lower (83%). After five years, the patient survival was 93%, 91%, 77% and 54% for patients transplanted between 1997-2002, 2003-2008, 2009-2014 and 2015-2019, respectively. The Log Rank test did not identify significant survival differences between the four different time eras (P=0.10).

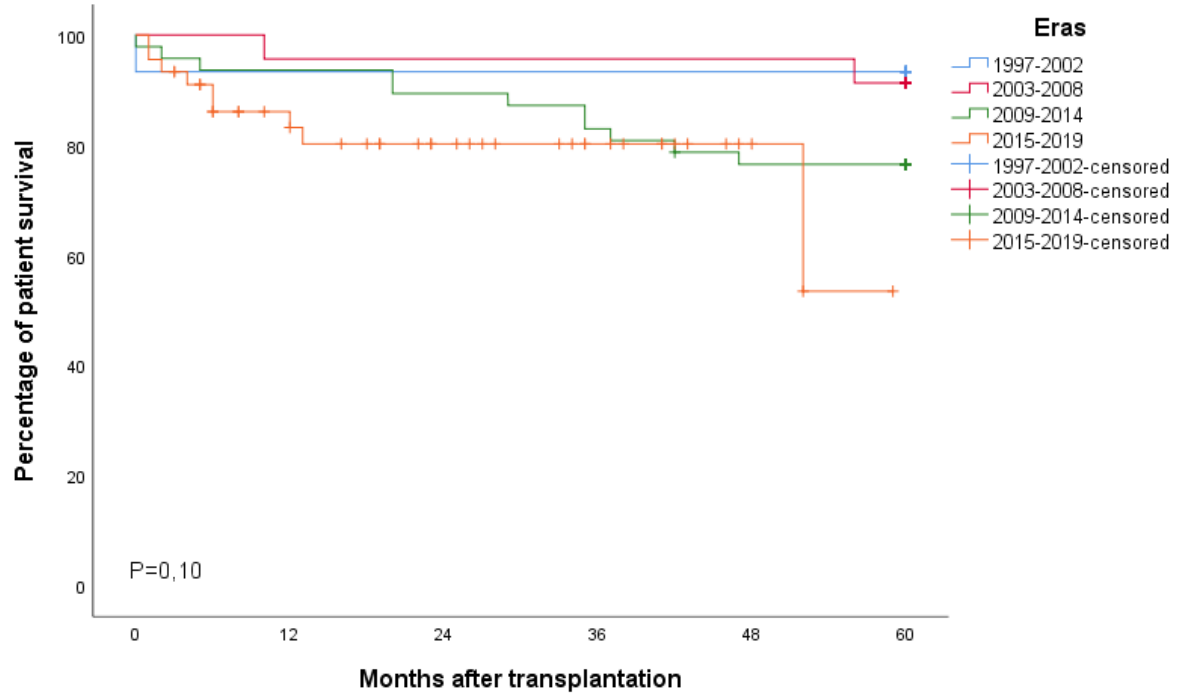


Figure 11: *Kaplan-Meier curve for patient survival for the different time eras.*

Table 6: *Graft and patient survival estimates at one, three and five years of the CLKT population between 1997 and 2019.*

	Era 1: '97-'02	Era 2: '03-'08	Era 3: '09-'14	Era 4: '15-'19
Liver graft survival, %				
1 year	87	91	92	83
n =	*15*	*23*	*47*	*34*
3 years	87	91	83	80
n =	*15*	*23*	*47*	*17*
5 years	87	87	77	54
n =	*15*	*23*	*47*	*2*
Kidney graft survival, %				
1 year	93*	96	92	83
n =	*15*	*23*	*47*	*34*
3 years	93*	96	81	81
n =	*15*	*23*	*47*	*17*
5 years	93*	87	77	27
n =	*15*	*23*	*47*	*2*
Patient survival, %				
1 year	93	96	94	83
n =	*15*	*23*	*47*	*34*
3 years	93	96	83	80
n =	*15*	*23*	*47*	*17*
5 years	93	91	77	54
n =	*15*	*23*	*47*	*2*
*1 missing value				

CLKT = combined liver-kidney transplantation.

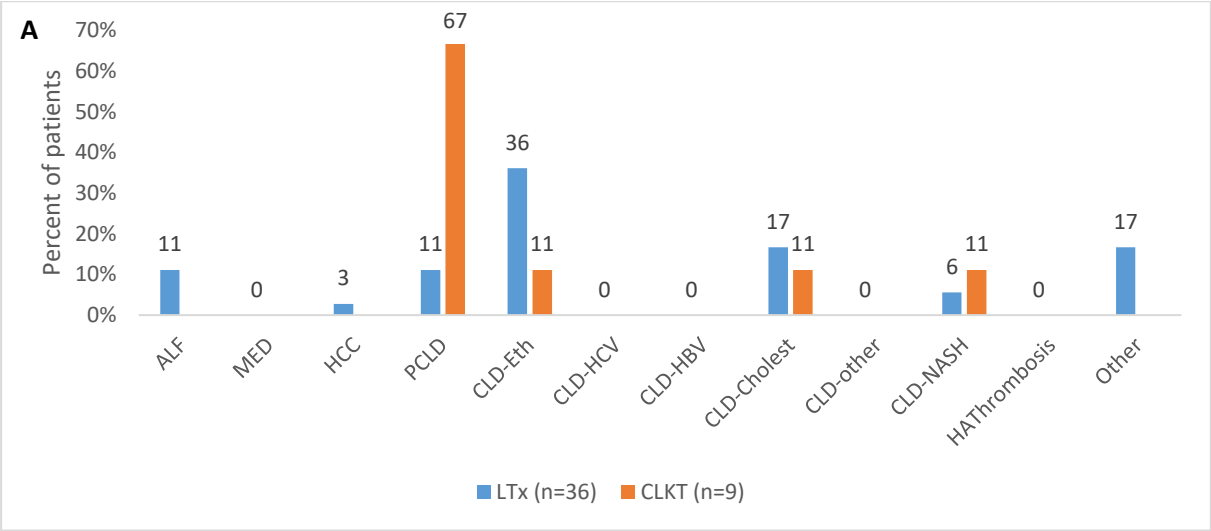
4.2 Part 2: Comparing complications after combined liver-kidney transplantation versus liver-only transplantation

4.2.1 Indications

In our second study, a total of nine CLKT patients and 36 liver-only transplant patients were included.

The liver indications for this patient population are shown in **Figure 12A**. The primary indications for liver-only transplant patients were CLD due to alcohol in 13 patients (36%), cholestatic disease in six patients (17%), NASH in two patients (6%), PCLD in four patients (11%), ALF in four patients (11%), HCC in one patient (3%) and other liver indications in six patients (17%). Eight liver-only transplant recipients had a second liver indication. These were HCC (n=6, 17%) or other liver indications (n=2, 6%).

PCLD (n=6, 67%), CLD due to alcohol (n=1, 11%), cholestatic disease (n=1, 11%) and NASH (n=1, 11%) were the liver indications for CLKT patients. Only PCLD was significantly higher in the CLKT group ($P<0.05$). The kidney indications for the CLKT patients are presented in **Figure 12B**. Five patients (56%) were transplanted for PKD disease, two patients for other chronic kidney indications (22%), one patient (11%) had diabetic nephropathy and one patient (11%) had HRS.



