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Renal Assessment in the Setting of Pediatric Living Related Liver Transplantation

Thesis

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in Pediatrics*

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List of Abbreviations

Abb.	Full term
AKIN	Acute Kidney Injury Network
ALT	Alanine amino transferase
ANOVA	Analysis of variance
APOLT	Auxilliary partial orthotopic LT
ARIC	Atherosclerosis Risks in Communities
ARPKD	Autosomal recessive polycystic kidney disease
AST	Aspartate amino transferase
B2M	Beta-2-microglobulin
BTP	Beta-trace protein
CHS	Cardiovascular Health Study
CKD	Chronic kidney disease
CMS	Center for Medicaid and Medicare Services
CMV	Cytomegalovirus
CNI	Calcineurin inhibitors
CNIs	Calcineurin inhibitors
CTS	Collaborative transplant study
DDLT	Countries deceased-donor liver transplant
e	Estimated
EBV	Epstein-Barr virus
ECM	Extracellular matrix
eGFR	Estimated GFR
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESLD	End-stage liver disease
FDA	Food and Drug Administration
GD	Graves' Disease
GFR	Glomerular filtration rate

List of Abbreviations Cont...

Abb.	Full term
GGTP	Gamma-glutamyl trans peptidase
GLDH	Glutamate dehydrogenase
GRWR	Graft-recipient body weight ratio
HAS	HA stenosis
HAT	HA thrombosis
HS	Highly significant
HTN	Hypertension
ICU	Intensive Care Unit
IDMS	Isotope dilution mass spectroscopy
IgAN	Immunoglobulin A nephropathy
KDIGO	Kidney Disease Improving Global Outcomes
LDLT	Living-donor-LT
LFTs	Liver function tests
LOS	Length of stay
LRLT	Liver transplanted children
LT	Liver transplantation
LTx	Liver transplantation
MCTs	Medium-chain triglycerides
MDRD	Modification of Diet in Renal Disease
MELD	Model for End Stage Liver Disease
mGFR	Measured GFR
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
mTOR	Mammalian target of rapamycin
NS	Non-significant
PCR	Polymerase chain reaction
PELD	Pediatric Model for End Stage Liver Disease

List of Abbreviations Cont...

Abb.	Full term
PKC-β	Protein kinase C beta
pLT	Pediatric LT
pRIFLE	Pediatric RIFLE
PTA	Percutaneous transluminal angioplasty
PTLD	Post transplant lymphoproliferative disorder
ptlds	Post-transplant lymphoproliferative disorders
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
ROC	Receiver-operating characteristics
RRT	Replacement therapy
S	Significant
SD	Standard deviation
SFS	Small for size graft syndrome
SPLIT	Studies of Pediatric LT
SPSS	Statistical Package for the Social Science
TAC	Tacrolimus
TGF-β1	Transforming growth factor beta 1
UCD	Urea cycle defect
UCLA	University of California, Los Angeles

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Introduction

Liver transplantation in the pediatric age group has become the last resort and yet the preferred option for many end stage liver disorders. This field has shown a great improvement and is considered a breakthrough achievement for previously fatal liver diseases.

In view of the fact that survival rate following liver transplantation has greatly improved over the past three decades, chronic renal insufficiency has become a vital and crucial problem, which increases the complexity of patient management and may in turn influence the survival rate (*Wenger et al., 2013; Basiratnia et al., 2020*).

The data available regarding the assessment of renal function in the setting of pediatric LRLT are limited unlike that of the adults. Moreover, a variety of studies have demonstrated that a calculated glomerular filtration rate (GFR) based on serum creatinine is inaccurate, especially in pediatric age group (*Anastaze et al., 2012*). Hence, this study will be used to determine the incidence of chronic renal insufficiency using more reliable renal testing techniques such as Cystatin C which was shown to be a better marker of GFR than creatinine, creatinine clearance, or eGFR for assessment of renal impairment (*Seronie-Vivien et al., 2008*).

Aim of the Work

- **Primary:** To determine the incidence of renal dysfunction among pediatric LT recipients using more reliable renal testing methods.
- **Secondary:** To determine the risk factors of renal dysfunction.

Chapter 1

Pediatric Liver Transplantation

In 1953, the pioneer of human orthotopic liver transplantation (LT), Thomas E Starzl, was the first to attempt an orthotopic liver transplant into a 3 years old patient suffering from biliary atresia. Thus, the first LT in humans was attempted in a disease, which, up until today, remains the main indication for pediatric LT (pLT). During the last sixty-eight years, refinements in diagnostics and surgical technique, the introduction of new immunosuppressive medications and improvements in perioperative pediatric care have established LT as routine procedure for childhood acute and chronic liver failure as well as inherited liver diseases.

