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LIFE AND HEALTH AFTER PEDIATRIC SOLID ORGAN TRANSPLANTATION

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ACADEMIC DISSERTATION

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"Quality of life is a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity." WHO

To my family

ABSTRACT

The aim of the study was to observe quality of life (QoL), psychosocial wellness (**study I**), changes in telomere regulation (**study II**) and cancer risk (**study III**) among young adults with a history of pediatric solid organ transplantation (SOT).

In **study I**, 29 males who received their first kidney transplant (KTx) during childhood or adolescence were included. The study had two different control groups: the first group included survivors of childhood acute lymphatic leukemia (ALL) and the second young males without any chronic disease during childhood. All study subjects completed questionnaires measuring QoL (RAND-36) and depressive symptoms (BDI-21). End-stage kidney disease (ESKD) and transplantation had influence on physical health, which was seen as impaired physical subscales of QoL, decreased vitality and general health. The KTx recipients' mean score in the depression inventory was significantly higher than that of controls, but none of the KTx recipients had severe depressive symptoms. Surprisingly, QoL, but also educational and employment aspects, were lower after pediatric SOT than after childhood ALL. When compared to healthy controls, the KTx recipients had significantly less relationships and offspring.

Study II also had three different study cohorts. The first group included 20 males with a history of pediatric kidney transplantation while the second group included survivors of childhood neuroblastoma (NBL) and the third included previously healthy young males. Clinical data and blood samples were collected from study subjects. Genomic DNA and RNA were extracted and leukocyte telomere length and gene expression levels of telomere binding proteins were measured. The shortest telomeres were found among the NBL survivors. KTx recipients' telomere length was reduced compared to healthy controls, but not significantly so. Interestingly, the gene expression levels of telomere binding proteins were highest among the KTx recipients. A statistically significant difference compared to other groups was found in telomerase components TRF2, RPA1 and tumor suppressor gene P16. KTx recipients' telomeres are shorter than those of healthy controls but gene expression levels are increased, which shows capacity of repair accelerated attrition.

Solid organ transplant (SOT) recipients' risk for malignancies is reportedly increased, caused mainly by prolonged exposure to immunosuppressive medication and viremias. In **study III,** the risk of post-transplantation malignancies after pediatric SOT was evaluated using national registries. All pediatric kidney, liver and heart transplant recipients who were transplanted in Finland after 1982 and were over 18 years at the time of the study were identified from the Digital and Population Data Services Agency registry. Each SOT recipient had three to five hometown, year of birth and gender matched controls. All cancer cases were searched from the Finnish Cancer Registry. This study confirmed earlier findings suggesting that post-transplant lymphoproliferative disorder (PTLD) is the main cancer type after pediatric SOT.

Mortality is very high and the course of PTLD is aggressive. Compared to the peers representing general population, the risk of non-PTLD cancers was three-fold higher after childhood SOT.

In the future, the challenge in the care of pediatric SOT recipients is to improve recipients' QoL and psychosocial skills and decrease the harmful effects of immunosuppressive medication, which are clearly important risk factors for physical unwellness and malignancies.

TIIVISTELMÄ

Tämän tutkimuksen tarkoitus oli selvittää elämänlaatua, psykososiaalista hyvinvointia (**osatyö I**), telomeerien pituutta ja telomeerien säätelyä (**osatyö II**) sekä syöpäriskiä (**osatyö III**) nuorilla aikuisilla, joille oli tehty elinsiirto lapsuudessa.

Osatyössä I oli yhteensä 29 miestä, jotka olivat saaneet munuaissiirron lapsuus-tai nuoruusikäisenä. Tutkimuksessa oli kaksi vertailukohorttia: ensimmäinen koostui lapsena akuutin lymfaattisen leukemian sairastaneista miehistä ja toinen ryhmä nuorista miehistä, joilla ei ollut tiedossa olevaa pitkäaikaissairautta. Kaikki tutkimuspotilaat täyttivät kyselylomakkeet, jotka koskivat elämänlaatua (RAND-36) ja depressio-oireita (BDI-21). Loppuvaiheen munuaistoiminnalla sekä elinsiirrolla oli vaikutusta elämänlaatukyselyn fyysisiin osa-alueisiin, vähentyneeseen energisyyteen ja yleiseen terveyden kokemukseen. Munuaissiirtopotilailla oli keskimääräistä korkeammat pisteet depressiokyselyssä verrokkiryhmiin verrattuna, mutta kellään ei ilmennyt vaikean depression oireita. Yllättävää oli, että munuaissiirron saaneilla niin elämänlaatu, koulutustaso kuin työllistyminenkin olivat heikompia kuin lapsuusiän leukemian sairastaneilla. Munuaissiirron saaneilla oli myös merkittävästi vähemmän parisuhteita ja biologisia lapsia terveisiin verrokkeihin verrattuna.

Osatyössä II oli myöskin kolme eri tutkimuskohorttia. Ensimmäinen ryhmä käsitti 20 miestä, jotka olivat lapsena saaneet munuaissiirron, mutta olivat tutkimushetkellä täysi-ikäisiä. Toisen ryhmän muodostivat lapsena neuroblastooman sairastaneet nuoret miehet, ja kolmannen terveet verrokit. Kliininen tutkimus ja laboratoriokokeet olivat suoritettu aiemman tutkimuksen puitteissa. Valkosoluista eristettiin DNA ja RNA, määritettiin telomeerien pituus sekä telomeraasin aktiivisuus. Neuroblastooman sairastaneiden miesten telomeerit olivat lyhyempiä muihin ryhmiin verrattuna. Munuaissiirron saaneiden miesten telomeerit olivat lyhyempiä kuin terveillä verrokeilla, mutta ero ei ollut tilastollisesti merkitsevä. Mielenkiintoinen löydös oli telomeraasin komponenttien TRF2, RPA1 sekä tuumorisuppressiogeenin p16 merkittävästi suurempi aktiivisuus munuaissiirron saaneilla. Munuaissiirron saaneiden telomeerit olivat lyhyempiä kuin terveillä verrokeilla, mutta telomeraasin aktiivisuus vaikutti olevan suurentunut, pyrkien korjaamaan telomeerin kulumista.

Elinsiirron saaneiden syöpäriski on merkittävästi lisääntynyt liittyen hyljinnänestolääkitykseen ja viremioihin. **Kolmannessa osatyössä** selvitimme kansallisista rekistereistä lapsena elinsiirron saaneiden syöpäsairastavuutta. Kaikki Suomessa vuoden 1982 jälkeen munuais-, maksa- tai sydämensiirron lapsena saaneet täysi-ikäiset selvitettiin Digi- ja väestötietorekisteristä. Yhtä tutkimushenkilöä kohden määritettiin kolmesta viiteen kotipaikka-, syntymävuosi- ja sukupuolivakioitua väestöverrokkia. Tiedot syöpäsairaudet selvitettiin Syöpä-rekisteristä. Tutkimus vahvisti aiempien tutkimusten löydöksen, että elinsiirron saaneilla oli suurin riski sairastua elinsiirron jälkeiseen lymfoproliferatiiviseen

sairauteen (PTLD). Kuolleisuus lymfoomaan oli suuri ja taudin luonne huomattavan aggressiivinen. Elinsiirron saaneiden syöpäriski, PTLD poisluettuna, oli kolme kertaa suurempi kuin väestöverrokeilla.

Tulevaisuuden haasteita ovat elinsiirron saaneiden lasten elämänlaadun ja psykososiaalisten taitojen lisääminen sekä immunosuppressiivisen lääkityksen haittojen vähentäminen, millä on vaikutusta sekä fyysiseen hyvinvointiin, että syöpäriskiin.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Endén K, Tainio J, Jalanko H, Jahnukainen K, Jahnukainen T: Lower quality of life in young men after pediatric kidney transplantation when compared to healthy controls and survivors of childhood leukemia - a cross-sectional study Transpl Int. 2018 Feb; 31(2): 157-164

II. Endén, K, Tainio J, Hou, M, Suominen A, Pakarinen M.P, Huang T, Söder O, Jalanko H, Jahnukainen K, Jahnukainen T. Telomere length regulators are activated in young men after pediatric kidney transplantation compared to healthy controls and survivors of childhood cancer—A cross-sectional study. Pediatr Transplant. 2019 Nov; 23(7): e13550

III. Endén K, Tainio J, Nikkilä J, Helanterä I, Nordin A, Pakarinen M.P, Jalanko H, Jahnukainen K, Jahnukainen T: Cancer morbidity and mortality after pediatric solid organ transplantation – a nationwide register study. Pediatric Nephrology Sept; 35 : 1719-1728

The publications are referred to in the text by their Roman numerals. These articles were reprinted with the permission of their copyright holders.

ABBREVIATIONS

ABOi	ABO-incompatible
ADPKD	autosomal dominant polycystic kidney disease
ALL	acute lymphatic leukemia
ATG	anti-thymocyte globulin
AU	arabian unit
BDI	Beck Depression Inventory
BMI	body mass index
BP	blood pressure
CAKUT	congenital anomalies of kidney and urinary
CHQ	Child Health Questionnaire
CNF	congenital nephrosis
CNI	calcineurin inhibitor
CsA	cyklosporin
DNA	deoxyribonucleic acid
DSA	donor-specific antibodies
EBV	Ebstein-Barr virus
ESKD	end-stage kidney disease
GFR	estimated glomerular filtration rate
GNF	glomerulonephritis
HD	hemodialysis
HHV8	human herpesvirus 8
HLA	human leukocyte antigens
HLHS	hypoplastic left heart syndrome
HRQoL	health-related quality of life
hsCRP	high sensitive c-reactive protein
ISH	*in situ* hybridization
KTx	kidney transplant
LTx	liver transplant

HTx	heart transplant
MDRD	Modification of Diet in Renal Disease
MMF	mycophenolate mofetil
mTOR	mammalian target of rabamycin inhibitor
NBL	neuroblastoma
NA	not applicable
NHL	non-Hodgkin lymphoma
NMSC	nonmelanoma skin cancer
P-Cr	plasma creatinine
PedsQL	Pediatric Quality of Life Inventory Generic Core Scale
PTLD	post-transplant lymphoproliferative disease
RNA	ribonucleic acid
RRT	renal replacement therapy
SOT	solid organ transplantation
SF-36	Short-Form Health Survey 36
THL	Finnish Institute for Health and Welfare
Tx	transplantation
QoL	quality of life
q-PCR	quantitative polymerase chain reaction
VAD	ventricular assist device

1 INTRODUCTION

Solid organ transplantation (SOT) is the only life-saving treatment of end-stage liver and heart failure and curative treatment for chronic kidney failure. Pediatric kidney transplantations have been performed in Finland since 1982 and in the Children's Hospital since 1986. Pediatric liver transplantations began to be performed in Finland in 1987 and heart transplantations for children in 1991. More than 500 solid organ transplantations have been performed since then in Finland and all transplantations have been centralized to Helsinki University Children's Hospital.

During the last decades, graft survival has improved [1-4] and attention has begun to be paid to the general health, quality of life and social aspects after pediatric solid organ transplantation.

In Finland, kidney transplant (KTx) recipients are younger compared to other countries due to the high prevalence of congenital nephrosis of Finnish type (CNF). During the first year of life, the CNF patients are mostly hospitalized, getting regular albumin infusions. Treatment of end-state kidney disease (ESKD) is supportive, consisting of medication, special diet, and often, limitation of fluid intake to prevent hypervolemia. Dialysis is started if other supportive treatment is insufficient. After SOT, recipients live their childhood with scheduled timetables, taking medicines, having regular visits to outpatient clinic, and also spending varying periods of time in the hospital.

Transplantation recipients visit their local hospital (central or university hospital) every week the first one to two months after transplantation; during the first post-transplant year, these visits gradually decrease, the average time interval being six to eight weeks. Every control visit includes physical examination, weight, height, blood pressure and laboratory tests. Heart transplant recipients visit a pediatric cardiology consult every three months. Follow-up visits to Helsinki University Hospital are scheduled three, six, twelve and eighteen months after transplantation, and after that, annually.

At least once a year, recipients and their families meet a social worker, psychiatric nurse or psychologist and dentist. Dietician and physiotherapist are consulted if needed. Neuropsychological investigations are made for all recipients at age five years to clarify special needs or need for support during pre-school and elementary school. The second time a neuropsychological evaluation is made is during the last part of elementary education to support the recipients choose further studies after comprehensive school.

In Finland, preschool lasts one or two years, followed by elementary school for an additional nine years. After elementary school, it is possible continue to college or to vocational studies. During longer hospital stays is possible to get learning support

from a hospital teacher. The purpose is to ensure that schoolwork can go on after discharge from hospital and after that, in the child's own school.

After the age of 19-20 years, SOT recipients are followed by an adult nephrologist, cardiologist or gastroenterologist. The moment of transition is scheduled individually depending on physical and mental development. The current state of studies and other life are also important factors to consider during the transition. All adolescents are invited to a CAMP weekend which prepares the youngsters for the transition.

The aim of this study was to investigate how solid transplant recipients manage their adult life after pediatric solid organ transplantation.

2 REVIEW OF THE LITERATURE

2.1 PEDIATRIC SOLID ORGAN TRANSPLANTATION

2.1.1 KIDNEY TRANSPLANTATION

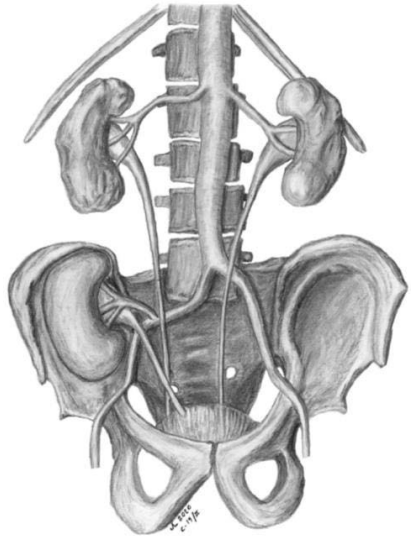


Figure 1 Kidney transplant. Illustration modified based on orginal by Roach et al. (2017) [5].