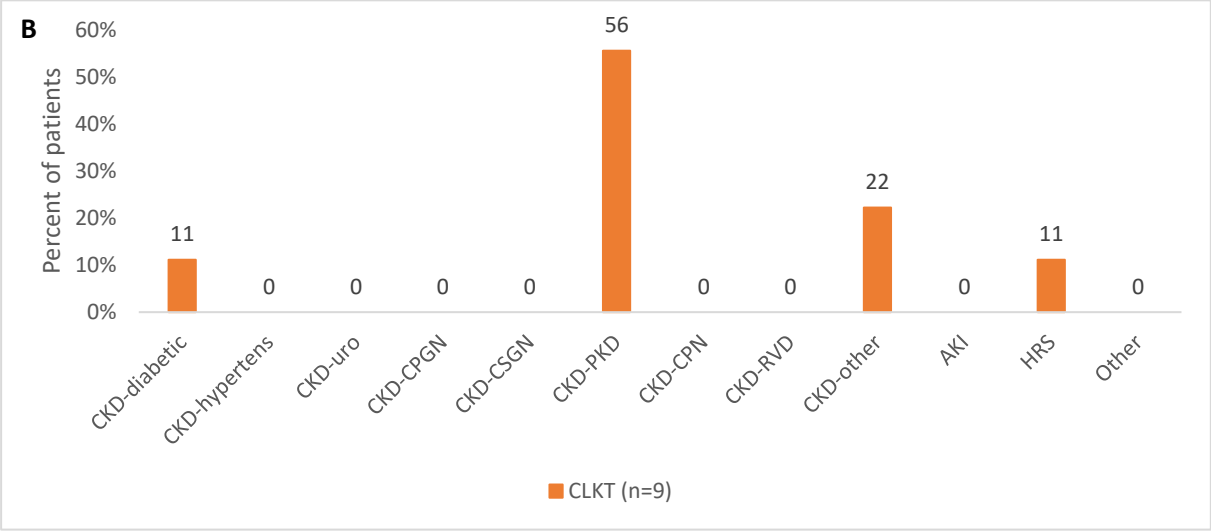


Figure 12: *Indications for LTx (blue) and CLKT (orange) patient population transplanted between July 2019 and March 2020. (A) Primary liver indications. (B) Kidney indications.*
AKI = acute kidney injury, ALF = acute liver failure, cholest = cholestatic, CKD = chronic kidney disease, CLD = chronic liver disease, CLKT = combined liver-kidney transplantation, CPGN = chronic primary glomerulonephritis, CPN = chronic pyelonephritis, CSGN = chronic secondary glomerulonephritis, diabetic = diabetic nephropathy, Eth = ethanol, HAThrombosis = hepatic artery thrombosis, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HRS = hepatorenal syndrome, hypertens = hypertensive nephropathy, LTx = liver-only transplantation, MED = metabolic / endocrine disease, NASH = non-alcoholic steatohepatitis, PCLD = polycystic liver disease, PKD = polycystic kidney disease, RVD = renovascular disease, uro = obstructive uropathy.

4.2.2 Recipient and donor demographics

Baseline characteristics of the patient population are shown in **Table 7**. There was no significant difference in recipient age between patients receiving a liver-only or a CLKT. In both groups the distribution of males and females was similar, with a slightly higher number of male recipients. Note that the CLKT recipients had a significantly higher MELD score than liver-only transplant recipients, 19 and 15 respectively. The median BAR score was similar for both groups.

Donor age was similar in both groups and most donors were male for both groups. Most often, DBD organs were used. Though the proportion of DCD donors was numerically lower in CLKT compared to liver-only (1/9 versus 13/36, respectively), this difference was not significant, likely due to the limited sample size. Trauma and anoxia were the most common cause of death in the liver-only transplant group. For CLKT, trauma was most common followed by cardiovascular accident (CVA) and anoxia on a shared second place.

Table 7: *Baseline characteristics of the patient and donor population for liver-only Tx and CLKT patients transplanted between 1 July 2019 and 20 March 2020.*

	Liver-only Tx (n=36)	**CLKT (n=9)**	**P-value**
Recipient			
Age (y)	58 (47 – 65)	52 (43 – 64)	0.52
Sex, n (%)			1.00
Male	19 (53)	5 (56)	
Female	17 (47)	4 (44)	
MELD score	15 (10 – 21)	19 (18 – 27)	**0.04**
BAR score	6 (3 – 9)	7 (6 – 11)	0.21
Liver CIT (h:mm)	5:38 (4:21 – 7:19)	5:38 (4:45 – 7:54)	0.69
Missing	*3*	*0*	
Donor			
Age (y)	56 (46 – 62)	52 (33 – 58)	0.20
Sex, n (%)			1.00
Male	26 (72)	7 (78)	
Female	10 (28)	2 (22)	
Cause of death, n (%)			0.26
Trauma	21 (58)	2 (22)	
CVA	5 (14)	3 (33)	
Anoxia	8 (22)	3 (33)	
Other	2 (6)	1 (11)	
Type of donor, n (%)			0.24
DBD	23 (64)	8 (89)	
DCD	13 (36)	1 (11)	

Continuous data are presented as median (interquartile range), categorical data as number and percentage.

BAR = balance of risk, CIT = cold ischemia time, CLKT = combined liver-kidney transplantation, CVA = cardiovascular accident, DBD = donation after brain death, DCD = donation after circulatory death, MELD = model for end-stage liver disease, Tx = transplantation.

4.2.3 Outcomes

This section summarizes the most common and important complications observed in this patient cohort. Less important complications can be found in **Appendix III, IV and V**.

General outcomes

The LOS on the ICU and LOS in the hospital was significantly longer for CLKT patients with a median of six ICU days and 40 hospital days compared with four ICU days and 19 hospital days for liver-only transplant patients. A slightly higher rate of re-admission to ICU and the hospital was observed in the CLKT compared with the liver-only population **(Table 8)**.

Observed mortality was higher in the CLKT group compared with the liver-only transplant group: two CLKT patients (22%) and one liver-only transplant patient (3%) died. Although this did not reach statistical significance, it is an important clinical observation. Similarly, liver graft loss was numerically higher in the CLKT compared with the liver-only transplant group, but this difference was not statistically significant **(Table 8)**.

Table 8: *General outcomes for liver-only Tx and CLKT patients transplanted between July 2019 and March 2020.*

	Liver-only Tx (n = 36)	**CLKT (n = 9)**	**P-value**
LOS ICU (d)	4 (3 - 6)	6 (5 – 18)	**0.04**
LOS hospital (d)	19 (13 – 25)	40 (26 – 63)	**<0.001**
Re-admission ICU, n (%)	2 (6)	2 (22)	0.17
Re-admission hospital, n (%)	14 (39)	5 (56)	0.46
Liver graft loss, n (%)	2 (6)	2 (22)	0.17
Kidney graft loss, n (%)	-	1 (11)	-
Mortality, n (%)	1 (3)	2 (22)	0.10

Continuous data are presented as median (interquartile range), categorical data as number and percentage.

CLKT = combined liver-kidney transplantation, ICU = intensive care unit, LOS = length of stay, Tx = transplantation, - = not available.

Any complications

Compared to the liver-only transplant group, CLKT patients suffered more complications during FU. These were most often related to medical complications, infections and malignancies **(Table 9)**. No differences were observed for liver-specific complications such as surgical complications, biliary complications, immunological complications and liver cancers. There were very little surgical, urological or immunological complications related to the kidney in the CLKT cohort.

Table 9: *Number of complications per patient for liver-only Tx and CLKT patients transplanted between July 2019 and March 2020.*

	Liver-only Tx (n = 36)	**CLKT (n = 9)**	**P-value**
General			
Any complications	3 (0 – 15)	4 (2 – 14)	**0.01**
Medical complications	1 (0 – 4)	3 (0 – 5)	**0.01**
Infections	0 (0 – 4)	1 (0 – 2)	**0.02**
TE	0 (0 – 1)	0 (0 – 0)	0.62
CV	0 (0 – 1)	0 (0 – 1)	0.28
Cerebrovascular complications	0 (0 – 0)	0 (0 – 0)	1.00
Malignancies	0 (0 – 0)	0 (0 – 1)	**0.05**
Liver			
Surgical complications	0.5 (0 – 6)	0 (0 – 2)	0.19
Biliary complications	0 (0 – 2)	0 (0 – 1)	0.65
Immunological complications	0 (0 – 1)	0 (0 – 0)	0.47
Malignancies	0 (0 – 0)	0 (0 – 0)	1.00
Kidney			
Surgical complications	-	0 (0 – 4)	-
Urinary complications	-	0 (0 – 0)	-
Immunological complications	-	0 (0 – 1)	-
Continuous data are presented as median with a minimum and maximum.			

CLKT = combined liver-kidney transplantation, CV = cardiovascular, Tx = transplantation, TE = thrombo-embolic, - = not available.