In contrast to adult recipients, pLT differs greatly in indications for LT, allocation practice, surgical technique, immunosuppression and post-operative life-long aftercare. Many aspects are focus of ongoing preclinical and clinical research (*Christina et al., 2015*)

LT is the only curative treatment option for patients with irrevocable acute or chronic liver failure and, in the last six decades, has developed from an experimental approach with very high mortality to an almost routine procedure with good short and long-term survival rates. In the early years, long-term survival rates after pediatric LT (pLT) were 11% - 39% (*Pichlmayr et al., 1984*) and, since then, have improved to up to 90% with long-term graft survival rates of > 80% (*Yazigi, 2013*).

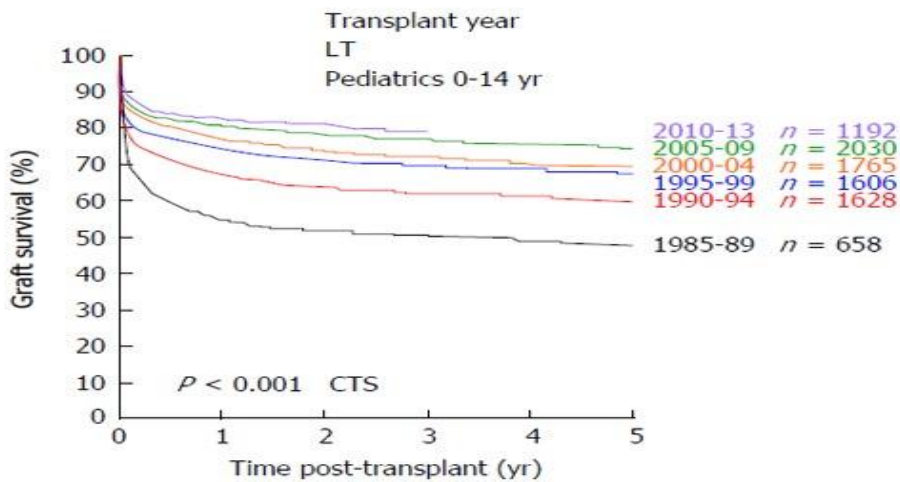


Figure (1): Development of graft survival after pediatric liver transplantation from 1985 until 2013 (collaborative transplant study data). CTS: Collaborative transplant study; LT: Liver transplants.

Due to continuing improvements of surgical and interventional techniques as well as perioperative neonatal and pediatric intensive care medicine, the average age of pediatric transplant recipients has steadily declined, with a continuous increase of patients transplanted within the first year of life. As of today, approximately 27% of pLT are performed in recipients younger than 12 months. Patients in this young age, which in former years could not be transplanted (and mostly died before reaching the size and age of transplant ability), today show a long-term survival of almost 90%, which is comparable to older children.

At the same time, long-term survival after pLT implies life-long aftercare in an interdisciplinary team to ensure a life with as little as possible secondary morbidity (*Christina et al., 2015*).

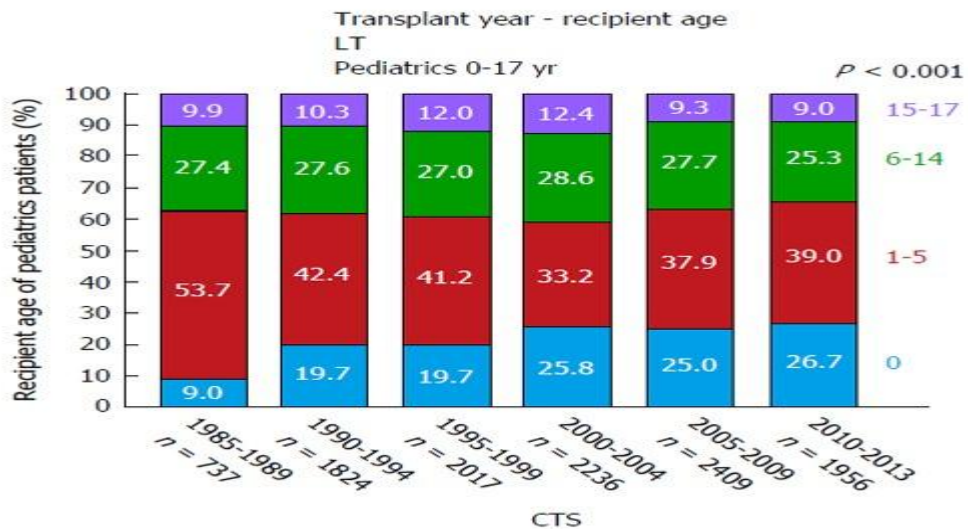


Figure (2): Age distribution of pediatric liver transplantation recipients from 1985 until 2013 (collaborative transplant study data). CTS: Collaborative transplant study; LT: Liver transplants.

Liver transplantation indications:

Indications for LT in pediatric patients are manifold and can be classified into cholestatic disorders, metabolic liver diseases causing liver cirrhosis, metabolic liver diseases without liver cirrhosis, acute liver failure, acute and chronic hepatitis, and liver tumors. With approximately 40%, the main indication for pLT is biliary atresia. Thus, the indications for pLT are significantly different to indications in adult LT recipients (*Melter et al., 2012*).