Kidney transplantation is the only curative treatment for end-stage renal disease (ESKD). The first successful kidney transplantation was performed in 1954 by Joseph Murray [6] between identical twins, and the first pediatric kidney transplantation was done in 1967 [7]. Major causes for transplantation are congenital anomalies of the kidney and urinary tract [8,9] and glomerulonephritis [4,5,10]. The Finnish pediatric kidney transplant population is special caused by high prevalence of Finnish type congenital nephrosis (CNF). CNF is caused by a mutation in the NPHS1 gene which encodes nephrin [11]. Nephrin is an adhesion molecule and it is localized in the glomerulus slit diaphragm. Total absence of nephrin causes massive proteinuria during the first months of life. The only available treatment is nephrectomy and kidney transplantation, typically during the first year of life [11,12]. For this reason, Finnish pediatric kidney recipients are younger at time of transplantation compared to recipients in other countries [13,14] and they are exposed to immunosuppressive treatment at a younger age and for a longer time.

Preparations for kidney transplantation are started at ESKD stage IV-V [15] when glomerular filtration rate is 20mL/min/1.73m^2 or less. If needed, renal replacement therapy (RRT) is started before transplantation, but pre-emptive transplantation without dialysis is also possible. All transplant candidates undergo extensive physical examinations and a comprehensive vaccination protocol before transplantation. Contraindications for transplantation are active infection or malignancy, active autoimmune disease, uncontrolled hypertension or progressive brain disorder [9]. A multidisciplinary team evaluates all candidates and makes the final decision.

Kidney transplantation is possible from a living donor [16] or deceased donor. The rate of living donation varies in different countries between 12 and 65% [1,10,17-19]. In Finland, the law on organ donation changed on 1 March 2019; the new law allows living donations also from close partners, not only from parents or adult siblings [20].

Tissue typing and ABO compatibility are determining factors of the kidney transplantation. Tissue typing, which means HLA (human leukocyte antigen) matching, is important for graft survival after transplantation. High HLA mismatch increases the risk for development of donor-specific antibodies (DSA), which can cause humoral rejection [21] and sensitization of the recipients. Good HLA matching, short cold ischemia time and young donor age [22,23] have influence on better graft survival [1,19,24-26] and especially in pediatric population it is crucial to attempt to maintain good graft function for as long as possible. Previously, only ABO-compatible kidney transplantations were done in Finland, but during the last decade, the results of living ABO-incompatible (ABOi) transplantations have been encouraging [27,28] and the number of ABOi transplantations has increased. This allows broadening of the donation pool and decreases waiting time on the transplant list.

During the last decades, graft function has improved significantly [1,4]. Graft survival after first post-transplantation year is 89-97% and 5-year survival is 79-88% [1,4,18,29]. Patient survival after kidney transplantation is 99% after the first year and 95-97% after five years [1,4,10,18,29]. As a result of excellent patient survival growing numbers of pediatric solid organ transplant recipients are reaching adult life.

2.1.2 LIVER TRANSPLANTATION

The first human liver transplantation (LTx) and the first pediatric liver transplantation was performed in 1963 for a 3-year-old girl with biliary atresia [30]. Despite the transplantation being unsuccessful, it marked the start of a liver transplantation program. The first Nordic liver transplantation was performed in 1982 in Finland [31] and the first pediatric liver transplantation was done in 1987 in Helsinki.

The main indications for liver transplantation can be divided into five categories; 1) extrahepatic cholestasis, 2) intrahepatic cholestasis, 3) metabolic disorders, 4) acute liver failure, and 5) others, including liver malignancies and cystic fibrosis [32,33]. The most common cause leading to liver transplantation is biliary atresia. The second most common causes are metabolic diseases followed by acute liver failure and

malignancies [34,35]. LTx recipients are mostly under school age during the transplantation and nearly one third undergo liver transplantation during the first year of life [34].

Pre-transplant evaluation and contraindications for transplantation are for the most part the same as for kidney transplantation [35]. Hepatoblastoma with metastases is not an absolute contraindication for liver transplantation [32,36] but careful evaluation is needed before the transplantation decision.

A liver transplant can be from a living donor or deceased donor. Surgical technique allows transplanting also part of the liver instead of the whole liver, using either liver resection or split liver [32,34]. Liver resection allows reduced liver size, which is needed in the case of a small-sized recipient. Most liver transplantations are ABO-compatible [34] but HLA matching is not required.

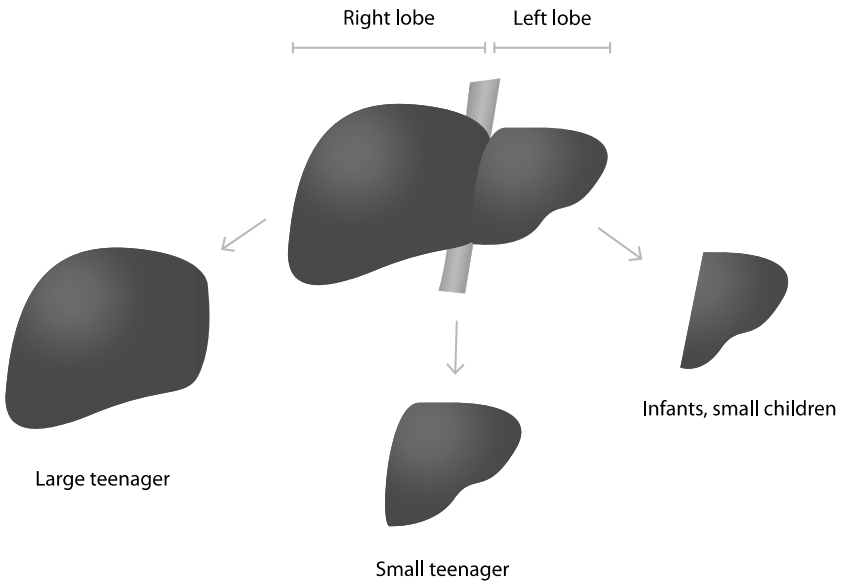


Figure 2 Liver transplant and graft types. Picture modified based on illustration by the www.clevelandclinic.org.

Post-transplantation graft survival has been around 73-89% after the first year and 67-93% five years after transplantation [3,37,38]. First-year patient survival after pediatric liver transplantation has been 86-97% and 5-year survival 80-96% [3,32,34,35,37,38]. Most short-term complications are associated with rejection, vascular or biliary complications [32,34,35]. Long-term complications are not only related to graft function but also to burden of infections, malignancies, cardiovascular diseases, chronic renal failure as medical complication and diminished quality of life [32,35].

2.1.3 HEART TRANSPLANTATION

The first experiments with heart transplantations (HTx) were made in dogs [39] and the first interhuman transplantation was performed in Cape Town, South Africa, in 1967 [40]. Only three days later, the first heart transplantation in a child was done in New York, US [41]. Although both recipients died shortly after the transplantation, the first steps towards curative treatment for end-stage heart disease had been taken. In Finland, heart transplantations were started in 1985 in adults and in 1991 in children.

The indication for heart transplantation is end-stage cardiac disease with maximum medical or other support therapies [42]. The main reason for infant heart transplantation is severe heart failure caused by congenital heart disease, and in older children, cardiomyopathy [43-46]. Other causes are myocardial damage caused by inflammation, genetic, autoimmune, toxic or metabolic disorders [47]. In some cases, mechanical circulatory support is a bridge to transplantation. The most commonly used device is ventricular assist device (VAD) [42,43].

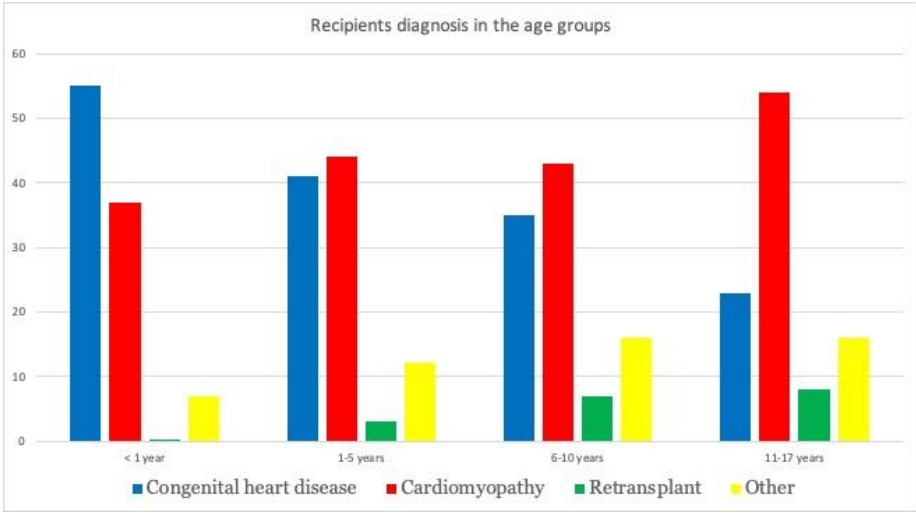


Figure 3 Diagnosis leading to heart transplantation in the different age groups. Modified based on Rossano et al. (2017) [43].

The selection of suitable heart transplant is based on ABO compatibility, but size match between the donor and recipient is also an important factor. A donor- recipient weight ratio of 1.0 to < 1.5 is considered preferable [43]. Infant recipients need pediatric donors for successful transplantation and in these cases, the waiting time can be long. During the last decade, oversize grafts have begun to be used, and the results are comparable with earlier heart transplantations [48]. Also ABOi heart transplantations have been performed successfully among this patient group.

The main purpose of pre-transplant evaluation is to exclude active infections, malignancies or other organ failures, which have to be taken into account at transplantation. It is necessary to evaluate anatomical and neurological aspects and exclude progressive systemic diseases [42].

Survival after pediatric heart transplantation is better among infant recipients versus adolescence recipients [44,49]. The International Society for Heart and Lung Transplantation's (ISHLT) International Thoracic Organ Transplant Registry data showed that cause of transplantation and age at time of transplantation have major influence on recipients' survival [44]. Cardiomyopathy as a diagnosis leading to HTx had superior outcome compared to other diagnoses. In addition, younger transplant recipients had better outcome after heart transplantation compared to older age groups [49].

In a previous study, long-term survival among the Finnish pediatric heart transplantation cohort during the first year was 90% and after five years, 68% [50]. Graft failure, infections, multiorgan failure, cerebro-vascular or pulmonology complications are the main reasons leading to death during the first year after transplantation. Later complications are related to vasculopathies or malignancies [51].

2.1.4 IMMUNOSUPRESSIVE AGENTS – IN GENERAL

The immunosuppressive regime after transplantation is principally the same after all types of solid organ transplantations. Post-transplant immunosuppression consists of steroids, calcineurin inhibitors and anti-metabolite agents [32]. After liver transplantation, also mono or dual therapy has been used [34] and steroids are withdrawn earlier.

The goal of immunosuppressive therapy is to prevent rejection, but on the other hand, avoidance of side effects is essential. Immunosuppression after transplantation has changed during the last decades [9] as awareness of late adverse effects has increased and new immunosuppressive agents have become available.

The first **calcineurin inhibitor (CNI)**, cyclosporine (CsA), has in most cases been replaced by tacrolimus [18,52]. CNIs block phosphatase activity and inactivate T-lymphocytes [53]. Typical side effects of CsA are hypertrichosis and gingival hypertrophia, but also nephrotoxicity. Tacrolimus lacks the first two adverse effects but it is nephrotoxic and the risk for inducing diabetes is higher than in CsA [54].

CNIs may have also neurological side effects; negative impact on cognitive function and even structural changes in brain tissue have been found [55].

Two **anti-metabolites**, azathioprine and mycophenolate mofetil (MMF), have been used as the immunosuppressive regimen in combination with CNI inhibitors and steroids. Azathioprine inhibits purine nucleotide synthesis and blocks cell proliferation [53]. Recently, studies have shown MMF to be superior to azathioprine in the prevention of acute rejection episodes [56] and in the last few years, MMF has increasingly replaced azathioprine [18,57]. The most common adverse effects are gastrointestinal (diarrhea, nausea), hematological (leuko-neutropenia), infections and malignancies [58].

Glucocorticosteroids are part of the immunosuppressive regimen at least during the first post-transplant year [57]. The immunosuppressive action of corticosteroids is not completely known, but the humoral effect is based on decreased expression of interleukines and cytokines. The cellular pathway reduces T lymphocyte proliferation [53]. Glucocorticoid side effects (growth restriction, cataract, obesity, hypertension, dyslipidemia) are well known and unfavorable, especially during childhood [59]. To diminish the adverse effects of corticosteroids, doses are reduced and in some centers, even discontinued in the first post-transplant years.

Novel immunosuppressive agents are **mammalian target of rapamycin inhibitors** (mTOR) [60] which allow using lower therapeutic levels of calcineurin inhibitors and thus diminish nephrotoxicity and the risk of viremias. The immunosuppressive action is based on binding and inhibiting kinase, an enzyme needed for cell cycle progression [53]. Adverse effects are connected to blocking of mTOR-inhibiting pathways. The most common side-effects are insulin resistance, leading to diabetes, glomerular dysfunction, hyperlipidemia and cytopenias [61].

A new field of treatment is genotype-guided dosing of immunosuppressive medicines [62]. Especially, evaluation of cytochrome CYP3A5 genotype helps to individualize treatment and diminish side effects [63].

2.2 QUALITY OF LIFE

In 1946, WHO defined quality of life (QoL) as follows: "*a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity*" [64]. This means that chronic disease should not be a barrier to a good and valuable life, and this should always be kept in mind when evaluating and treating solid organ transplant recipients.

There have been many definitions of QoL and health-related quality of life (HRQoL) [65] which are somewhat confusing, making it difficult to evaluate and compare research works. A more precise definition of HRQoL states that it is quality of life which is related to health and includes physical, emotional and social aspects.