Complications according to Clavien-Dindo

We evaluated the number of complications per patient according to the Clavien-Dindo scale. CLKT patients developed significantly more minor complications (grade < III) compared to liver-only transplant patients. However, no significant difference was observed for severe (grade ≥ III) complications between both groups **(Table 10)**.

Table 10: *Number of complications per patient according to Clavien-Dindo for liver-only Tx and CLKT patients transplanted between July 2019 and March 2020.*

	Liver-only Tx (n = 36)	**CLKT (n = 9)**	**P-value**
Grade < III	2 (0 – 12)	4 (2 – 10)	**0.01**
Grade ≥ III	0 (0 – 3)	0 (0 – 6)	0.54
Continuous data are presented as median with a minimum and maximum.			

CLKT = combined liver-kidney transplantation, Tx = transplantation.

Proportion of patients with ≥ 1 complications

The proportion of patients who experienced ≥ 1 complications, divided in subcategories, was evaluated. Compared to liver-only transplant patients, more CLKT patients seemed to suffer

from medical complications and infections, but these differences were not statistically significant **(Table 11)**.

Table 11: *Proportion of liver-only Tx and CLKT patients, transplanted between July 2019 and March 2020, with at least one general complication, according to class.*

	Liver-only Tx (n = 36)	**CLKT (n = 9)**	**P-value**
Medical complications, n (%)	24 (67)	8 (89)	0.25
Acute kidney injury	6 (17)	4 (44)	0.09
Ascites	8 (22)	3 (33)	0.67
Pleural fluid	12 (33)	5 (56)	0.27
Delirium	6 (17)	4 (44)	0.09
Urinary tract infection	6 (17)	5 (56)	**0.03**
Primary UTI	6 (17)	5 (56)	**0.03**
Recurrence UTI	0	2 (22)	**0.04**
De novo diabetes mellitus	7 (19)	2 (22)	1.00
Respiratory failure	1 (3)	1 (11)	0.36
Infections, n (%)	13 (36)	7 (78)	0.06
Viral	4 (11)	0	0.57
Bacterial	10 (28)	7 (78)	**0.02**
Pneumonia	3 (8)	1 (11)	1.00
Gastro-intestinal	3 (8)	3 (33)	0.08
Sepsis	1 (3)	1 (11)	0.36
Other bacterial	5 (14)	3 (33)	0.33
Fungi	3 (8)	3 (33)	0.08

CLKT = combined liver-kidney transplantation, Tx = transplantation, UTI = urinary tract infection.

Table 12: *Proportion of liver-only Tx and CLKT patients, transplanted between July 2019 and March 2020, with at least one liver complication, according to class.*

	Liver-only Tx (n = 36)	**CLKT (n = 9)**	**P-value**
PNF, n (%)	0	0	-
EAD, n (%)	5 (14)	2 (22)	0.61
Donor cultures, n (%)			
Preservation fluid			0.41
Positive	7 (21)	3 (33)	
Negative	27 (79)	6 (67)	
Missing	*2*	*0*	
Aortic patch			0.33
Positive	6 (32)	3 (60)	
Negative	13 (68)	2 (40)	
Missing	*17*	*4*	
Surgical complications, n (%)	18 (50)	2 (22)	0.26
Bleeding	3 (8)	1 (11)	1.00
Wound dehiscence	9 (25)	1 (11)	0.66
Arterial	4 (11)	0	0.57
Veneus	2 (6)	1 (11)	0.50
Portal	3 (8)	0	1.00
Biliary complications, n (%)	6 (17)	1 (11)	1.00

CLKT = combined liver-kidney transplantation, EAD = early allograft dysfunction, PNF = primary non function, Tx = transplantation, - = not available.

The number of patients who experienced a urinary tract infection (UTI) was significantly higher in the CLKT group. Five CLKT patients (56%) experienced UTI compared with six liver-only transplant patients (17%). Also, significantly more bacterial infections were observed in CLKT patients (n=7, 78%) compared with liver-only transplant patients (n=10, 28%) **(Table 11)**. Regarding liver-specific complications, no differences were observed between both groups **(Table 12)**.

Table 13 shows the proportion of patients who experienced ≥ 1 kidney complications after a CLKT. Two patients (22%) experienced kidney DGF and acute kidney rejection after CLKT.

Table 13: *Proportion of CLKT patients, transplanted between July 2019 and March 2020, with at least one kidney complication, according to class.*

	CLKT (n = 9)
DGF, n (%)	2 (22)
Donor cultures, n (%)	
Preservation fluid	
Positive	2 (22)
Negative	6 (67)
Missing	*1*
Aortic patch	
Positive	3 (33)
Negative	4 (44)
Missing	*2*
Bladder fluid	
Positive	1 (11)
Negative	7 (79)
Missing	*1*
Surgical complications, n (%)	1 (11)
Wound infection	1 (11)
Evisceration	1 (11)
Seroma	1 (11)
Arterial	0
Venous	0
Ureter complications, n (%)	0
Immunological complications, n (%)	2 (22)
Acute rejection	2 (22)

CLKT = combined liver-kidney transplantation, DGF = delayed graft function.

5. Discussion and conclusion

With an increasing number of CLKTs reported worldwide and in UZ Leuven, we set out to evaluate the UZ Leuven clinical practice and outcomes after CLKT between 1997 and 2019, providing the most comprehensive review of our experience so far. Furthermore, we examined the postoperative complication rate after CLKT and compared these to liver-only transplants in the same period (1 July 2019 and 1 March 2020).

5.1 Part 1: UZ Leuven experience with combined liver-kidney transplantation

Most of the 130 CLKTs taking place in UZ Leuven between 1997 and 2019 were performed for both primary liver and kidney indication. The most common liver indication for CLKT was PCLD and the most common kidney indication was PKD. The percentage of PCLD and PKD increased over the four time eras. The number of patients with HU status decreased significantly over the time eras, with no HU patients in the last ten years. To receive the HU status the indication to transplant is ALF (31,32,53). Mostly patients receiving both liver and kidney have a more chronic character of end-stage liver and kidney disease. This might explain the small number of HU patients in CLKTs.

Recipient, liver and kidney graft survival were comparable or might be even better than the survivals of other cohorts **(Table 1)**, including two large studies with CLKT recipients based on the UNOS database from Martin et al. (n=2327) (4) and Coquillard et al. (n=5163) (5). Only the UZ Leuven recipient survival at five years was lower compared with a specific CLKT patient population (n=107) transplanted for PCLD and PKD. But the report of this study is not clear on the definition for graft failure which might have been different than the definition used in this thesis (5).

Our CLKT population had also a comparable or supposable better patient and liver graft survival when compared with liver-only transplant patients from previous studies **(Table 1)**.

It is important to note that FU for patients in Era 4 (2015-2019) only reaches a median of one year. As such, it is difficult to formulate any conclusions regarding long-term patient and graft survival for the entire cohort. Note that also in other literature only a small amount of long-term data is available, so comparisons are hard to make.

Although this study was not set up to run direct comparisons with a similar liver-only or kidney-only cohort, we can draw some preliminary comparisons with recently reported graft outcomes of UZ Leuven cohorts of liver-only and kidney-only recipients. Patient survival in the UZ Leuven CLKT cohort seems comparable with those recently reported for the UZ Leuven liver-only cohort (2000-2015), namely 90% at one year and 76% at five years after transplantation compared to 92% and 83% in the CLKT cohort (51). Also, liver graft survival in the UZ Leuven CLKT cohort seems comparable with the UZ Leuven liver-only cohort (2000-2015), 89% and

87% at one year and 81% and 72% at five years, respectively (personal communication dr. N. Gilbo). Kidney graft survival in the UZ Leuven CLKT cohort (91%, 84%, 80% at one, three, and five years) seems similar to that of the UZ Leuven DBD kidney-only cohort (2004-2012) where we recently reported one, three and five year survival rates of 93%, 88% and 82% (survival rates were extracted from the Kaplan-Meier curve using Digiteltz) (52).

Importantly, ICU and hospital stay have increased remarkably over time. There are no obvious explanations for this increase detectable from the available data, except the increased recipient age. It is generally believed that the recipient population has become sicker and more fragile over the last decade and that a change in transplant indications might have contributed to this. However, the available data do not support these statements. Indeed, MELD and BAR score remained stable when comparing time eras. In our cohort, we observed a majority of patients transplanted for PCLD. This is a condition with mostly a very low MELD score as the laboratory MELD score does not reflect the severity of the condition (53). Furthermore, most liver transplants at UZ Leuven are offered based on exceptional MELD score and not laboratory MELD, which could explain the stable laboratory MELD scores over the years (6). BAR scores only generally become high when patients are ICU bound, which is not the typical candidate for a CLKT, though patients can be sarcopenic and frail which has been shown to influence outcomes (54,55). Likely, the right measure for patient sickness and frailty are not captured in the current datasets.

An increased ICU and hospital stay might also be related to post-transplant organ failure, delayed recovery of function or other complications (the latter were investigated in Part 2 of this thesis). However, liver PNF and kidney PNF rates are low and comparable to reported proportions for liver-only or kidney-only outcomes (51,56). Liver EAD rates (20%) were comparable, perhaps a little lower, than the 27% reported for the UZ Leuven liver-only cohort of 2000-2016 (57). DGF rates (10%) for kidneys were comparable, perhaps a little lower, than the 17% reported for the UZ Leuven DBD kidney-only cohort of 2004-2012 (52) and certainly lower than that the DGF rates usually reported in kidney transplantation (58). It is difficult to speculate why these outcomes are better than liver-only or kidney-only transplants from the data available as no direct comparisons to a matched liver-only or kidney-only cohort was done. However, we can note that overall donor quality for CLKT was good with mostly DBD organs with acceptable DRI and short CIT.

Liver rejection rates have decreased significantly between Era 1 (1997-2002) and the later eras with an overall incidence of only 8%, comparable with liver rejection after liver-only transplantation in other studies (59). Also, biliary complications showed a trend towards decrease. According to Gilbo et al. a shorter CIT can reduce the risk of developing non-anastomotic biliary strictures in DCD livers (60). So, the decreasing CIT we observed

when comparing the time eras, might be a contributing factor to our decreased biliary complications.

Kidney rejection rates were 21%, this is comparable to acute kidney rejection after kidney-only transplantation (61). Looking at the eGFR at three and six months and at one year we observed similar values in the different eras. When comparing to a study from Kivelä et al. (61) our patient population had a lower eGFR at one year, 74.0 ml/min/1,73 m^2 vs 51.2 ml/min/1,73 m^2 respectively. The study from Kivelä et al. had a younger patient population so this might explain the observed difference. The study is also not clear on the criteria for the use of eGFR which might have been different than the criteria used in this thesis. Overall we see a good kidney graft function in our patient population, which is comparable to our DBD kidney-only transplant cohort of 2004-2012 (52). For the other kidney outcomes, no trends or remarkably differences were found.

From the current data we can conclude that, over the course of the four described time eras, outcomes remain stable and this despite a clinically important increase in DRI (i.e. decreasing donor quality). Indeed, the donor population became more at risk with a slightly older donor population, more DCD donors and a clinically important increase in DRI over the time eras. According to Feng et al. (47) a DRI from 1.36 (between 1997-2002) was associated with a one- and three-year liver graft survival of 82% and 74% respectively. Where a DRI from 1.57 (between 2015-2019) was associated with a liver graft survival of 80% and 71%, respectively at one and three years post-transplantation. A similar decrease in liver graft survival was shown in our patient population. Perhaps the significantly decreasing CIT of the liver is one of the responsible factors that has contributed to stable and good results despite the increase in high-risk donors. According to Adam et al. (62) and Totsuka et al. (63) a prolonged CIT was associated with PNF, biliary complications, poorer long-term graft survival and lower patient survival, especially when the CIT was more than 12h.

The decrease of CIT might be explained by improved operation techniques and improvement of transplant logistics. The one-step (midline) incision was introduced in 2013 as an alternative for the two-step incision. For certain patients the one-step technique can provide more advantages than the traditional separate implantation, for example, for patients with polycystic diseases. For hemodynamically unstable patients the two-step incision with delayed kidney implantation can be more beneficial (34). To our knowledge only one trial investigated the safety comparing one-step incision with two-step incision, a study from Jochmans et al. (n=35) (34). They included a part of the patient cohort described in this thesis and concluded that the one-step implantation and the separate implantation (two-step) had comparable outcomes for morbidity, patient and graft survival (34).

Other papers suggested that the patient and graft survival is better when the kidney implantation is delayed (7,38). In our cohort a total of 12% of the transplantations were delayed.

Between 2009-2014 no delayed transplantations were performed. In the other time eras around 20% of transplantations was delayed.

The limitations of this study are mostly related to its retrospective nature. We had hoped to identify the kidney donor risk index (KDRI) and to make conclusions about the relation between the KDRI and the patient and kidney graft survival. According to the literature a lower kidney donor profile index (KDPI) will result in better patient and kidney graft survival (64). The KDPI can be extracted from the KDRI (65), but due to a lot of missing creatinine values, the KDRI could not be calculated.

We can conclude that the patient and graft survival in UZ Leuven was very good over the last 22 years and comparable to reported outcomes of other large CLKT cohorts. Recently, CLKT patients stayed in the ICU and hospital for a considerable length of time, longer than in the earlier days of our experience. We did not observe a sound explanation for this observation, though no multivariable analyses to identify risk factors for ICU and hospital stay were performed. In the future, it would be good for the prospectively kept UZ Leuven liver database to include information on other variables that reflect patient sickness, such as sarcopenia (55) and frailty (54).

5.2 Part 2: Comparing complications after combined liver-kidney transplantation versus liver-only transplantation

A CLKT is probably one of the most invasive surgeries one can undergo and we hypothesized that these patients would experience more postoperative complications than patients undergoing a liver-only transplantation. To the best of our knowledge, there are no published papers detailing postoperative complications in CLKTs and comparing those to liver-only recipients. In this study it was investigated by analyzing the prospectively collected M&M information of all liver transplant recipients transplanted between 1 July 2019 and 1 March 2020. A total of 45 patients were transplanted, 36 liver-only recipients and nine CLKT recipients. As numbers are small, the interpretation of these data needs to be done cautiously and needs to be validated in larger cohorts. Therefore, prospective collection of M&M data has become part of routine clinical FU in the UZ Leuven Abdominal Transplant ward.

As expected, CLKT patients experienced significantly more complications compared to liver-only transplant patients. This difference was due to a higher proportion of general medical complications and not, as one intuitively might think, due to graft-related complications. Indeed, very few kidney-graft specific complications occurred in CLKTs. It seemed that the addition of a kidney transplantation, which inherently has lower risk than a liver transplantation, does not importantly increase the risk of graft-specific complications post-transplant. Ideally, this needs to be investigated in much larger cohorts.

Furthermore, there were more minor (grade < III) complications in CLKT compared to liver-only recipients, while the proportion of severe complications (grade ≥ III) was similar in both groups. Part of these minor complications can be assigned to the standard drug therapy administered after a transplantation (36,66). Immunosuppression post-CLKT is higher compared to liver-only, as tacrolimus levels are kept higher and the initial dose of corticosteroids is higher as well. In this limited patient cohort, there was no difference in rejection episodes for both liver or kidney. In fact, hardly any rejection episodes were detected. This might be related to a relatively short FU period and low overall numbers in the cohort.

Compared to liver-only transplant recipients, CLKT recipients had significantly longer ICU and hospital stays and a higher ICU and hospital re-admission rate. It would be reasonable to state that the increased rate of minor complications underlies this difference, though we could not formally investigate this in this small cohort. In addition, mortality and liver graft loss were more often, although non-significantly, observed in CLKT patients compared with liver-only transplant patients. This might be an overestimation because of the small numbers, though the difference observed in this small series is clinically relevant.

The most common primary liver indication for liver-only transplant patients was CLD due to alcohol, for CLKT patients this was PCLD. The most common kidney indication for CLKT patients was PKD.

CLKT patients had a slightly lower recipient and donor age, though this was not significant. Their MELD score was higher compared to liver-only recipients, which can likely be explained by the kidney failure as creatinine is an integral part of the MELD calculation. BAR scores, an alternative measure of patient sickness, were similar between the two groups. As sarcopenia and frailty data are not collected as part of the current dataset, it is difficult to assess whether CLKT recipients are sicker and more prone to complications compared to liver-only recipients.