Evaluation of QoL or HRQoL, especially in patients with chronic diseases or history of extensive therapies such as transplantation, is crucial in order to find out aspects that need more attention. Using QoL questionnaires makes it possible to compare different study groups and evaluate not only status of the disease, but also the general health and psycho-social wellness of the subject. Transplant recipients' QoL is composed not only of graft function, but also of general health and psycho-social well-being (Figure 4). QoL questionnaires mainly evaluate the subject's estimation of general health and psychosocial well-being.

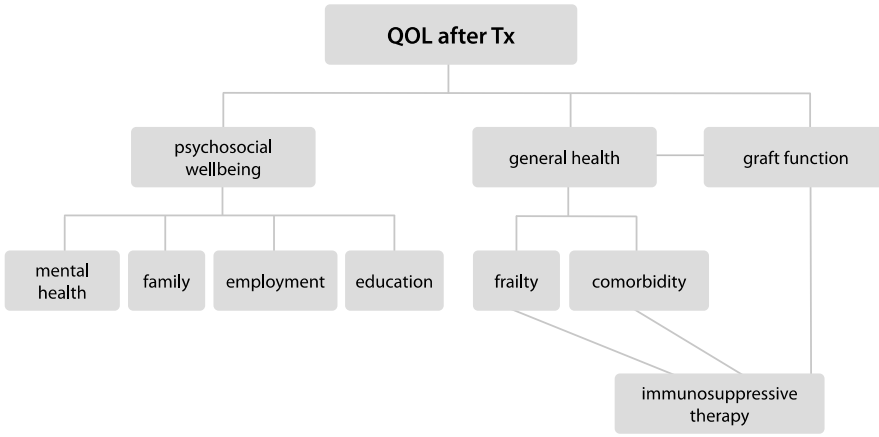


Figure 4 Components of quality of life.

There are two main types of questionnaires to measure QoL;

1) Generic QoL questionnaires are generally used in patients with different disease conditions. They do not include disease specific aspects but are used to evaluate general health and psycosocial wellness. The most commonly used questionnaires are **RAND 36**, **EuroQOL 5D** (EQ5D) and **Short form 15** (SF-15) [66,67].

2) Targeted QoL questionnaires include disease spesific elements like symptoms which are typical/specific for the disease or treatment toxicity [67]. Spesific questionnaires for SOT recipients are scarce. Some instruments have been designed for liver and kidney transplant recipients like **Liver Disease Quality of Life** (LDQOL) and **End-state renal disease symptom checklist-transplant module** (ESRDSCL-TM) [67,68].

Pediatric Quality of Life Inventory Generic Core Scale (PedsQL), **Child Health Questionnaire** (CHQ), **Child Health Questionnaire** (CHQ) and **Short form 36** (SF-36) are the most commonly used generic tools for pediatric population [69,70]. CHQ and PedsQL have different questionnaires for children and their parents. Children's QoL can be evaluated directly by using children's questionnaire tool, but some parent proxy QoL instruments have been made. Questionnaires for parents are mostly used to evaluate QoL of small children, but also to compare scoring by children and parents. Questionnaires for caregivers have also been used for patients' QoL evaluation [71].

PedsQL also has a separate questionnaire to evaluate especially transplant recipients [72]. This tool includes questions on medication's effect on QoL, but also on social, physical and mental aspects.

2.2.1 QOL AFTER KTX

QoL studies among adult KTx recipients with history of pediatric solid organ transplantation are scarce.

Evaluations of QoL of children and adolescents with RRT or KTx show varying results. QoL has been scored from good [73] to significantly lower than in controls [8,74]. The variable QoL results probably depend on whether QoL is reported by patients themselves or parents. Children and adolescents have good adaptation and positive attitude to existing circumstances and report higher scores than parents who report more problems in their children's lives [75,76]. Comparison with other severe childhood diseases has revealed that QoL is significantly lower after pediatric KTx than after diagnosis of other chronic conditions [77]. Emotional, self-esteem and social subscales are scored lower than in controls [74,77].

In the recent study by Adamczuk [78] life activity, disease acceptance and QoL were evaluated during renal replacement therapy and after KTx among young adults. Satisfaction with life was significantly lower in the RRT/ KTx group than in the control group. Young age at time of kidney disease diagnosis, multiple transplants, poor economical situation or comorbidities had significant negative correlation to

QoL and emotional well-being [79]. A Dutch study with follow-up of 30 years after RRT showed that only physical subscales were diminished whereas mental health scores were normal compared to controls [80]. Most of the study subjects had received KTx. Employment, having offspring and good economical status diminished the risk for lower QoL.

A study from Norway showed that physical activity had a positive effect not only on cardiorespiratory health but also on HRQoL and mental healthy after pediatric KTx [81].

2.2.2 QOL AFTER LTX

LTx recipients under 18 years old scored lower on subscales of psychosocial, social and school functioning than the normal population, but physical and emotional components were comparable [82].

In previous studies among adults who had undergone LTx during childhood, physical components of QoL scores were lower than in the general population [83-85]. In addition, the social functioning score in the SF-36 questionnaire was lower when compared to general US population [85]. In a Finnish study, general health was impaired, but still 64% of the childhood LTx recipients felt that they had excellent health [84].

After childhood LTx, physical condition and general health are more decreased than social or emotional components. A significant finding is that higher QoL has been associated with higher educational and employment level and fewer visits to hospital [83].

2.2.3 QOL AFTER HTX

In HTx recipients aged under 18 years, QoL was significantly lower in all subscales when compared to healthy controls, both by self report and parent proxy. Physical, psychosocial and social functioning were significantly decreased compared to children with a history of curative cardiac surgery, but comparable to cardiac patients with non-curative surgery [86]. Chronic disease causes long hospital stays and impaired physical condition, both of which makes it difficult to keep up with social relationships and school work.

Surprisingly, previous studies among adults with a history of childhood HTx have shown that HTx recipients scored their QoL at the same level as general population [87-89].

In a recent study from Italy comparing adult HTx recipients, one cohort was transplanted in adulthoods and the other at under 18 years of age. Recipients with transplantation during childhood had higher QoL in all dimensions. The difference was statistically significant in physical functioning, role limitations due to physical, health problems, bodily pain and general health [90]. In general, adult HTx recipients

after childhood Tx have good physical and social functioning and have valuable and satisfactory lives.

2.3 EDUCATION AND SOCIAL INTERACTION

2.3.1 EDUCATION AND EMPLOYMENT AFTER SOLID ORGAN TRANSPLANTATION

In most of the previous studies, educational level after pediatric KTx was significantly lower or comparable with that of general population. A total of 8% of the study subjects had only comprehensive education after pediatric RRT or KTx [91]. Secondary grade education (general or vocational training) was completed by 20-50% and 14% had finished university studies after childhood ESKD [80,91,92]. In a Polish study, education level after pediatric RRT with or without KTx was comparable with that of general population. Most study subjects had secondary education (64%) [78]. Employment rate after pediatric KTx varies between 47 and 62% [78,80,91] (Table 1). In a small Italian study, only 30% of the KTx recipients were part-time or full-time employed [79]. Among younger study populations, some subjects are still studying, which decreases the number of those with full-time employment.

LTx recipients' educational level was lower compared to healthy controls. Most pediatric LTx recipients have low or middle educational level and only few have graduated from university [93,94]. In the Finnish study, 17% of young adults with a history of pediatric LTx had only compulsory education [84]. Employment rate varied: 38-100 % of pediatric LTx recipients worked full-time or part-time. In case-control studies, unemployment rate has been higher among LTx recipients than among controls, which may be due to lower educational level, but also to the age of the study subjects [83-85,95]. Unemployment rate is remarkably higher among adults after pediatric LTx than among recipients of LTx in adulthood (50% vs. 28%) [85].

After pediatric HTx, a total of 16-100% graduated from high school, most recipients studied after high school (68%), and 7-26% achieved a bachelor degree [88,89,96]. Half (47-58%) of the pediatric HTx recipients were employed and 11% were unable to work [88,96]. HTx recipients with development delay were excluded from these studies.

In the Finish general population, secondary grade is completed by 56% of and university grade by 13% of all age groups. A total of four percent of young adults (20-39 years) had only elementary education [97].

2.3.2 RELATIONSHIPS AND OFFSPRING

Study subject's age has influence on the number of marital relationships and offspring. In a Dutch study, at the age of 40, 67% of childhood RRT survivors were married and 32% had children [80]. Among young adults with a history of pediatric KTx, only 3-18% had a family and 10-12% had children [78,79,91].

In the studies of pediatric LTx recipients, 23-42% of young adults were married or living in partnership [85,93,98]. Half of HTx recipients over 30 years old had a partner [88]

while in the younger HTx cohort (mean age 25 years), only 9% were in a relationship. A total of 70% of young adults lived with their parents or family member [89].

According to Statistics Finland, the proportion of Finns who were married at the age of 23 and 30 years was 20% and 60%, respectively,[99] and 39% of their families included at least one child [100].

Table 1 *Main studies of socioecomical situation after pediatric solid organ transplantation. NA, not available, n= number of study subjects, y= years*

Study Number of study subjects	Study population (age at time of study)	Graduated from high school (%)	Employed (%)	Married or relationship (%)	Biological children (%)
Tjaden et al. 2014 [80] n= 89	KTx recipients (mean 41y)	NA	62	67	32
Mellerio et al. 2014 [91] n= 374	KTx recipients (median 27y)	56	54	31	12
Adamczuk et al. 2019 [78] n= 45	KTx recipients and RRT patients (mean 27y)	82	47	18	10
Duffy et al. 2010 [85] n= 38	LTx recipients (mean 23y)	92	42	28	NA
Mohammad et al. 2012 [83] n= 37	LTx recipients (mean 23y)	78	62	22	NA
Lind et al. 2015 [93] n= 39	LTx recipients (mean 23y)	NA	51	23	NA
Petroski et al. 2009 [89] n= 23	HTx recipients (mean 25y)	100	33	22	NA
Hollander et al. 2015 [88] n= 20	HTx recipienst (median 31y)	90	47	50	NA
Grady et al. 2018 [96] n= 88	HTx recipients (mean 21y)	87	49	8	NA

2.4 TELOMERES

History of telomeres began nine decades ago, when two Nobel Prize winners, Hermann Muller and Barbara McClintock, studied chromosomes and found out that broken ends of chromosomes never fuse. Muller and McClintock also suspected that the ends of chromosomes are protected somehow. In the 1970s James Watson and Alexey Olovnikov both recognized that chromosomes couldn't replicate their ends. A couple years later Elisabeth Blackburn discovered that telomerase replenish the telomere [101].

As we know now the ends of eukaryotic chromosomes are called telomeres and their function is to protect the chromosomes from deterioration. Telomeres consist of multiple copies of short nucleotide repeats. Human, and all vertebrates telomeric DNA consist of sequence nucleotides (TTAGGG). At the end of telomere is a looped structure called T-loop. T-loop is associated to specialised proteins which compose shelterin complex [102]. These proteins stabilise T-loop and regulate length of telomere. Part of these proteins are also associated with other shelterin proteins and regulate their function [102].

Telomere length is regulated by telomerases, which replenish shortened telomeres and sustain replicative potential. Telomerase is a ribonucleoprotein complex which regulates telomere length by synthesizing telomeric deoxyribonucleic acid (DNA) [103].

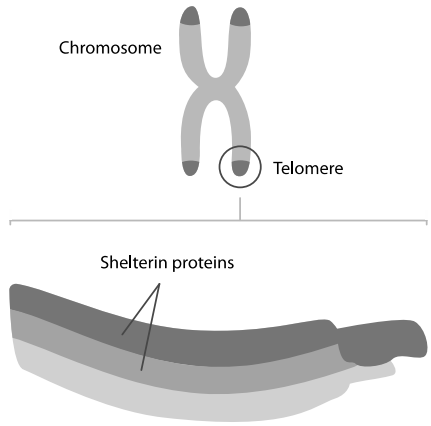


Figure 5 Structure of telomere. Illustration modified based on Blackburn et. al. (2015) [104]

Studies have showed that telomeres are shortening during aging [105-107]. Different disease conditions, such as cardiovascular diseases [108-110] and type II diabetes [107,111], have been shown to accelerate leukocyte telomere shortening. Telomere attribution is a multifactorial process, and reducing of telomere length is associated to environmental and lifestyle aspects like oxidative stress, smoking and over-weight [112-114].

In some studies short telomeres have been associated with frailty phenotype [115], but in the previous study among NBL survivors was not found association [116]. Chronic kidney failure and uremia causes susceptibility to cardiovascular events, decreases muscular mass, and leads to low-grade inflammation process. All these accelerate aging, finally causing frailty [117]. Previous studies have shown that patients with chronic kidney disease and hemodialysis have shorter telomeres and their telomerase activity is increased more than among healthy controls [118-120].

Also transplantation and immunosuppressive medication accelerate telomere attribution, and SOT recipients' risk for premature aging and frailty is increased [120]. ATG, which was previously regularly used as induction therapy, and anti-metabolite MMF accelerate telomere shortening after KTx [120-122]. Mostly used immunosuppressant agents, CNIs, decreased telomere length more than rapamycin among healthy study subjects [123]. The study by Meijers et al. showed that kidney transplant recipients have increased risk for premature aging during dialysis, but also after transplantation, and these changes are not reversible [124].

2.5 MALIGNANCIES AFTER TRANSPLANTATION

Risk for malignancies is increased after solid organ transplantation [125-127]. After transplantation, cancer risk is two [127,128] to six times [129] higher than that of general population.

The most common type of post-transplant cancer is post-transplant lymphoproliferative disease (PTLD) and the second common is nonmelanoma skin cancer (NMSC) [127,130] (Table 2). The risk for PTLD is highest during the first years after SOT [131,132], but aging increases the risk for NMSC [127,133,134]. The incidence of solid tumors is lower after pediatric SOT when compared to lymphomas. A study in pediatric KTx recipients showed that the most common solid tumor among pediatric KTx recipients is renal cell carcinoma [135]. Solid tumors are frequently located in the native kidneys, for example in patients with autosomal dominant polycystic kidney disease (ADPKD). In the study by Åberg et al. [136], predominant solid tumors after LTx were colorectal and hepatocellular carcinomas.