In conclusion, CLKT recipients experience more postoperative complications compared to liver-only recipients, but they are not more serious and not graft-specific. The CLKT population has considerably longer ICU and hospitals stay and needs to be readmitted to ICU and hospital more often than liver-only recipients. Larger datasets are needed to further examine these findings and identify potential areas of improvement. A formal comparison with kidney-only recipients would also be valuable.

6. Nederlandstalige samenvatting

6.1 Inleiding

Gecombineerde lever-niertransplantatie (CLKT) is een levensreddende behandeling voor patiënten met eindstadium lever- en nierziekte. In sommige gevallen zijn de indicaties onduidelijk: de lever of nier faalt en het andere orgaan wordt preventief getransplanteerd. Door de lange wachtlijst voor transplantatie is het belangrijk om deze overweging grondig te maken. Momenteel is er weinig geweten over de resultaten, morbiditeit en mortaliteit na CLKTs in het veranderende landschap van orgaantransplantaties.

Sinds 1997 hebben in UZ Leuven 130 patiënten een lever en een nier gekregen. Het aantal CLKT-operaties is doorheen de jaren toegenomen en zal waarschijnlijk nog stijgen.

De allocatie van de lever en de nier voor CLKT gebeurt in Eurotransplant volgens de lever-allocatieprocedure, aan de hand van de 'model for end-stage liver disease' (MELD) score. Deze wordt berekend op basis van creatinine, bilirubine en 'international normalized ratio' (INR) van de receptor. Patiënten met een hogere MELD-score zijn zieker en zullen eerder een transplantatie krijgen.

CLKTs worden meestal uitgevoerd via een twee-staps-procedure. Eerst wordt de lever getransplanteerd en daarna de nier. De timing van de niertransplantatie kan onmiddellijk na de lever plaatsvinden of enkele uren of dagen later. Een zeldzame methode is de één-stap-transplantatie. Hierbij worden de lever en de nier getransplanteerd via een middenlijnincisie.

De meest voorkomende complicaties na een levertransplantatie zijn leverdysfunctie, chirurgische complicaties, galwegproblemen en immunologische complicaties. Na een niertransplantatie kunnen gelijkaardige complicaties optreden. Daarnaast kunnen er ook uretercomplicaties voorkomen. Na een CLKT kunnen zowel bij de lever als bij de nier complicaties optreden.

6.2 Doel

Het doel van deze masterthesis is om de CLKT-populatie in UZ Leuven te onderzoeken en om de UZ Leuven data te vergelijken met andere transplantatiecentra. We bekijken hiervoor de korte-termijnresultaten, morbiditeit en mortaliteit van CLKT-patiënten.

De hypotheses hierbij zijn:

1) UZ Leuven bereikt goede resultaten na een CLKT ondanks de verwachte gestegen risicofactoren voor zowel donor als receptor.
2) In vergelijking met levertransplantatiepatiënten ondervinden CLKT-patiënten meer en ernstigere complicaties. Hierover is op heden nog geen onderzoek gedaan. We hopen

de ernst van deze operatie te verduidelijken en meer informatie te kunnen verlenen aan toekomstige patiënten.

6.3 Methoden

6.3.1 Deel 1: Ervaringen van UZ Leuven met gecombineerde lever-niertransplantatie

Deel 1 van deze masterthesis was een retrospectieve studie waarin volwassen CLKT-patiënten, met transplantatie tussen 01/01/1997 en 20/12/2019, onderzocht werden. Zij hadden een follow-up (FU) van minstens drie maanden. De patiënten werden arbitrair opgedeeld in vier tijdperken: 01/01/1997-31/12/2002, 01/01/2003-31/12/2008, 01/01/2009-31/12/2014 en 01/01/2015-20/12/2019.

Verschillende demografische en klinische gegevens van zowel donor als receptor werden geïdentificeerd. De primaire eindpunten van deze studie waren patiënt-, lever- en nier-greffe-overleving. Deze werden gevolgd tot vijf jaar na transplantatie. Secundair werd er onder andere gekeken naar het verblijf op intensieve zorgen (ICU) en in het ziekenhuis, primaire greffe dysfunctie (PNF) van zowel lever als nier, 'early allograft dysfunction' (EAD) van de lever en 'delayed graft function' (DGF) van de nier.

6.3.2 Deel 2: Vergelijking van complicaties na gecombineerde lever-niertransplantatie versus levertransplantatie

In deel 2 vergeleken we volwassen patiënten die tussen 01/07/2019 en 01/03/2020 een CLKT of een levertransplantatie ondergingen. Hun complicaties werden, minstens twee weken, prospectief geregistreerd in de morbiditeit & mortaliteit (M&M) tool. Deze tool werd ontwikkeld door Beatrijs Steelandt (thesis student 2018-2019) en verder uitgebreid met de optie om gecombineerde transplantaties aan te duiden en de mogelijkheid om de belangrijkste complicaties na een niertransplantatie te vermelden. Deze data werden retrospectief geanalyseerd. Zowel het aantal complicaties per patiënt als het percentage patiënten met minstens één complicatie werden vergeleken. Er werd gekeken naar algemene complicaties, specifieke levercomplicaties en specifieke niercomplicaties. Daarnaast werd de ernst van de complicaties onderzocht volgens het Clavien-Dindo score systeem.

6.4 Resultaten

6.4.1 Deel 1: Ervaringen van UZ Leuven met gecombineerde lever-niertransplantatie

In het eerste deel van de studie werden er 130 CLKT-patiënten geïncludeerd in vier tijdperken: 1997-2002 (n=15), 2003-2008 (n=23), 2009-2014 (n=47) en 2015-2019 (n=45). De mediane FU-periode was vijf jaar.

De meest frequente indicatie voor transplantatie was primair lever- en nierfalen (n=63, 48%). 15% van de CLKT-patiënten hadden een dubbele leverindicatie. De meest voorkomende primaire leverindicatie in deze populatie was polycystische leverziekte (PCLD) en de meest

voorkomende secundaire leverindicatie was hepatocellulair carcinoom (HCC). De meest voorkomende nierindicatie was polycystische nierziekte (PKD).

Receptoren met transplantatie tussen 1997-2002 waren significant jonger dan receptoren met transplantatie tussen 2003 en 2019. De MELD- en 'balance of risk'- (BAR) scores waren gelijkaardig in de vier tijdperken met een mediaan van respectievelijk 23 en negen. De donorleeftijd steeg, niet-significant, naar het laatste tijdperk toe. De meest voorkomende doodsoorzaken waren trauma en cardiovasculair falen (40% en 45%). In de vier tijdperken werden voornamelijk hersendode (DBD) donoren gebruikt. Slechts 11% van de donoren waren hartdood (DCD) en deze kwamen voor tussen 2009 en 2019. De 'donor risk index' (DRI) steeg significant tussen de vier tijdperken.

Significant meer uitgestelde niertransplantaties werden uitgevoerd tussen 2003-2008 en 2015-2019, ten opzichte van de periode 2009-2014. De meeste CLKTs werden uitgevoerd door een twee-staps-incisie (89%). De koude-ischemietijd (CIT) van de lever daalde significant tussen tijdperk 2 (2003-2008) en tijdperk 4 (2015-2019), respectievelijk 8u15 en 6u17. De mediane CIT voor de hele cohorte was 7u10.

Voor deze populatie was er een lever-greffe-overleving van 89%, 83%, 81% en 61% op één, drie, vijf en tien jaar na de transplantatie. Er waren geen significante verschillen tussen de verschillende tijdperken (P=0,44). De nier-greffe-overleving op dezelfde tijdsstippen bedraagt respectievelijk 91%, 84%, 80% en 55%. Eveneens zonder significante verschillen tussen de tijdperken (P=0,12). De patiëntenoverleving bedraagt respectievelijk 92%, 85%, 83% en 67% op één, drie, vijf en tien jaar. Er waren geen significante verschillen tussen de tijdperken (P=0,10).