Cancer risk depends on many factors, the transplanted organ being one of them. The highest risk for post-transplanted malignancies is among lung [127,137] and intestinal transplant recipients [138]. Rejection episodes are frequent after small intestine and lung transplantation and they are causing higher exposure to immunosuppressive treatment. A large registry study showed that over one fourth of the lung and heart transplant recipients developed cancer within 15 years' follow-up time [139].

After SOT, the risk for infection-related cancer is also increased [128]. Ebstein Barr-virus (EBV) infection may lead to long-lasting viremia and increased risk for PTLD and nasopharyngeal cancers [128]. Kaposi sarcoma is caused by human herpesvirus 8 (HHV 8) [137].

The results of studies of immunosuppressive agents' role in cancer risk are controversial [130]. A study among HTx recipients compared the cancer risk in patients on sirolimus and CsA treatment. In the sirolimus treatment group, the incidence of *de novo* malignancies was lower and after switching from CsA-based immunosuppression to sirolimus, cancer risk was decreased [140]. The everolimus treatment group also had better survival after post-transplant cancer [141]. LTx recipients on tacrolimus treatment had significantly lower risk for solid organ tumors compared to CsA-based treatment [142]. Exposure to high therapeutical levels of CNIs increases risk for malignancies [143,144].

The risk factors for *de novo* malignancy after SOT are

1) use of two or more immunosuppressive agents [139]
2) older age of the recipient [127,128,130,133,136,137,140,145]
3) male gender [127,128,137,139,145]
4) deceased donor [146]
5) pre-transplant cancer [145,147,148]
6) sun exposure [149]

The incidence of breast and prostate cancers has been lower after SOT than in the general population [128]. A large registry study from Australia and New Zealand showed that SOT recipients' cancer risk increased during aging and was comparable to that of general population 25-30 years older [133]. NMSC occurred at a median of 17 years after transplantation. PTLD was an exception; the median post-transplant time at appearance of PTLD was relatively short, seven years.

In a Dutch study, 23% of the pediatric KTx recipients had at least one cancer and mortality to cancer was 13% [150].

Malignancy is one of the most common causes of death after SOT [151,152] and cancer-caused mortality is as much as 25% higher in SOT recipients than in the general population [153,154]. In the pediatric SOT population, the highest mortality is connected to PTLD [155] and the overall mortality from hematological disorders is higher than mortality from solid tumors or skin cancers [142].

Table 2 *Malignancies after pediatric solid organ transplantation.*
**- LTx recipients 0-30 years old, **- mean, NA- not available*

Study	Study population	Number of recipients with cancer of all study subjects (%)	Median follow-up time (years)	Main cancer diagnosis, number of all cancers (%)	Cancer mortality; number of all cancer cases (%)
Koukourgianni et al. 2010 [154]	KTx recipients	16/219 (7)	10.4	PTLD 10/16 (63)	4/16 (25)
Ploos van Amstel et al. 2015 [150]	KTx recipients	54/231 (23)	25.3 (post tx)	NMSC 39/54 (72) PTLD 6/54 (11)	12/54 (22)
Francis et al. 2017 [133]	KTx recipients	289/1734 (17)	13.4	NMSC 196/289 (68) PTLD 40/289 (14)	NA
Serrano et al. 2017 [125]	KTx recipients	136/882 (15)	19.6	Skin cancer 72/136 (53) PTLD 47/136 (35)	30/136 (22)
Karakoyun et al. 2018 [156]	LTx recipients	13/206 (6)	NA	PTLD 7/13 (54) Kaposi sarcoma 2/13 (15)	2/13 (15)
Åberg et al. 2018* [136]	LTx recipients	37/923 (4)	8.5**	NHL 14/37 (38) colorectal ca 4/37 (11) hepatocellular ca 4/37 (11)	NA
Gajarski et al. 2011 [157]	HTx recipients	122/2374 (5)	3.0	PTLD 114/122 (93)	NA
Endén et al. 2020 [158]	KTx, LTx, HTx recipients	18/233 (8)	18.0	PTLD 14/18 (78) Skin cancer 2/18 (11)	7/18 (40)
Simard et al. 2011 [159]	KTx, LTx, HTx, lung, multiorgan, pancreas, intestine	24/536 (4)	9.5	NHL 13/24 (54) Renal cell ca 3/24 (13) Vulva/vagina 3/24 (13)	NA
Yanik et al. 2017 [160]	KTx, LTx, HTx, lung, multiorgan, intestine, other	392 /17958 (2)	4.0	NHL 279/329 (85) Hodgkin lymphoma 30/329 (9)	NA
Kitchlu et al. 2018 [161]	KTx, LTx, HTx, lung, multiorgan, intestine	84/951 (9%)	NA	PTLD 65 (77%)	NA

2.5.1 PTLD

The most common malignancy after pediatric solid organ transplantation is PTLD. The incidence of PTLD varies depending on transplant population; 1-4% in KTx, 3-16% in LTx, 5-12% in HTx, and 15-17% in intestinal transplant recipients [133,162-171].

Majority of all cancer cases (77-97%) after pediatric SOT are PTLDs, depending on the study population [128,133,138,147,157,161,167].

PTLD is divided into early and late onset types depending on the time between Tx and PTLD diagnosis. No definition has been established, but most studies use the definition of early onset PTLD if the diagnosis is made during the first year after transplantation. Late onset PTLD is diagnosed more than a year after SOT [172-174]. Some studies define early onset PTLD as appearance during up to two post transplant years after Tx and late onset as appearance two or more years after Tx [170,175,176].

Because early and late onset diseases have distinct pathological and clinical characteristics, the division into two types of PTLD is relevant. Risk for early onset PTLD is higher among young patients [170,173,175,177] and in EBV or CMV seronegative recipients [175]. Immunosuppressive treatment based on tacrolimus [162] and mycophenolate have been recognized as risk factors for early onset PTLD [173]. Increased immunosuppression due to rejection or other reason increases the probability of EBV viremia and further increases the risk for both early and late onset PTLD [170,177,178]. Non-Hispanic white race and older age at the time of Tx are risk factors for late onset PTLD [175].

PTLD has been classified by WHO into four main categories: 1) early lesions, including plasmacytic hyperplasia, infectious mononucleosis and florid follicular hyperplasia, 2) polymorphic, 3) monomorphic, diving B- and T-cell neoplasm and 4) classical Hodgkin lymphoma [179]. Histology of early onset PTLD is mostly polymorphic, diffuse large B-cell or other B-cell lymphoma [173].

Pediatric SOT population's risk for PTLD is increased compared to adult SOT recipients [147,159,168]. After pediatric transplantation, PTLD occurred earlier than other post-transplant malignancies [159].

General risk factors for PTLD after pediatric SOT are

1) high EBV viral load [140,180] or primary EBV infection after tx [168,181]

2) lung or multiorgan transplantation [132]

3) young age at the time of transplantation [171,175]

The most frequent anatomical sites of PTLD are gastrointestinal tract [131,147,162,164,178], lymph nodes and tonsils [132,182]. Early lesions are found predominantly in the graft or at extranodal location [173].

Among SOT recipients, the 1- and 5-year survival after PTLD diagnosis has been 88-90% and 70-90%, respectively [131,173]. The survival of intestinal transplant recipients with PTLD is poor when compared to other SOT recipients, one-year survival being 57% and five-year survival only 39% [169]. In the study by L'Huillier et al. [132] the survival

were better in the case of tonsillar/adenoidal tumors than in other anatomical sites. In a recent study, the long-term survival after PTLD was comparable between early and late onset cases [173].

2.5.2 SKIN CANCERS

Skin cancers are divided into two categories: melanoma and nonmelanoma skin cancers. The most common types of nonmelanoma skin cancers (NMSC) are squamous cell carcinoma, basal cell carcinoma and actinic keratosis [183].

Also in the pediatric Tx-population, NMSC is a common post-transplant malignancy and the risk increases with time [184]. A recent review by Howard et al. [185] compiled the risk factors for skin cancers after Tx. Cumulative doses and multiple immunosuppressive medications increased the risk for NMSC [184,186]. Pre-transplant immunosuppressive medication or cytostatic treatment were also remarkable risk factors.

Azathioprine is one of the immunosuppressive medicines which have been associated with higher risk for NMSC [187]. A recent study among HTx recipients showed that the risk for NMSC and other post-Tx malignancies decreased after switching from CsA to sirolimus [140,188]. In a meta-analysis among adult nonrenal transplant recipients, the risk for secondary NMSC but not for primary NMSC was reduced with mTOR inhibitor based immunsuppressive treatment [189].

Age over 50 years at time of transplantation, male sex and pre-transplant NMSC are risk factors for post-transplant NMSC [185,187]. Heart and lung Tx recipients also have higher risk for NMSC [190]

UV radiation is know to increase the risk for skin cancers among SOT recipients [149,185]. The prevalence of NMSC is increased especially in the regions where exposure to sunlight is higher [133]. Skin type is one predisposing factor for malignancies. Highly sensitive, easily burning skin type (Fitzpatrick type 1) and Caucasian ethnicity predispose to NMSC [185,186,188]. It is highly recommended to avoid straight sunlight and to use UV filters and sun-protective clothing to reduce exposure for UV radiation after SOT [191].

Compared to NMSC, melanoma is an uncommon skin malignancy, but the incidence of melanoma after SOT is increasing [192]. The risk factors for melanoma are mainly the same as for NMSC: older age, male sex and white race [193]. In the large registry study sirolimus or CsA therapy and living donor increased the melanoma risk among kidney transplant recipient [193].

2.5.3 OTHERS

Solid tumors are more common among adult SOT recipients than among pediatric recipients [142]. After pediatric transplantation, the incidence of solid malignancies is 4-31 times higher than in the general population. The most common forms of non-hematological cancers are renal, liver, genitourethral, head or neck cancers and sarcomas [160,161].

3 AIMS OF THE STUDY

The aims of this study was:

1) To study the social-economical status of young males who had kidney transplantation during childhood but were adults at the time of study,
2) To assess quality of life after pediatric KTx and compare it with that of healthy volunteers and childhood acute lymphatic leukemia survivors,
3) To analyze telomere length and telomerase function after pediatric KTx,
4) To evaluate cancer risk among pediatric solid organ transplantation recipients and control population.

Graft survival has improved during the last decades and the importance of post-transplant social well-being, education and employment status has increased. It is not enough that the graft survives; survival of the recipient is even more important. As WHO described, QoL consists of many different aspects and all of them are important to achieve valuable and happy life after solid organ transplantation.

In the present study, different components of QoL were examined: social aspects, which include relationships and reproduction; economical aspects, such education and employment; and also parts of general health after transplantation, like telomere length and morbidity and mortality to malignancies.

The study is a summary of overall well-being and health after pediatric solid organ transplantation.

4 PATIENTS AND METHODS

4.1 PATIENTS

4.1.1 KIDNEY TRANSPLANT MALES (I-II)

This study was a continuation to a previous study about long-term survival, fertility, and sexual health among young males with a history of pediatric Ktx [194]. All male pediatric or adolescence kidney transplant recipients who were transplanted between August 1983 and September 2011 in the Helsinki University Hospital were identified from the transplant database. Inclusion criteria were age over 18 years at the moment of the study and post-transplant time over five years.

A total of 79 males fulfilled the inclusion criteria. Seventeen transplant recipients were excluded because of significant co-morbidities; three subjects had mental retardation, 11 had significant psychosocial problems, two had tetraplegia, and one a history of lung transplantation.

Sixty-two males were contacted and a total of 30 responded to the invitation. All but one of these completed the questionnaires and were included in the study. Median age in the KTx group was 27.1 (range 19.0-41.8) years and median age at time of kidney transplantation was 8.6 (range 1.5-18.1) years (Table 3).

Study I had two different age-matched control groups. The first control group consisted of survivors of childhood acute lymphatic leukemia (ALL). These 52 males were part of a larger study on male acute lymphoblastic leukemia survivors that assessed reproduction, bone health, and overall wellbeing in adulthood [195]. Median age at the time of the study was 28.5 (range 25.0-38.0) years and at time of ALL diagnosis 4.5 (range 0.0-15.0) years.

The other control group included 56 male subjects, median age 30.0 (range 24.0-36.0) years. These controls were recruited from occupational health service in the Helsinki municipal area and Helsinki University. These males were previously healthy and had no history of malignancies. All were employed at the time of study.

Statistically significant differences between the KTx recipients and controls health were found in height and weight measures (170.5 vs. 180.0 cm, $p<0.001$, 72.6 vs. 82.5kg, $p<0.001$, respectively). In addition, ALL survivors were significantly taller than the KTx recipients (176.0 cm, $p=0.001$). BMI did not differ between the study groups.

Table 3 *Characteristics of study I KTx recipients. Data presented as median (IQR).*

	KTx
Age at time of study, years (IQR)	27.1 (23.7–31.8)
Height, cm (IQR)	170.5 (165.3–174.2)
Weight, kg (IQR)	72.6 (62.3–83.3)
Body mass index, kg/m^2 (IQR)	24.2 (22.2–27.4)
Age at first dialysis, years (IQR)	7.5 (1.9–13.5)
First transplant, number (%)	19 (66)
P-creatinine, µmol/L (IQR)	168 (132–261)
Blood pressure, mmHg (IQR)	134/80 (127-146/75-89)
eGFR, mL/min/1.73m^2 (IQR)	51.7 (29.8–59.5)

In study II (Table 4), the first control group consisted of eight males who had a history of childhood neuroblastoma (NBL). They had participated in a previous study on adult and adolescence survivors after childhood NBL [116,196]. The second control group consisted of nine healthy controls without a history of severe pediatric diseases. These controls were recruited among medical students and adolescent children of hospital employees. All study subjects and controls were males.

Plasma creatinine was measured from 22 male kidney recipients and recent laboratory tests of the remaining seven transplant recipients were collected from the Finnish Registry for Kidney Disease.