PNF van lever en nier voor deze populatie waren laag, respectievelijk 0% en 3%. EAD van de lever kwam voor in 20% van de patiënten, DGF van de nier in 10%. We stelden bij 8% van de patiënten leverrejectie vast en bij 21% van de patiënten nierrejectie. Er was een significant verschil in leverrejectie tussen tijdperk 1 (1997-2002) en tijdperk 3 (2009-2014), respectievelijk 27% en 0%. Nierfunctie was goed met een mediane glomerulaire filtratiesnelheid (eGFR) op drie, zes en 12 maanden van 58,9 ml/min/1,73m^2; 58,2 ml/min/1,73m^2 en 51,2 ml/min/1,73m^2, respectievelijk. De mediaan van het verblijf op ICU was vijf dagen en van het ziekenhuisverblijf 24 dagen. Er was een, respectievelijk significante en niet-significante, stijging van het aantal ICU- en ziekenhuisdagen naar het recentste tijdperk toe.

6.4.2 Deel 2: Vergelijking van complicaties na gecombineerde lever-niertransplantatie versus levertransplantatie

In dit deel werden CLKT-patiënten (n=9) en levertransplantatiepatiënten (n=36) vergeleken. Chronische leverziekte door alcohol was de meest voorkomende primaire leverindicatie voor de levertransplantatiepatiënten (n=13, 29%). Bij de CLKT-patiënten was dit PCLD (n=6, 13%)

en de nierindicatie PKD (n=5, 56%). Levertransplantatiepatiënten waren enigszins ouder dan CLKT-patiënten. De MELD-score voor CLKT-patiënten was significant hoger, 19 versus 15. De BAR-score was gelijkaardig voor CLKT-patiënten en levertransplantatiepatiënten, respectievelijk zeven en zes. De donorleeftijd was gelijkaardig in beide groepen. Hoofdzakelijk organen van DBD-donoren werden gebruikt in beide groepen. Trauma was de meest voorkomende doodsoorzaak.

CLKT-patiënten verbleven significant langer op de ICU en in het ziekenhuis in vergelijking met levertransplantatiepatiënten, respectievelijk zes en vier dagen op ICU en 40 en 19 dagen in het ziekenhuis. Mortaliteit was niet-significant hoger in de CLKT-groep in vergelijking met de levertransplantatiegroep, respectievelijk 22% en 3%. Ook lever-greffeverlies was niet-significant hoger in de CLKT-groep, respectievelijk 22% en 6%. CLKT-patiënten hadden significant meer complicaties dan levertransplantatiepatiënten, respectievelijk vier en drie complicaties per patiënt. Vooral de algemene complicaties kwamen meer voor in de CLKT-groep. De majeure complicaties waren gelijkaardig in beide groepen en de mineure complicaties kwamen significant meer voor in de CLKT-groep in vergelijking met de levertransplantatiegroep (vier versus twee complicaties). In vergelijking met de levertransplantatiepatiënten, leden meer CLKT-patiënten aan medische complicaties (67% versus 89%) en infecties (36% versus 78%), deze verschillen waren niet significant.

6.5 Discussie en conclusie

6.5.1 Deel 1: Ervaringen van UZ Leuven met gecombineerde lever-niertransplantatie

Receptor-, lever- en nier-greffe-overleving waren vergelijkbaar of mogelijks zelfs beter dan in andere cohorten. Ook wanneer we onze CLKT-populatie vergelijken met levertransplantatiepatiënten waren de resultaten gelijkaardig of vermoedelijk beter. In onze studie noch in de literatuur waren er voldoende gegevens over de tienjaarsoverleving om betrouwbare lange-termijnconclusies te trekken. Wanneer we deze studie vergelijken met levertransplantaties in UZ Leuven (2000-2015) zien we voor zowel receptor- als lever-greffe-overleving gelijkaardige resultaten voor beide populaties. Ook de nier-greffe-overleving van deze UZ Leuven CLKT-cohorte is vergelijkbaar met de UZ Leuven DBD niercohorte van 2004 tot 2012. Opmerkelijk is de verlenging van het ICU- en ziekenhuisverblijf over de verschillende tijdperken. Er zijn geen duidelijke verklaringen voor deze stijging, enkel de gestegen patiëntleeftijd kan dit deels verklaren. De patiëntenpopulatie lijkt het laatste decennium zieker en zwakker te zijn geworden. De beschikbare data ondersteunt deze stelling echter niet. De MELD- en BAR-score bleven stabiel over de tijdperken. Door het hoge aantal PCLD-indicaties, geeft de MELD-score echter geen realistisch beeld van de ernst van de ziekte in onze populatie. CLKT-patiënten zijn meestal niet ICU gebonden waardoor de BAR-score ook laag blijft. CLKT-patiënten kunnen sarcopeen en frail worden en dit kan de resultaten beïnvloeden. Deze parameters werden niet meegenomen in de huidige database.

Een gestegen aantal dagen in de ICU en het ziekenhuis kunnen gerelateerd zijn aan post-transplant orgaanfalen, langere hersteltijd en andere complicaties (zie Deel 2). Nochtans zijn het aantal lever PNF, lever EAD, leverrejectie, biliaire complicaties, nier PNF, nier DGF en nierrejectie laag en vergelijkbaar met resultaten na alleen-lever- of alleen-niertransplantaties. Aangezien we geen directe vergelijking hebben gemaakt tussen deze studies, is het moeilijk om te verklaren waarom de resultaten na CLKT beter zijn dan na alleen-lever- of alleen-niertransplantatie. We zien wel een goede algemene donorkwaliteit in de CLKT-populatie, dit kan het lage aantal complicaties deels verklaren. Uit de data kunnen we concluderen dat de resultaten, over de verschillende tijdperken, stabiel bleven en dit ondanks een stijgende DRI en dus een dalende donorkwaliteit. Mogelijk heeft de significant dalende CIT van de lever voor de goede resultaten in onze populatie gezorgd ondanks de stijgende hoog-risicodonoren. De dalende CIT kan verklaard worden door verbeterde operatietechnieken (zoals één-stap-incisie) en transportlogistiek. In de toekomst is het aangewezen om prospectief bepaalde parameters te registreren, zoals sarcopenie en ‘frailty’, die de ernst van de ziekte van de patiënt, weergeven.

6.5.2 Deel 2: Vergelijking van complicaties na gecombineerde lever-niertransplantatie versus levertransplantatie

De complicaties na CLKT en na levertransplantatie werden onderzocht aan de hand van een zeer kleine populatie lever- en CLKT-patiënten. Zoals we verwachtten, hebben CLKT-patiënten meer complicaties in vergelijking met levertransplantatiepatiënten. Vooral het aantal mineure complicaties was hoger in de CLKT-groep, terwijl we een gelijkaardig aantal ernstige complicaties (graad ≥ III) zien in beide groepen. De mineure complicaties kunnen mogelijk veroorzaakt worden door de standaardmedicatie na een transplantatie. Immunosuppressieve medicatie is hoger na een CLKT in vergelijking met een levertransplantatie en dit kan mogelijk onze waarnemingen verklaren. We zagen een opmerkelijk verschil in het aantal ICU- en ziekenhuisdagen en in het aantal heropnames tussen de CLKT-groep en de levertransplantatiegroep. Het verhoogde aantal mineure complicaties kunnen aan de basis liggen van dit verschil. Ook de MELD-score was hoger in de CLKT-groep. Dit kan verklaard worden door de verhoogde creatinine, welke een rol speelt bij de berekening van de MELD-score bij nierfalen. De BAR-scores waren gelijkaardig in beide groepen. Gegevens over sarcopenie en ‘frailty’ werden niet bijgehouden, dit maakt het moeilijk om een besluit te vormen omtrent de ernst van de ziekte en vatbaarheid voor complicaties van CLKT-patiënten in vergelijking met levertransplantatiepatiënten. We kunnen concluderen dat CLKT-patiënten meer complicaties hadden in vergelijking met leverpatiënten maar deze zijn niet ernstiger en ook niet greffe-specifiek. Het ICU- en ziekenhuisverblijf was langer voor CLKT-patiënten. Grotere datasets zijn nodig om deze bevindingen verder te onderzoeken. Een vergelijking met niertransplantatiepatiënten zou ook waardevol zijn.