Leukocyte telomere length and gene expression level of telomere binding proteins were analyzed from 23 kidney transplant recipients, eight NBL survivors, and nine healthy controls. Three kidney recipients were excluded from the study; one patient's clinical characteristics were missing, one analysis was unsuccessful, and one study subject lost his kidney function during the study.

Table 4 *Clinical characteristics of the kidney transplant (KTx) patients, neuroblastoma (NBL) survivors, and healthy controls in study II. Data is presented as median. [a] p-value between the KTx patients and the NBL survivors. [b] p-value between the KTx patients and the controls. NA, not applicable. Statistically significant values bolded. * One study subject's P-creatinine value was incorrect in the original article.*

	KTx (n=20)	**NBL (n=8)**	**Controls (n=9)**	**p-value[a]**	**p-value[b]**
Age at time of study, years (IQR)	28.1 (25.0–31.8)	24.1 (17.3–27.6)	21.2 (17.5–25.2)	0.063	**0.010**
Follow-up time, years (IQR)	18.3 (15.9–23.4)	21.4 (14.8–25.5)	NA	0.469	
Height, cm (IQR)	170.1 (165.8–173.1)	160.4 (152.8–173.4)	181.1 (176.4–187.5)	0.079	**0.002**
Body mass index, kg/m^2 (IQR)	24.3 (20.0–27.4)	20.8 (15.9–26.3)	22.3 (21.9–25.3)	0.304	0.501
Plasma creatinine, µmol/L (IQR)	154.0 (125.3-225.6)*	68.5 (63.3–77.0)	83.0 (71.0–93.5)	**<0.001**	**<0.001**
hsCRP, mg/L (IQR)	0.9 (0.4–1.8)	2.61 (0.9–6.7)	0.3 (0.3–1.2)	0.061	0.251
HbA1C (%) (IQR)	5.1 (4.9-5.5)	5.1 (4.9-5.2)	5.1 (4.9-5.3)	0.666	0.760

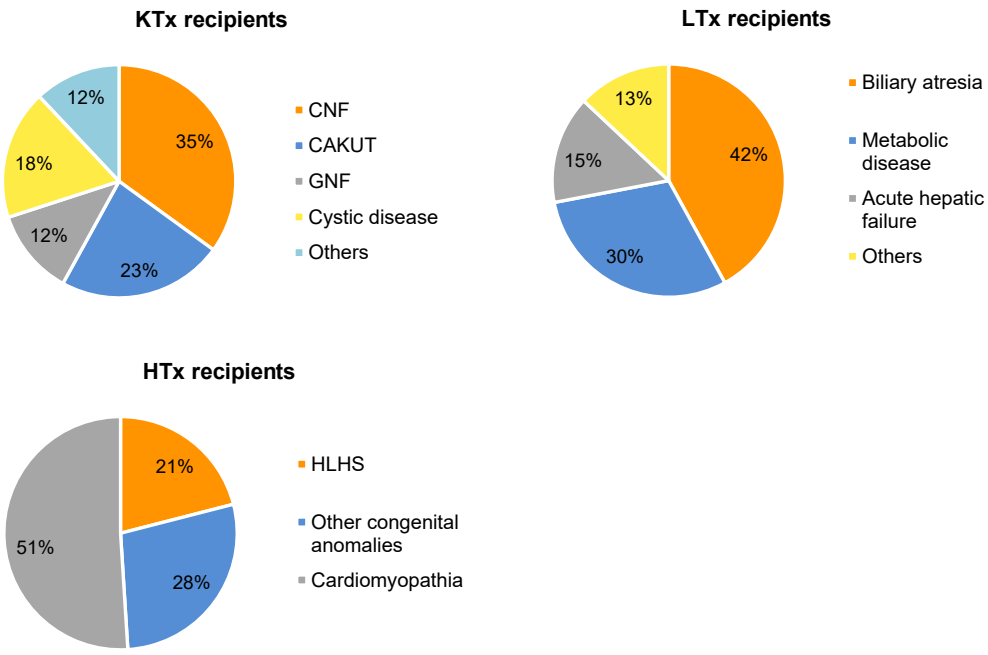
4.1.2 KIDNEY, LIVER AND HEART TRANSPLANT RECIPIENTS (III)

In study III, all pediatric KTx, LTx and HTx recipients who were transplanted at the Helsinki University Hospital between January 1, 1982 and December 31, 2015 were identified from the transplantation database. Inclusion criteria were age under 16 years during the transplantation and age over 18 years at the last follow-up date, December 31, 2015. Transplant recipients who had died during childhood but would have been over 18 years at last follow-up date were included in the study.

A total of 233 Tx recipients fulfilled the inclusion criteria and were included in the study (Table 5). In the transplant cohort there were 137 kidney, 53 liver and 43 heart transplant recipients. Two third (n=139, 60%) were males and the median age at time of transplantation was 7.9 (0.4-15.9) years. Median age at time of study was 27.8 (18.3-44.0) years for those who were alive. A total of 173 (74%) transplant recipients were alive at the last follow-up date (December 31, 2015). Main diagnosis of the study subjects have been presented in the Graphic 1.

Table 5 *Clinical characteristics of the kidney (KTx), liver (LTx), and heart transplant (HTx) recipients. P^a = Ktx vs. LTx, p^b= LTx vs. HTx, p^c= KTx vs. HTx. Data presented as median and statistically significant values are bolded.*

	KTx n=137	LTx n=53	HTx n=43	p^a-value	p^b-value	p^c-value
Age at time of study (alive), (range)	26.3 (22.7–29.7)	25.7 (23.2–29.8)	24.4 (20.3–35.6)	0.949	0.563	0.657
Post-Tx time (range)	20.0 (0.7–30.0)	15.0 (0.4–27.0)	13.0 (0.3–25.0)	**0.009**	0.524	**<0.001**
Males, n (%)	92 (67.2)	25 (47.2)	22 (51.2)	**0.013**	0.838	0.070
Age at time of Tx, (range)	7.9 (1.1–15.9)	4.9 (0.4–15.9)	10.3 (1.0–15.9)	**0.023**	**0.005**	0.081
Malignancy, n (%)	14 (10.2)	2 (3.8)	2 (4.7)	0.243	0.831	0.365
Alive, n (%)	117 (85.4)	30 (56.6)	26 (60.5)	**<0.001**	0.835	**0.001**
Age of cancer diagnosis, (range)	18.7 (4.1–25.6)	18.6 (3.3–33.9)	17.3 (12.2–22.3)	0.533	0.667	0.933
Time from Tx to cancer diagnosis, (range)	13.3 (6.9–23.6)	10.7 (1.8–19.7)	7.9 (4.7–11.1)	0.933	0.667	0.417



Graphic 1 Diagnoses in the study groups. CNF- Finnish type congenital nephrosis. CAKUT- congenital anomalies of kidney and urinary tract, GNF- glomerulonephritis, HLHS- hypoplastic left heart syndrome.

The year of birth, gender and hometown matched controls were identified from the Digital and Population Data Services Agency registry. A total of 1,157 controls were searched; 691 (60%) were males and median age at time of study was 26.4 (18.1-44.1) years. Two control subjects had died (0.2%).

Immunosuppression after pediatric solid organ transplantation consists of induction therapy in the operation room and continues after the operation with triple medication. At the beginning of the transplantation program in Finland, anti-thymocyte globulin (ATG) was used as induction therapy for all solid organ recipients. After 2000, basiliximab has been used as induction therapy for all kidney and liver transplant recipients and only heart transplant recipients receive ATG.

The most commonly used combination is calcineurin inhibitor (tacrolimus or cyclosporine A), azathioprine or mycophenolic acid and methylprednisolone. After KTx or LTx, the most frequently used combination has been CsA, azathioprine and methylprednisolone. HTx recipients primarily received CsA, azathioprine and methylprednisolone until the year 2010; after that, most of the HTx recipients have been on a combination of tacrolimus with mycophenolic acid and methylprednisolone. The first three to six months after solid organ transplantation methylprednisolone has been used daily and after that, switched to alternate-day dosing.

4.2 METHODS

4.2.1 QUESTIONNARIES (I)

The RAND-36 is a self-report generic questionnaire which has been developed to measure health related quality of life (HRQoL). The questionnaire subscales are physical functioning, bodily pain, role of limitations due to physical health problems, role of limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perception [197]. The questionnaire consists of 36 simple questions and each dimension is scored between 0 and 100. Each subscale is composed of 2-10 questions and mean is computed by question scores. A higher score indicates better QoL.

The Beck Depression Inventory (BDI-21) is self-administered questionnaire to detect depressive symptoms [198]. A Finnish version of the BDI-21 was used in this study. The BDI-21 consists of 21 items. Each item includes four statements that have a numerical value from 0 to 3. Total score ranges from 0 to 63. Scores between 10 and 18 indicate mild disturbance, while severe depression is suspected with scores over 30.

4.2.2 TELOMERE LENGTH ANALYSIS AND RNA EXTRACTION (II)

Telomere analysis was performed in the Karolinska Institute, Sweden, by Mi Hou, PhD. Genomic DNA and RNA were extracted from frozen peripheral blood and measured by real-time PCR assay [199].

4.2.3 NATIONAL HEALTH REGISTERIES

The Digital and Population Data Services Agency (previous name: Population Registry Center) is a database which includes basic information about Finnish citizens and foreign citizen residing in Finland. The data include name, personal identity code, date of birth and death, address, citizenship, native language and family relations.

The Finnish Institute for Health and Welfare (THL) is an independent expert agency which produces social welfare and health statistics. THL has many registries which include data of diseases, treatments and services. In the current study, data were obtained from the Finnish Cancer Registry, which maintains the national registry of THL. In Finland, health care organizations have an obligation to report all cancer diagnoses to the Finnish Cancer Registry.

The Causes of Death Registry is one of the data collections produced by **Statistics Finland.** Time of death, age, diagnosis and type of death are collected from death certificates and archived in the registry.

4.2.4 STATISTICAL METHODS

SPSS statistic 22 and 24 (SPSS Inc., Chicago, IL, USA) and R version 3.4.4 were used for data analysis. Kruskal-Wallis test was used to compare more than two subject groups and Mann-Whitney U-test for continuous variables. Pearson chi-squared test and Fisher's exact test were used for categorical variables. Spearmans's rank correlation coefficient was used to assess correlation. The survival analyses were carried out with Cox proportional hazard models and the PH assumption was evaluated with Scoenfelt residuals. Cumulative survival was evaluated with Kaplan-Maier estimator.

P-values less than 0.5 were considered statistically significant and all tests were two-tailed.

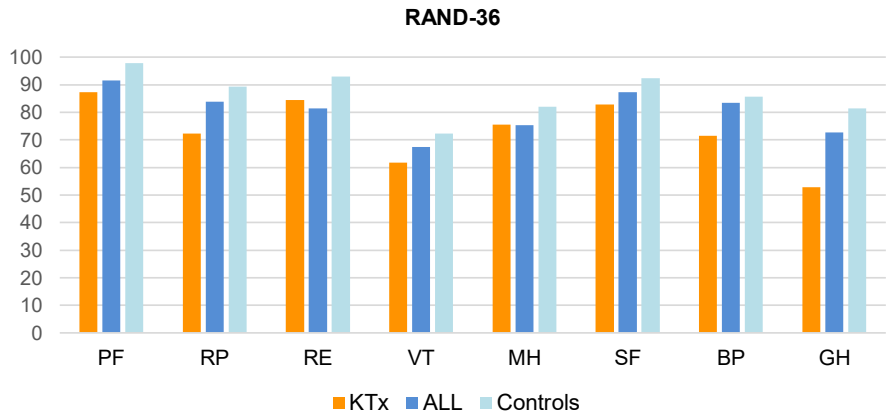
4.2.5 ETHICAL CONSIDERATIONS

The Research Ethics Committee of Helsinki University Hospital, the Finnish Institute for Health and Welfare and the Office of the Data Protection Ombudsman approved the study protocol.

5 RESULTS

5.1 QUALITY OF LIFE

A total of 29 KTx recipients, 52 childhood acute lymphatic leukemia (ALL) survivors and 56 healthy controls filled in the RAND-36 and BDI-21 questionnaires. QoL and depressive symptoms were evaluated based on these results.



Graphic 2 RAND-36 categories in the study groups. PF- physical functioning, RP- physical limitations, RE- emotional limitations, VT- vitality, MH- mental health, SF- social functioning, BP- bodily pain, GH-general health

Graphic 2 shows the RAND-36 subscales in different study groups. In general, KTx recipients had the lowest scores in all RAND-36 subscales, except in the role of limitations due to personal or emotional problems. ALL survivors scored lower on limitations caused by physical health problems than the KTx recipients. The status of mental health scores was the same among KTx recipients and ALL survivors. Compared to healthy controls, KTx recipients had significantly declined mental health scores (KTx vs. controls p=0.009). Scores measuring role limitations due to physical health problems were statistically significantly lower in the KTx group than among the healthy controls (p=0.026). Also vitality (energy/fatigue) and mental health scores were significantly lower in the KTX group than in the controls (p=0.008, p=0.009). Scores of social functioning were lower among KTx recipients, but the difference to ALL survivors or healthy controls was not statistically significant. Remarkably, both general health and increased bodily pain were diminished among KTx recipients when compared to ALL survivors and healthy controls. KTx recipients' mean score of bodily pain was 72 and ALL recipients' 84 (p=0.043). Healthy controls' mean score of pain was 86 and the difference to KTx recipients' score was statistically

significant (p= 0.031). General health score was 52.8 in the KTx group, 72.6 in ALL, and 81.0 in healthy controls (p<0.001).

According to these results, pediatric KTx recipients have lower QoL than survivors of childhood malignancy or healthy controls. The experience of own general health was scored very low among the KTx recipients, being only about half of the highest score.

Correlation between clinical characteristics and RAND-36 subscales was observed in the KTx group (Table 6). Age at time of study had a negative correlation with RAND-36 subscales, but the correlation was not statistically significant. Age at start of dialysis had negative correlation with physical functioning and general health; correlations with other subscales were positive, but statistical significance was not achieved.

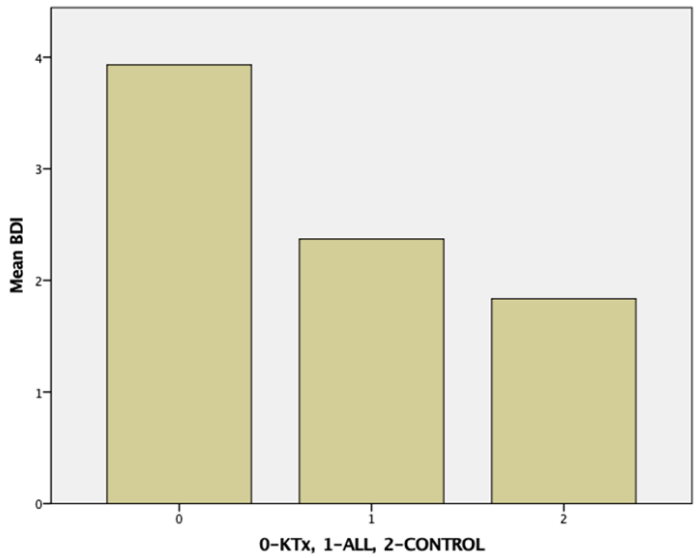
Table 6 *RAND-36 subscales correlation with kidney function and transplantation. Significant p-value bolded.*

RAND-36 subscale	Dialysis duration	Age at first KTx	Number of KTx	GFR
Physical functioning	-0.293 (0.123)	-0.034 (0.861)	-0.436 (0.180)	0.394 (0.063)
Role/physical	-0.357 (0.062)	0.069 (0.728)	-0.380 (**0.046**)	0.319 (0.148)
Role/emotional	-0.420 (**0.026**)	0.147 (0.454)	-0.421 (**0.026**)	-0.074 (0.745)
Vitality	-0.132 (0.495)	0.116 (0.548)	-0.203 (0.292)	0.504 (**0.014**)
Mental health	-0.194 (0.312)	-0.002 (0.992)	-0.383 (**0.040**)	0.022 (0.920)
Social functioning	-0.244 (0.202)	0.053 (0.786)	-0.369 (**0.049**)	0.287 (0.184)
Bodily pain	-0.398 (**0.033**)	0.102 (0.598)	-0.278 (0.144)	0.422 (**0.045**)
General health	-0.076 (0.694)	-0.067 (0.730)	-0.222 (0.247)	0.433 (**0.039**)

Duration of dialysis had a negative correlation with all subscales. Long time on dialysis had a statistically significant negative correlation with physical health problems that caused limitations. Also bodily pain was significantly increased during long-lasting dialysis treatment. Multiple transplantations had a major negative influence on QoL. Both physical and mental health was significantly decreased and also social functioning was impaired. Decreased kidney function and low GFR had a statistically significant correlation with vitality and bodily pain. Impaired kidney function, long time on dialysis and re-transplantations are the main factors decreasing kidney transplant recipients' QoL.

5.2 BDI-BECK DEPRESSION INVENTORY

The BDI questionnaire was used to investigate signs of depression. The mean BDI among Ktx recipients was 3.9 (4.3 SD), which was statistically significantly higher than among ALL survivors (2.4 (3.9 SD), p=0.006) or healthy controls (1.8 (4.7 SD), p < 0.001) (Graphic 3). Variation of standard deviation was large in all groups.



Graphic 3 Mean BDI scores in the different study groups.

In all, three (10%) of the KTx recipients had BDI scores ≥ 10. The highest score among KTx recipients was 14, showing that all recipients had only mild depressive symptoms. Among ALL survivors, four (8%) had scores between 10-18 and in the control group, there was one subject (2%) with scores between 10-18 and one (2%) with scores between 19 and 29, indicating moderate depressive symptoms.

KTx recipients' mean score of depressive symptoms was higher than among ALL survivors or controls, but none of the KTx recipients had serious symptoms, contrary to the healthy controls.

Correlation between KTx recipients' BDI scores and RAND-36 was analyzed. High BDI scores had a negative effect on QoL. There was a statistically significant negative correlation with vitality (r -0.714, p<0.001), mental health (r -0.368, p=0.049), social functioning (r -0.591, p=0.001) and general health (r -0.402, p=0.031). Depression or depressive symptoms have a remarkably negative effect on QoL. KTx recipients' clinical characteristics, kidney function or transplantations had no influence on BDI.

5.3 EDUCATION, EMPLOYMENT AND SOCIAL LIFE

Data about educational level, employment status, relationship and biological children were collected from the study subjects. One Ktx recipient (4%), a total of seven ALL survivors (14%) and ten controls (18%) achieved the highest educational level, minimum 17 years. Majority of the KTx recipients (62%) had upper secondary or vocational education, 12 years in all. The finding was comparable with ALL survivors (69%), but most of the healthy controls (41%) achieved lower tertiary education (15 years). Only comprehensive education was found to be more common among the KTx recipients than among the controls (17% vs. 5%, p=0.006).

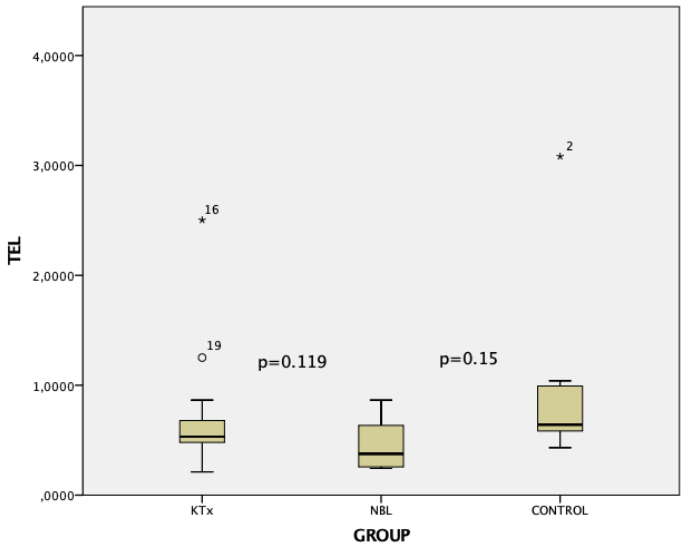
At time of the study, all study subjects were young adults. Employment rate was comparable between KTx recipients and ALL survivors (76% vs. 90%, p= 0.105). Because healthy controls were recruited from the occupational health service the employment rate was 100%. In 2014, the unemployment rate among adolescents (15-24 years) was 21% in Finland. In the present study, 24% of KTx recipients and 10% ALL survivors were unemployed at the time of study. The number of retired persons is not available.

Most (80%) of the healthy, young males were married or cohabiting at the time of study. Half (50%) of the ALL survivors and 41% of KTx recipients were in a relationship, which was statistically lower when compared to the healthy controls ($p < 0.001$).

Three (10%) KTx recipients had at least one biological child. The proportion of patients with children was significantly lower than among controls (43%, p=0.002) and even lower than among ALL survivors (21%, p=0.217); however, the difference did not reach statistical significance.

5.4 LEUKOCYTE TELOMERE LENGTH

Leukocyte telomere length was analyzed in 20 KTx recipients, eight NBL survivors, and nine healthy controls.



Graphic 4 Median telomere length in the study groups.

Graphic 4 shows median length of telomeres in all study groups. NBL survivors had the shortest telomeres; median length was 0.38 AU, (interquartile range (IOR) 0.47 AU). KTx recipients' median telomere length was 0.53 AU (IQR 0.21 AU). Compared to NBL survivors, the difference was not statistically significant (p=0.119). Healthy controls had significantly longer telomeres than NBL survivors (median 0.64 AU, IQR 0.48 AU, p=0.015), but the difference to KTx recipients did not reach statistical significance.

Correlation with clinical parameters was studied by pooling all study subjects (n=37) in one group. Correlations were calculated with **age at time of study** (r=0.039, p=0.826), **age at time of diagnosis** (r=0.306, p=0.114), **body height** (r=0.273), p=0.103), **body mass index** (BMI) (r=-0.032, p=0.853), **systolic blood pressure** (BP) (r=-0.038, 0.829), **diastolic BP** (r=-0.159, p=0.369), **plasma creatinine** (r=0.153, p=0.367), **high sensitive C-reactive protein** (hsCRP) (r=-0.264, p=0.114) and **eGFR** (r=-.150, p= 0.390). BMI, BP, hsCRP and eGRF had a negative correlation with telomere length, but none of these correlations were statistically significant.

KTx recipients' age at time of study, start of dialysis or transplantation had no significant correlation with telomere length (Table 7). Duration of RRT, re-transplants or kidney function had no effect on telomeres, either.

Table 7 *The correlation between key clinical parameters and telomere length in the kidney transplant recipients.*

	r	p
Age at time of study	0.421	0.064
Age at time of first dialysis	0.253	0.283
Dialysis age	0.263	0.262
Duration of dialysis	-0.130	0.585
Tx age	0.288	0.219
Time after Tx	0.165	0.486
Number of Tx	-0.041	0.829
Plasma creatinine	0.253	0.283
eGFR	-0.334	0.150

5.5 TELOMERE BINDING PROTEINS

Gene expression levels of telomere-binding proteins were measured from eight KTx recipients, eight NBL survivors, and nine controls. The exceptions to these numbers are indicated in Table 8.

Table 8 *Median of 2ΔΔ-CT telomerase components of kidney transplant recipients (KTx), neuroblastoma survivors (NBL) and healthy controls. SD- standard deviation. P^A difference between KTx and NBL, P^B KTx vs. control. Significant p-values bolded. † n=6, * n=7, ‡n=9*

	KTX	NBL	CONTROL	P^A	P^B
TRF1	0.01056	0.00065	0.000036	0.463	0.050
(SD)	(0.0168)	(0.0612)*	(0.0167)		
TRF2	0.02344	0.00008	0.000099	0.091	**0.006**
(SD)	(0.0449)‡	(0.0191)*	(0.0003)		
TPP1	0.15570	0.04319	0.020035	0.574	0.574
(SD)	(2.7275)	(0.1806)	(0.9187)		
TIN2	0.00653	0.00002	0.000010	0.321	0.114
(SD)	(0.0389)‡	(0.0241)	(0.0076)		
POT1	1.16942	0.22649	0.025177	0.878	0.382
(SD)	(2.0609)	(1.0254)	(0.1302)		
RPA1	1.92338	0.00052	0.004057	**0.041**	**0.029**
(SD)	(5.6010)†	(0.3891)†	(0.0380)		

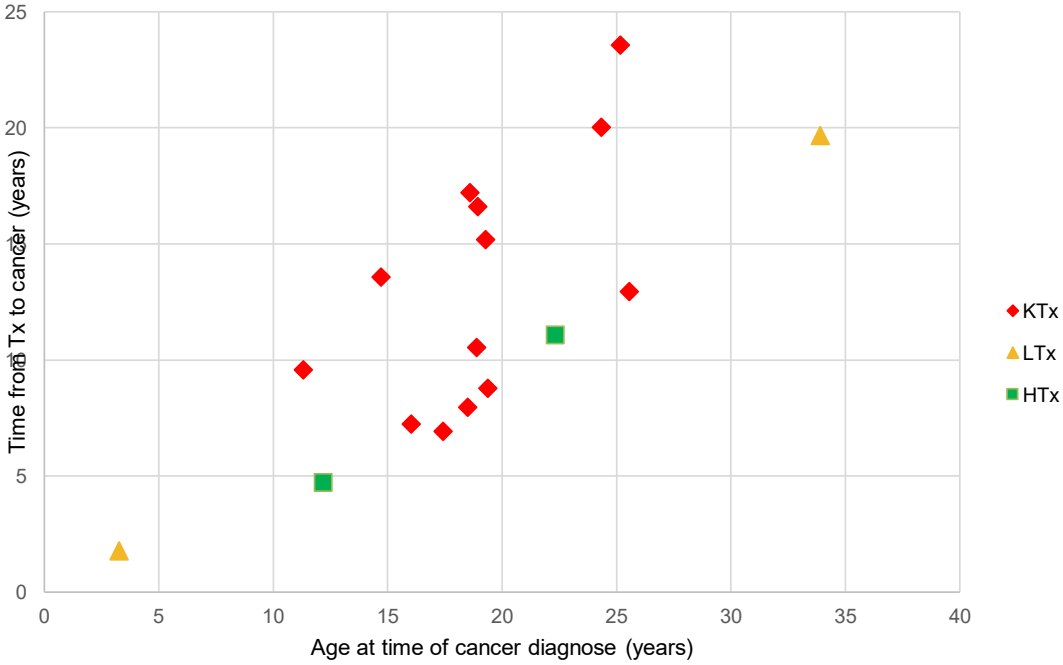
Tumor suppressor gene (P16) level was significantly higher among KTx recipients than controls (0.1312 vs. 0.0004, p=0.021), while NBL survivors' P16 level was even lower (0.00009), but the difference to KTx survivors (p=0.055) or controls (p=0.779) was not statistically significant.

Telomerase (hTERT) level among KTx recipients was 0.0590, among NBL survivors 0.0027 and among controls, 0.0007. Differences between the study groups did not reach statistical significance; KTx recipients vs. NBL survivors, p=0.121, KTx recipients vs. controls, p=0.050.

Spearman's rank correlation coefficient was used to assess correlations between the clinical characteristics and gene expression levels. Age of study subject had a positive correlation with all gene expression levels, but there was a statistically significant correlation with TRF2 ($r=0.435$, $p=0.034$) and P16 ($r=0.495$, $p=0.014$). Body height, weight and BSA did not have a statistically significant correlation with gene expression levels. Plasma creatinine (P-Cr) level and hsCRP had a statistically significant positive correlation with TRF2 ($r=0.496$, $p=0.014$, $r=0.527$, $p=0.008$). eGFR had a statistically significant negative correlation ($r=-0.492$, $p=0.015$) with TRF2. Impaired kidney function increased the gene expression levels. HbA1c correlation with gene expression levels did not achieve statistical significance. HsCRP had a significant positive correlation with TRF2 and TIN2.