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Appendix I: Morbidity and mortality tool

Morbiditeit en mortaliteit na levertransplantatie

KWS PID Naam:
KWS PID Voornaam:
KWS PID Eadnr:
KWS PID Geslacht:
KWS PID Geboortedatum:
Datum van transplantatie: (datum van reperfusie)
Datum einde Follow-up: (90 dagen post Tx)

Gecombineerde levertransplantatie: o Ja o Nee
Orgaan:
- o Nier
- o Pancreas
- o Dunne darm
- o Hart
- o Long

Ging patiënt naar ITE tussen de transplantaties van de verschillende organen: o Ja o Nee

Datum ontslag ITE:
Datum ontslag na LTx:
Heropname op ITE: o Ja o Nee
Heropname op verpleegafdeling: o Ja o Nee

Algemeen:

Mortaliteit:
o Ja
o Nee
Datum:

✓ **Medische complicaties:**
- ✓ Acuut nierinsufficiëntie — Dialyse: o Ja o Nee
- ✓ Ascites — Behandeling:
- ✓ Pleuravocht — Behandeling:
- ✓ Delirium
- ✓ Urineweginfectie
  - o Primair — Pathogeen:
  - o Recidief — Pathogeen:
- ✓ de novo Diabetes Mellitus
- ✓ Respiratoir falen

✓ **Infecties:**
- ✓ Viraal
  - ✓ Cytomegalovirus
    - o Asymptomatisch
    - o Symptomatisch:
  - ✓ Epstein Barr Virus
    - o Asymptomatisch

o Symptomatisch:
✓ Hepatitis B Virus
o Asymptomatisch
o Symptomatisch:
✓ Hepatitis C Virus
o Asymptomatisch
o Symptomatisch:
✓ Herpes Simplex Virus
0 Type 1 0 Type 2
o Asymptomatisch
o Symptomatisch:
✓ Varicella Zoster Virus
o Asymptomatisch
o Symptomatisch:
✓ Influenza
o Asymptomatisch
o Symptomatisch
✓ Polyoma Virus
o Asymptomatisch
o Symptomatisch
✓ Andere:
✓ Bacterieel
✓ Pneumonie
✓ Gastro-intestinaal
Pathogeen:
o Clostridium difficile
o Andere
✓ Sepsis Pathogeen:
✓ Andere:
✓ Fungi
Waar gekweekt?:
o Aspergillus Fumigatus
o Candida Albicans
o Cryptococcus Neoformans
o Andere:
✓ Parasiet
o Toxoplasma Gondii
o Trypanosoma Cruzii
o Andere:

✓ **Trombo-embolische complicaties:**
✓ Longembolie
✓ Diepe Veneuze Trombose Locatie:
✓ Andere:

✓ **Cardiovasculair event:**
✓ Myocardinfarct
✓ De novo hartfalen
✓ Hartritmestoornissen

✓ **Cerebrovasculair event:**
✓ Ischemisch

✓ Hemorragisch

✓ **Maligniteiten:**

✓ Huidkanker:

o Basaal celcarcinoom
o Squameus celcarcinoom
o Melanoom

✓ Donor-derived:

✓ Andere:

Lever

Primary Non Function:

(D3 post tx OPTN urgent list criteria (biliaire obstructies geëxcludeerd): AST ≥ 3000 U/L en één van volgende: INR ≥ 2,5 en/of s-lactaat ≥ 4 mmol/L en/of totaal bilirubine ≥ 10 mg/dL)

o Ja
o Nee

Retransplantatie: o Ja o Nee
Datum reTx:

Early Allograft Dysfunction:

(Olthoff Criteria: bilirubin ≥ 10 mg on day 7and/or INR ≥ 1.6 on day 7 and/or AST or ALT > 2000 IU/L within the first 7 days)

o Ja
o Nee

Donorculturen:

Preservatievocht:
Beschikbaar: o Ja o Nee
o Positief
o Negatief
Organisme:

Aortapatch:
Beschikbaar: o Ja o Nee
o Positief
o Negatief
Organisme:

Perfusaat:
Beschikbaar: o Ja o Nee
o Positief
o Negatief
Organisme:

Machineperfusaat:
Beschikbaar: o Ja o Nee
o Positief
o Negatief
Organisme:

✓ **Chirurgische complicaties:**

✓ Arterieel:

✓ Trombose Arteria Hepatica

Datum:
Behandeling:
o Retransplantatie
o Trombectomie
o Andere:

✓ Stenose Arteria Hepatica

Datum:
Behandeling:

✓ Mycotisch Aneurysma
Datum:
Verwekker:
Presentatie: o Bloeding
o Toevallige vondst
Behandeling:

✓ Veneus:

✓ Trombose Vena Cava Inferior — Datum:
Behandeling:

✓ Stenose Vena Cava Inferior — Datum:
Behandeling:

✓ Trombose Vena Hepatica — Datum:
Behandeling:

✓ Portaal:

✓ Trombose Vena Porta — Datum:
Behandeling:

✓ Stenose Vena Porta — Datum:
Behandeling:

✓ Bloeding — Datum:
Locatie: arteria hepatica, vena porta, inferior vena cava, spieren, diffuus

✓ Wonddehiscentie: — Datum:
Behandeling:

✓ Wondinfectie: — Datum:

✓ Evisceratie: — Datum:
Behandeling:

✓ Seroma:

✓ Lymphocele:
Waar?
o oksel
o lies
o elders

✓ Andere:

✓ **Galwegproblemen:**

✓ Gallek: — Datum:
o Asymptomatisch
o Symptomatisch:
Behandeling:

✓ Strictuur:
- Klinisch vermoeden
- Toevallige vondst

✓ Anastomose — Datum:
o Asymptomatisch
o Symptomatisch:

Behandeling:
- o Conservatief — Datum:
- o ERCP + stent — Datum:
- o PTC + stent — Datum:
- o Heraanleggen — Datum:
- o Andere: — Datum:

✓ Non-anastomose — Datum:
- o Asymptomatisch
- o Symptomatisch:

Behandeling:
- o Conservatief — Datum:
- o ERCP + stent — Datum:
- o PTC + stent — Datum:
- o Retransplantatie — Datum:
- o Andere — Datum:

✓ Choledocholithiasis: — Datum: Behandeling:

✓ Cholangitis: — Datum: Behandeling:

✓ Immunologische complicaties:

✓ Acute rejectie
- Klinisch vermoeden
- Toevallige vondst

Datum:
Biopsie: o Ja o Nee
Oorsprong: o Cellulair o Antibody mediated o Ductopeen
Behandeling:

✓ Maligniteiten:

✓ Recidief Hepatocellulair Carcinoma

Nier

Delayed Graft Function:
(Criteria: ≥1 dialyse in de eerste 7 dagen na transplantatie)
o Ja
o Nee

Donorculturen:
Preservatievocht:
o Positief — Organisme:
o Negatief
o Niet beschikbaar

Aortapatch:
o Positief — Organisme:
o Negatief
o Niet beschikbaar

Perfusaat:
o Positief — Organisme:
o Negatief
o Niet beschikbaar

Machineperfusaat:
o Positief — Organisme:
o Negatief
o Niet beschikbaar

Ontvanger culturen:
Blaasvocht:
o Positief — Organisme:
o Negatief
o Niet beschikbaar

✓ **Chirurgische complicaties:**

- ✓ Arterieel
  - ✓ Trombose arteria renalis
    Datum
    Behandeling:
    - Transplantectomie
    - Trombectomie
    - Andere:
  - ✓ Stenose arteria renalis
    Datum:
    Behandeling:
    - Angioplastie — Datum:
    - Angioplastie + stent — Datum:
    - Chirurgie — Datum:
- ✓ Veneus
  - ✓ Trombose vena renalis
    Datum:
    Behandeling:
    - Transplantectomie
    - Trombectomie
    - Andere:
- ✓ Bloeding — Datum:
  Locatie: arteria renalis, vena renalis, external iliac artery, external iliac vein, internal iliac artery
- ✓ Wonddehiscentie: — Datum:
  Behandeling:
- ✓ Wondinfectie: — Datum:
- ✓ Evisceratie: — Datum:
  Behandeling:
- ✓ Seroma:
- ✓ Lymphocele:
- ✓ Andere:

✓ **Ureter complicaties:**

- ✓ Urine lek

Datum:
Behandeling:

✓ Ureter obstructie
- o Anastomotische strictuur
- o Compressie door bloedklonter
- o Compressie door lymphocele

Behandeling:

✓ **Immunologische complicaties:**

✓ Acute rejectie
- o Klinisch vermoeden
- o Toevallige vondst

Datum:
Biopsie: o Ja o Nee
Oorsprong: o Cellulair o Antibody mediated
Behandeling:

Pancreas

Dunne darm

Hart

Long

Appendix II: Extra pretransplant information of the combined liver-kidney population transplanted between 1997 and 2019.