5.6 MALIGNANCIES AFTER PEDIATRIC SOLID ORGAN TRANSPLANTATION

Cancer morbidity and mortality after pediatric kidney, liver and heart transplantation was evaluated based on the Cancer Registry data. Cancer incidence among SOT recipients was compared to population-based controls. A total of eighteen transplant recipients had been diagnosed with malignancy after pediatric SOT (Graphic 5) and eight of controls had malignancy. One liver transplant recipient and one control subject had two different cancers. The LTx recipient had small B-cell lymphoma at the age of three years and 23 years later he was diagnosed with large B-cell lymphoma. The control subject had a Hodgkin lymphoma at age 13 years; ten years later, basal cell carcinoma was diagnosed.



Graphic 5 Age and post-Tx time, at the time of cancer diagnosis.

The most common cancer among transplant recipients was PTLD, with 14 cases in all. The predominant histological diagnosis was large B-cell lymphoma (n=9, 64%). In nine cases, EBER *in situ* hybridization (ISH) was performed and in four cases, EBER ISH was positive at the time of PTLD diagnosis. EBV viral load at the time of PTLD diagnosis was available from half of the cases. In three cases, the number of EBV copies was <500 copies/mL and in four cases, 8,400-225,200 copies/mL. Among PTLD patients, mean age at time of transplantation was 4.2 (range 1.1-12.6) years and at time of diagnosis, 18.9 (11.3-25.6) years. Nine (64%) of the PTLD patients were males. Median time between transplantation and cancer diagnosis was 12.9 (4.7-23.6) years. A total of eight of PTLD patients died; six (75%) deaths were caused by cancer.

Other diagnosed cancers after transplantation were small B-cell lymphoma, teratocarcinoma in the testis, and two skin cancers: squamous cell carcinoma and basal cell carcinoma. Age at time of cancer diagnosis was comparable to the PTLD patients, the median age being 17.3 (3.3-33.9) years. Tx recipients with non-PTLD cancer tended to be older at the time of transplantation, with median age of 9.7 (1.5-14.3) years, but the difference was not statistically significant when compared to the PTLD group (p=0.382). Median time between transplantation and cancer diagnosis was 7.9 (1.8-19.7) years. Only one patient (25%) died from non-PTLD cancer.

Tx recipients' cancer risk was nearly 15-fold higher than that of controls (HR 14.7; 95% CI 6.4–33.9). The risk for cancer was increased after kidney transplantation (HR 27.7; 95% CI 8.0-96.6). Among LTx and HTx recipients, the risk for malignancy was lower (HR 5.6, 95% CI 0.9–33.6; and HR 6.4, 95% CI 0.9–45.9, respectively). Risk for non-PTLD was three-fold higher among SOT recipients than in the control subjects (HR 3.4; 95% CI 1.0-11.4).

In the multivariate analysis, type of **transplanted organ** (liver HR 0.50 (95% CI 0.11–2.24), heart HR 0.63 (95% CI 0.14-2.87)), **age at time of transplantation** (5–9.99 years HR 0.94 (95% CI 0.25–3.55), ≥ 10 years HR 0.83 (95% CI 0.27–2.55)), **transplantation era** (1994–2003 HR 1.27 (95% CI 0.46–3.49), 2004–2015 HR 1.56 (95% CI 0.16–15.9)) or **gender** (female HR 0.92 (95% CI 0.35–2.42)) did not influence the cancer risk.

5.6.1 MALIGNANCIES AFTER KTX

Over three fourths (85%) of KTx recipients were alive at the end of study. Fourteen (10%) of the KTx recipients were diagnosed with cancer during the follow-up. All cancers were late onset malignancies; median time between transplantation and cancer diagnosis was 13.3 (range 6.9-23.6) years. The most common type of cancer was PTLD (n=12). Median age at time of transplantation was 3.2 (1.1-12.6) years and age at time of cancer diagnosis 18.9 (11.3-25.6) years. Most of the PTLD cases were diagnosed during adulthood; only four recipients (33%) were under 18 years old at time of cancer diagnosis. Seven of the PTLD patients were males (58%) and six (50%) had died. All but one of the deaths were caused by cancer.

Other diagnosed malignancies were teratocarcinoma in the testis at the age of 19 years, and one 16-year-old KTx recipient had NMSC (squamous skin cancer).

5.6.2 MALIGNANCIES AFTER LTX

Cancer after pediatric liver transplantation was rare in this study. Only two (4%) post-transplant cancer cases were found among the LTx recipients. Just over half of the LTx recipients were alive at last follow-up date, which means that mortality for other causes after LTx was relatively high. One male LTx recipient had intrathoracic small B-cell lymphoma at the age of 3 years, 1.8 years after transplantation. The other diagnosed cancer case was basal cell carcinoma in the eyelid at the age of 34 years, 19.7 years after the liver transplantation.

5.6.3 MALIGNANCIES AFTER HTX

Two recipients (5%) with a history of pediatric HTx had post-transplant malignancy; both cases were PTLD. The first case was NHL at the age of 13 years, 4.7 years after the heart transplantation. The other PTLD case was a large B-cell lymphoma, 11 years after the HTx. The HTx recipient was 22 years old at the time of the diagnosis and the lymphoma was located in the small intestine. Both recipients died about one and half year after cancer diagnosis and at least one of these deaths was caused by cancer. It is remarkable that 26/43 (60%) of the heart transplant recipients were alive at the end of the study.

5.6.4 MALIGNANCIES IN THE CONTROL POPULATION

Cancer incidence was significantly lower in the control group when compared to the Tx recipients (18 vs. 8, $p<0.001$). All in all, 0.7% of the controls were diagnosed with cancer during the follow-up period. Only two of the control subjects had died (0.2%), the mortality rate was also significantly lower than among Tx recipients ($p<0.001$).

Median age at time of cancer diagnosis was 26 years (range 13-29) years. Compared to the Tx recipients with cancer diagnosis (median age 19 years, range 3-34), the difference was not statistically significant ($P=0.13$). The characteristics of the malignancies are shown in Table 9.

Table 9 *Cancer diagnoses in the control population.*

DIAGNOSIS	AGE	GENDER	LOCATION
HODGKIN LYMPHOMA	13.0	male	lymph nodes, head/neck
SEMINOMA	28.8	male	testis
MIXED ADENONEUROENDOCRINE CARCINOMA	24.8	male	appendix
FOLLICULAR ADENOMA	29.3	female	thyroid gland
MUCINOUS CYSTIC TUMOR	17.9	female	ovary
TERATOCARCINOMA	27.7	male	testis
INTRADUCTAL CARCINOMA	28.2	female	breast
OSTEOSARCOMA	16.9	female	lower limb

6 DISCUSSION

6.1 QOL AND DEPRESSIVE SYMPTOMS AMONG ADULT MALES WITH A HISTORY OF PEDIATRIC KIDNEY TRANSPLANTATION (I)

Previous studies have shown that children with kidney transplant have decreased QoL when compared to healthy controls or controls with severe childhood disease [8,72,77]. QoL after pediatric KTx has been impaired on both children's self-reports and proxy reports. Studies in young adults with a history of pediatric ESKD are scarce. The results of the present study are similar as in a previous Norwegian study evaluating QoL during childhood; QoL after pediatric KTx was significantly lower than among ALL survivors or healthy controls [77]. The subscales in general health and bodily pain were most impaired. A similar finding was see in a previous study about QoL by Tjaden et al. [200]. In the present study comparing KTx recipients and healthy controls, the KTx recipients had significantly lower vitality and physical health. Mental health was also impaired, which is opposite to the findings among older KTx recipients [80]. Study subjects with decreased kidney function had a significantly more feeling of pain and less vitality. As is known, uremia causes physical unwellness and decreased QoL [201]. In a previous study, 5- to 18-year-old children receiving HD treatment scored lower on QoL than their peers who received KTx [76].

In the current study, low general health and vitality scores were connected to depressive symptoms and higher BDI. Impaired social function and mental health also had a negative correlation with BDI. In the study by Diseth et al. [78], multiple transplantations had a negative effect on emotional well-being, a finding that was confirmed in the present study; both physical and emotional health were significantly decreased and also social functioning and mental health were impaired in the case of re-transplantation.

A total of ten percent of the KTx recipients had depressive symptoms in this study, which is less than in the clinical screening among adult Ktx recipients, where over 22% had significant signs of depression [202]. In a previous study kidney function had no influence on BDI. In the study by Kogon et al. pediatric KTx recipients had more depressive symptoms than patients on dialysis or pre-ESKD [203] and in the study among pediatric RRT and KTx recipients, kidney function had no effect on BDI [204]. Depressive symptoms are associated with social aspects and decreased QoL rather than graft function. An important observation is also that depressive symptoms have a negative influence on compliance, and harmful health behavior, such as smoking, increases with mental health problems [75]. Despite the fact that KTx recipients had only mild depressive symptoms and evaluated their QoL as only moderately impaired, screening and support is important and has impact not only on QoL, but also on social relationships and adherence.

6.2 SOCIO-ECONOMICAL STATUS AFTER PEDIATRIC KIDNEY TRANSPLANTATION (I)

In this cohort study in adult males with a history of pediatric kidney transplantation, education level, employment and number of social relationships was lower in comparison to healthy controls. Only primary education had a significantly higher proportion among KTx recipients than controls. These result are in accordance with a recent study by Adamczuk et al. among childhood ESKD patients, where 18% had primary education and 64% secondary education [78].

Intelligence and neuropsychological capability have influence on educational level. In the recent study by Francis et al., up to 50% of children with ESKD, RRT or KTx self-reported decreased cognition [13]. In addition, the study by Lee et al. showed that long pre-transplant period had a negative effect on intelligence [205]. KTx recipients have many physical risk factors for impaired cognitive function, but their possibilities to attend normal school work are also diminished. Chronic disease causes long hospital stays and regular outpatient visits disturb normal school work. The study by Lewis et al. compared young adults with a history of either pediatric KTx or transplantation during adult age. Educational level and employment rate were both lower among adults with a history of pediatric KTx [206]. Pediatric KTx recipients are at increased risk of low educational level and consequently, their risk for unemployment is higher than general.

Employment not only allows economical independency but is also factor for valuable life [207]. Unemployment has been related to fatigue and mental health problems in the KTx population [208]. In the present study, 76% of the KTx recipients were employed or studying at the time of study. The number was higher than in the previous studies and comparable to general employment rate among young adults in Finland.

It is crucially important to support SOT recipients to achieve an adequate education level and to get possibilities for employment.

In the present study, KTx recipients had less relationships compared to ALL survivors or healthy controls. Most of the KTx recipients (59%) were single, while 80% of the healthy controls were married or cohabiting. According to a French study, a total of 27% of male Ktx recipients were living with a partner. The age of the study subjects was comparable with the present study [91]. In an Italian study, 29% of the younger KTx recipients, at age of 23 years, were in a relationship [79]. It is likely that age and cultural factors have influence on relationships and cohabiting. In the study by Tjaden et al., 67% of childhood RRT survivors were married or in a relationship at the age of 40 years [91]. The number was still significantly lower than in the general population. Chronic disease, surgical operations, long hospitalizations and medications may have negative influence on body image, self-confidence and mental health [209]. In addition, Tx recipients have reportedly decreased social functioning after transplantation [206]. All these factors disturb normal social life.

In this study, every tenth male had a biological child, which is comparable to an earlier study among young adults with a history of pediatric RRT [91], but significantly lower than among the general population. One main factor is poor quality of semen [194] which affects the fertility of young males after pediatric transplantation and which has been recognized during the last decade. Poor physical and mental conditions influence family plans. In addition, difficulties with social relationships can be reflected in reproduction and number of offspring.

6.3 TELOMERES AFTER PEDIATRIC KIDNEY TRANSPLANTATION (II)

The present study confirmed the finding from earlier studies that chronic kidney disease and kidney transplantation accelerate telomere attribution [120,124]. All KTx subjects had a history of CKD and in this study population, also dialysis. No correlations were found between clinical characteristics of the study population and telomere length. The small number of KTx recipients may have influenced the correlation analysis and statistical significance was not achieved.

The other factor affecting telomeres after transplantation is immunosuppressive medication [121,210,211]. ATG was used as induction therapy for KTx recipients until 2000; most of the KTx recipients in this study probably received ATG. CsA was the most commonly used calcineurin inhibitor after KTx during the last decade. Both of these medications have a negative effect on telomere length [121,123]. None of the KTx recipients were on mTOR inhibitor, which in the study by Chebel et al. did not affect straight telomere length but reduced DNA damage and rescued shelterin expression [211]. Unfortunately, the exact medical history of the KTx recipients was not known and the effect of treatment on telomere length could not be analyzed.

In this study, the KTx population had higher gene expression levels of TRF2, RPA1 than other study groups. p16 levels were also significantly higher than in controls, which is supported by the results of Li et al. [212]. This finding suggests that even if telomere length is reduced, shelterin gene expression is activated to decelerate telomere shortening.

6.4 CANCER RISK AFTER PEDIATRIC SOLID ORGAN TRANSPLANTATION (III)

In the present study kidney, liver and heart transplant recipients' risk for all *de novo* malignancies was nearly 15-fold higher than in controls, whereas in the earlier studies, the risk has been two to six times higher [125,127,128]. In this study the follow-up time was long, up to 20 years, which might have contributed to the higher cancer incidence.

Surprisingly, the KTx recipients' cancer cases were overrepresented: 10% of the KTx recipients had a cancer diagnosis during the follow-up time. This number is comparable with earlier studies from France and USA, where 7-15% of Ktx recipients had post-transplant malignancy [125,213]. In our KTx cohort the risk for cancer was higher (27-fold) than in controls. In the previous study from Netherland, the risk for *de* novo tumors was 17-fold higher after pediatric KTx when compared to general population [150]. The absolute number of cancer cases was higher in the Dutch study: a total of 23% of KTx recipients were diagnosed with post-transplant malignancy during the 30-year follow-up time.