Information about nephrectomy and HLA-matching is presented in

The withdrawal of a kidney (unilateral or bilateral) has changed over the different time eras, we can see a significant difference between 2009-2014 and 2015-2019. The nephrectomy can occur pre-, per- or post-transplantation. This timing of nephrectomy is significantly different over the eras, when correcting for multiple testing no longer a difference is found.

Table 14: *Extra pretransplant information of the CLKT population transplanted between 1997 and 2019.*

	Total (n=130)	**Group 1: '97-'02 (n=15)**	**Group 2: '03-'08 (n=23)**	**Group 3: '09-'14 (n=47)**	**Group 4: '15-'19 (n=45)**	**P-value**
Nephrectomy, n (%)	56 (43)			*		**0.03**
Left	4 (3)	1 (7)	1 (4)	0	2 (4)	
Right	17 (13)	1 (7)	4 (17)	11 (24)	1 (2)	
Bilateral	35 (27)	6 (40)	5 (22)	8 (17)	16 (36)	
Timing nephrectomy, n (%)						
Left						**<0.05**
Pre-operative	20 (15)	6 (40)	5 (22)	5 (11)	4 (9)	
Peroperative	15 (12)	1 (7)	0	2 (4)	12 (27)	
Postoperative	3 (2)	0	1 (4)	1 (2)	1 (2)	
Right						0.57
Pre-operative	18 (14)	5 (33)	3 (13)	6 (13)	4 (9)	
Peroperative	34 (26)	2 (13)	6 (26)	13 (28)	13 (29)	
Postoperative	1 (1)	0	0	0	1 (2)	
HLA mismatch, n (%)						
HLA-A mismatch						0.91
0 MM	15 (12)	2 (13)	4 (17)	4 (9)	5 (11)	
1 MM	68 (52)	7 (47)	12 (52)	27 (57)	22 (49)	
2 MM	46 (35)	5 (33)	7 (30)	16 (34)	18 (40)	
Missing	*1*	*1*	*0*	*0*	*0*	
HLA-B mismatch						0.08
0 MM	6 (5)	2 (13)	3 (13)	1 (2)	0	
1 MM	44 (34)	4 (26)	8 (35)	19 (40)	13 (29)	
2 MM	79 (61)	8 (53)	12 (52)	27 (57)	32 (71)	
Missing	*1*	*1*	*0*	*0*	*0*	
HLA-DR mismatch						0.59
0 MM	4 (3)	1 (7)	1 (4)	2 (4)	0	
1 MM	51 (40)	5 (33)	9 (39)	21 (45)	16 (36)	
2 MM	74 (57)	8 (53)	13 (57)	24 (51)	29 (64)	
Missing	*1*	*1*	*0*	*0*	*0*	

Categorical data are presented as number and percentage.

CLKT = combined liver-kidney transplantation, HLA = human leucocyte antigen, MM = mismatch.

Appendix III: Proportion of liver-only and combined liver-kidney patients with at least one general complication

Table 15: *Proportion of liver-only Tx and CLKT patients, transplanted between July 2019 and March 2020, with at least one general complication, according to class.*

	Liver-only Tx (n = 36)	**CLKT (n = 9)**	**P-value**
Infections, n (%)	13 (36)	7 (78)	0.06
Viral	4 (11)	0	0.57
CMV	1 (3)	0	1.00
EBV	0	0	-
HBV	0	0	-
HCV	0	0	-
HSV	1 (3)	0	1.00
VZV	0	0	-
Influenza	1 (3)	0	1.00
Polyoma	0	0	-
Missing	*18*	*7*	
Other viral	1 (3)	0	1.00
Fungi	3 (8)	3 (33)	0.08
Aspergillus fumigatus	0	0	-
Candida albicans	3 (8)	1 (11)	1.00
Cryptococcus neoformans	0	0	-
Other fungi	1 (3)	2 (22)	0.10
Parasite	0	0	-
Toxoplasma gondii	0	0	-
Trypanosoma cruzii	0	0	-
Other parasite	0	0	-
TE, n (%)	1 (3)	0	1.00
Lung embolism	0	0	-
DVT	1 (3)	0	1.00
Other TE	0	0	-
Cardiovascular event, n (%)	1 (3)	1 (11)	0.36
Myocardinfarct	0	0	-
De novo heart failure	0	0	-
Cardiac arrythmias	1 (3)	1 (11)	0.36
Cerebrovascular event, n (%)	0	0	-
Ischemic	0	0	-
Hemorraghic	0	0	-
Malignancies, n (%)	0	1 (11)	0.20
Skin cancer	0	0	-
Donor derived	0	0	-
Other malignancies	0	1 (11)	0.20

Categorical data are presented as number and percentage.

CLKT = combined liver-kidney transplantation, CMV = cytomegalovirus, DVT = deep vein thrombosis, EBV = Epstein barr virus, HBV = hepatitis B virus, HCV = hepatitis C virus, HSV = herpes simplex virus, TE = thromboembolic, Tx = transplantation, VZV = varicella zoster virus, - = not available.

Appendix IV: Proportion of liver-only and combined liver-kidney patients with at least one liver complication

Table 16: *Proportion of liver-only Tx and CLKT patients, transplanted between July 2019 and March 2020, with at least one liver complication, according to class.*

	Liver-only Tx (n = 36)	**CLKT (n = 9)**	**P-value**
Surgical complications, n (%)	18 (50)	2 (22)	0.26
Wound infection	2 (6)	0	1.00
Evisceration	0	0	-
Seroma	3 (8)	0	1.00
Lymphocele	0	0	-
Other surgical complications	0	0	-
Arterial	4 (11)	0	0.57
Thrombose arteria hepatica	0	0	-
Stenose arteria hepatica	4 (11)	0	0.57
Mycotic aneurysm	1 (3)	1 (11)	1.00
Venous	2 (6)	1 (11)	0.50
Thrombose vena cava inferior	1 (3)	0	1.00
Stenose vena cava inferior	1 (3)	1 (11)	0.36
Thrombose vena hepatica	0	0	-
Portal	3 (8)	0	1.00
Thrombose vena porta	0	0	-
Stenose vena porta	3 (8)	1 (11)	1.00
Biliary complications, n (%)	6 (17)	1 (11)	1.00
Biliary leak	0	0	-
Biliary stricture	6 (17)	1 (11)	1.00
Choledocholithiasis	0	0	-
Cholangitis	2 (6)	0	1.00
Immunological complications, n (%)	2 (6)	0	1.00
Acute rejection	2 (6)	0	1.00
Malignancies, n (%)	0	0	-
Recurrence HCC	0	0	-

CLKT = combined liver-kidney transplantation, HCC = hepatocellular carcinoma, Tx = transplantation, - = not available.

Appendix V: Proportion of combined liver-kidney patients with at least one kidney complication

Table 17: *Proportion of CLKT patients, transplanted between July 2019 and March 2020, with at least one kidney complication, according to class.*

	CLKT (n = 9)
Surgical complications, n (%)	1 (11)
Bleeding	0
Wound dehiscence	0
Lymphocele	0
Other surgical complications	0
Arterial	0
Thrombosis arteria renalis	0
Stenosis arteria renalis	0
Venous	0
Thrombosis vena renalis	0
Ureter complications, n (%)	0
Urine leak	0
Ureter obstruction	0

CLKT = combined liver-kidney transplantation.