Mortality to other complications than cancer was significantly higher after liver and heart transplant, which can be one reason for the lower cancer incidence among LTx and HTx recipients. In addition, the majority of the study subjects were KTx recipients.

As in the earlier studies, the most common histological diagnosis in this study was PTLD. All PTLD cases were late onset and most were diagnosed over the age of 18 years. The median time after Tx was 13 years. The time between Tx and PTLD diagnosis was longer than in a large study from the USA, where two peaks of PTLD appearance were found: during the first year and the fifth year after Tx [128]. After Tx, EBV copies have been monitored at least every other month and in the case of high virus load, immunosuppressive medication has been reduced. Active follow-up and reduced immunosuppression may have contributed to prevent early PTLD cases. The immunosuppressive regimen has been based on CsA, whereas a previous study among pediatric solid organ transplant recipients found that tacrolimus and MMF increase the risk for burden of early onset PTLD [173].

Two (11%) NMSC cases were diagnosed in the Tx population. The number was lower than in the earlier studies, where 53-72% post-transplant malignancies among KTx recipients have been reported to be skin cancers [125,133,150]. Exposure to ultraviolet radiation is lower in the Nordic countries and Tx recipients are well educated to avoid straight sunlight, which reduces the risk for NMSC.

Post-transplant malignancies are the leading cause of deaths after SOT and cancer-related mortality is higher than in the general population [134,214]. In the present study, the number of cancer-related deaths was higher than in previous studies (40% vs. 15-25% [154,156]). PTLD was the predominant type of cancer and it is known that mortality to PTLD is higher than to solid tumors or NMSC [214]. In addition, the study population

included children and young adults whose risk to develop PTLD is higher than in the older population [215]. It is a cause for concern that the time between cancer diagnosis and death was remarkably short, only 0.7 years, reflecting the aggressive nature of post-transplant lymphoma. Early diagnosis is a challenge in the future.

6.5 STRENGTHS AND LIMITATIONS OF THE STUDY (I-III)

Studies I-II were limited by the small sample size. The small study cohorts may have influenced the statistical analysis and probably precluded statistically differences between groups in some analyses.

Another limitation in this study was lack of information about parents' educational level, employment and family income. A previous study showed that these facts have influence on QoL [13] and most likely also on the educational level of offspring.

A methodological weakness in study II was the method to measure telomere length. In the present study, the quantitative polymerase chain reaction (q-PCR) method was used to determine telomere length. Q-PCR has been shown to be a relatively inaccurate method in the case of measuring both extremely short and long telomeres [216]. However, the same method was used for all study subjects and comparing these groups was relevant.

A strength of all the studies was that all study subjects have been treated and followed up at one center (Helsinki University Hospital) and we had comprehensive records of patients history.

A strength of studies I-II was the inclusion of two different control groups: healthy controls and controls with survivors of severe childhood disease. Comparison with another patient group with chronic condition is more valuable than comparing with healthy controls only.

The major strength of the present study is that in study III we had a total of four different study groups; recipients after pediatric kidney, liver and heart transplantation, and population-based controls. The treatment and follow-up after SOT was organized by one center, which reduced the influence of different therapeutic strategies.

One strength is also that in Finland, it is obligatory by law to report all cancer diagnoses to the Cancer Register. Because of this, the coverage of cancer diagnosis is nearly 100%.

6.6 IMPLICATIONS FOR CLINICAL PRACTICE

Survival after pediatric SOT has improved during the last decades. Most solid organ transplant recipients reach adult age and become part of society. It is necessary to pay increasing attention to the quality of life of these patients. Encouragement and assistance is needed during their studies and student counseling is mandatory. It is important to improve social skills at any age during childhood and youth. Social co-operation is needed not only for school or work, but it is also crucial for relationships.

To diminish both short- and long-term side effects, immunosuppressive medication must be individually tailored [217]. Side effects have a negative effect on QoL and they decrease compliance, which exposes to rejection and graft failure. In addition, immunosuppressive medication increases risk for malignancies and probably causes telomere shortening and frailty.

Structural follow-up from childhood to adult age must be planned for all transplant recipients.

6.7 CHALLENGES FOR FUTURE RESEACH

Fertility after transplantation and the health of offspring are themes for future research. Elements of cancer risk also need more evaluation. A question for the future is whether we can find any genetic basis for PTLD and how we could reduce recipients' risk after transplantation. Evaluating and treating co-morbidities after transplantation is needed to decrease the risk of preterm death.

Little is known about the effect of immunosuppressive medication on telomeres and telomerase. The premature aging caused by treatment calls for further research. Reducing shortening of telomeres might have a positive effect on general health and even QoL.

7 CONCLUSION

The main conclusions are:

Study I: Young adults with a history of pediatric kidney transplantation scored their QoL lower compared to survivors of childhood severe disease or healthy controls. Physical and mental components were the most impaired. Kidney transplant recipients mostly have less education than controls, but in the present study the unemployment rate was comparable with the general Finnish population and was lower than in the earlier studies.

Study II: Telomeres attribution is accelerated after pediatric kidney transplantation compared to healthy controls. Increased telomerase activation is remarkable, showing that despite telomere shortening, capacity to repair still exists.

Study III: A total of eight percent of solid organ transplant recipients and 0.7% of controls had a cancer diagnosis during the follow-up time. SOT recipients' risk was nearly 15-fold higher and mortality was increased compared to controls. In the present study, number of malignancies was higher after KTx than after liver or heart transplantation. The high rate of PTLD and early diagnosis are challenges for future research.

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REFERENCE

1. Jahnukainen T, Bjerre A, Larsson M, et al. The second report of the Nordic Pediatric Renal Transplantation Registry 1997-2012: More infant recipients and improved graft survivals. *Pediatr Transplant*. 2016;20:364-371.
2. Van Arendonk KJ, Boyarsky BJ, Orandi BJ, et al. National trends over 25 years in pediatric kidney transplant outcomes. *Pediatrics*. 2014;133:594-601.
3. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2017 Annual Data Report: Liver. *Am J Transplant*. 2019;19:184-283.
4. Cordinhã C, Rodrigues L, Carmo C, et al. Pediatric Kidney Transplantation: Experience of a Center Over 4 Decades. *Transplant Proc*. 2019;51:1579-1584.
5. Roach JP, Bock ME, Goebel J. Pediatric kidney transplantation. *Semin Pediatr Surg*. 2017;26:233-240.
6. Harrison Jh Fau - Merrill JP, Merrill Jp Fau - Murray JE, Murray JE. Renal homotransplantation in identical twins. *Surg Forum*. 1956;6(0071-8041 (Print)).
7. Starzl TE, Marchioro TL, Porter KA, Faris TD, Carey TA. The Role of Organ Transplantation in Pediatrics. *Pediatr Clin North Am*. 1966;13:381-422.
8. Anthony SJ, Hebert D, Todd L, et al. Child and parental perspectives of multidimensional quality of life outcomes after kidney transplantation. *Pediatr Transplant*. 2010;14:249-256.
9. Chinnakotla S, Verghese P, Chavers B, et al. Outcomes and Risk Factors for Graft Loss: Lessons Learned from 1,056 Pediatric Kidney Transplants at the University of Minnesota. *J Am Coll Surg*. 2017;224:473-486.
10. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2016 Annual Data Report: Kidney. *Am J Transplant*. 2018;18:18-113.
11. Holmberg C, Jalanko H. Congenital nephrotic syndrome and recurrence of proteinuria after renal transplantation. *Pediatr Nephrol*. 2014;29:2309-2317.
12. Holmberg C, Laine J Fau - Ronnholm K, Ronnholm K Fau - Ala-Houhala M, Ala-Houhala M Fau - Jalanko H, Jalanko H. Congenital nephrotic syndrome. *Kidney Int Suppl*. 1996;53(0098-6577 (Print)).
13. Francis A, Didsbury MS, van Zwieten A, et al. Quality of life of children and adolescents with chronic kidney disease: a cross-sectional study. *Arch Dis Child*. 2019;10:134.
14. Aoki Y, Hamasaki Y, Satoh H, et al. Long-term outcomes of pediatric kidney transplantation: A single-center experience over the past 34 years in Japan. *Int J Urol*. 2020;27:172-178.
15. Ariffin H, Azanan MS, Abd Ghafar SS, et al. Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging. *Cancer*. 2017;123:4207-4214
16. Helanterä I HE, Huhti J, Isoniemi H, Jalanko H, Lempinen M, Miettinen M, Nordin A, Tertti R, Mäkelä S. Living donor kidney transplantation. *Duodecim*. 2017;133:937-944.
17. Antunes H, Parada B, Tavares-da-Silva E, et al. Pediatric Renal Transplantation: Evaluation of Long-Term Outcomes and Comparison to Adult Population. *Transplant Procs*. 2018;50:1264-1271.
18. Mumford L, Maxwell H, Ahmad N, Marks SD, Tizard J. The impact of changing practice on improved outcomes of paediatric renal transplantation in the United Kingdom: a 25 years review. *Transplant Int*. 2019;32:751-761.
19. Trnka P, McTaggart SJ, Francis A. The impact of donor/recipient age difference and HLA mismatch on graft outcome in pediatric kidney transplantation. *Pediatr Transplant*. 2018;22:e13265.

20. Finlex. Laki ihmisen elimien, kudoksien ja solujen lääketieteellisestä käytöstä annetun lain muuttamisesta. 2019.
21. Castro A, Malheiro J, Tafulo S, et al. Role of de novo donor-specific anti-HLA antibodies in kidney graft failure: A case-control study. *HLA*. 2017;90:267-275.
22. Fujita T, Kato M, Funahashi Y, et al. Factors Having Effect on Graft Survival in Cadaveric Renal Transplantation. *Transplant Procs*. 2014;46:457-459.
23. Hansson J, Mjörnstedt L, Lindnér P. The risk of graft loss 5 years after kidney transplantation is increased if cold ischemia time exceeds 14 hours. *Clin Transplant*. 2018;32:e13377.
24. Opelz G, Döhler B, Middleton D, Süsal C, Report ACTS. HLA Matching in Pediatric Kidney Transplantation: HLA Poorly Matched Living Donor Transplants Versus HLA Well-Matched Deceased Donor Transplants. *Transplantation*. 2017;101:2789-2792.
25. Ruck JM, Jackson AM, Massie AB, Segev DL, Desai N, Garonzik-Wang J. Temporal Changes in the Impact of HLA Mismatching Among Pediatric Kidney Transplant Recipients. *Transplantion*. 2019;103:1267-1271.
26. Williams RC, West LJ, Opelz G. The Risk of Failure With HLA Mismatch and Recipient Age in First Pediatric (<18 years) Kidney Transplants. *Transplant direct*. 2018;4:e365-e365.
27. Hattori M, Mieno M, Shishido S, et al. Outcomes of Pediatric ABO-incompatible Living Kidney Transplantations From 2002 to 2015: An Analysis of the Japanese Kidney Transplant Registry. *Transplantation*. 2018;102:1934-1942.
28. Shishido S, Hyodo YY, Aoki Y, et al. Outcomes of Pediatric ABO-Incompatible Kidney Transplantations Are Equivalent to ABO-Compatible Controls. *Transplant Procs*. 2012;44:214-216.
29. Friedersdorff F, Koch TM, Banuelos-Marco B, et al. Long-Term Follow-Up after Paediatric Kidney Transplantation and Influence Factors on Graft Survival: A Single-Centre Experience of 16 years. *Urol Int*. 2018;100:317-321.
30. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. HOMOTRANSPLANTATION OF THE LIVER IN HUMANS. *Surg Gynecol Obstet*. 1963;117:659-676.
31. Fosby B, Melum E, Bjøro K, et al. Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013. *Scand J Gastroenterol*. 2015;50(6):797-808.
32. Cuenca AG, Kim HB, Vakili K. Pediatric liver transplantation. *Semin Pediatr Surg*. 2017;26:217-223.
33. Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. *World J Gastroenterol*. 2009;15:648-674.
34. Elisofon SA, Magee JC, Ng VL, et al. Society of pediatric liver transplantation: Current registry status 2011-2018. *Pediatr Transplant*. 2020;24:e13605.
35. Rawal N, Yazigi N. Pediatric Liver Transplantation. *Pediatr Clin North Am*. 2017;64:677-684.
36. Héry G, Franchi-Abella S, Habes D, et al. Initial liver transplantation for unresectable hepatoblastoma after chemotherapy. *Pediatr Blood Cancer*. 2011;57:1270-1275.
37. Ekong UD, Gupta NA, Urban R, Andrews WS. 20- to 25-year patient and graft survival following a single pediatric liver transplant—Analysis of the United Network of Organ Sharing database: Where to go from here. *Pediatr Transplant*. 2019;23:e13523.
38. Venick RS, Farmer DG, Soto JR, et al. One Thousand Pediatric Liver Transplants During Thirty Years: Lessons Learned. *Journal of the American College of Surgeons*. 2018;226:355-366.
39. Stolf NAG. History of Heart Transplantation: a Hard and Glorious Journey. *Braz J Cardiovasc Surg*. 2017;32:423-427.

40. Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. *S Afr Med J*. 1967;30(0256-9574 (Print)).
41. Kantrowitz A, Haller JD, Joos H, Cerruti MM, Carstensen HE. Transplantation of the heart in an infant and an adult. *Am J Cardiol*. 1968;22:782-790.
42. Reinhardt Z. Paediatric heart transplantation: an update. *Arch Dis in Child*. 2019;104:1216.
43. Rossano JW, Cherikh WS, Chambers DC, et al. The Registry of the International Society for Heart and Lung Transplantation: Twentieth Pediatric Heart Transplantation Report—2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant*. 2017;36:1060-1069.
44. Rossano JW, Singh TP, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric heart transplantation report - 2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant*. 2019;38:1028-1041.
45. Dipchand AI, Kirk R, Mahle WT, et al. Ten yr of pediatric heart transplantation: A report from the Pediatric Heart Transplant Study. *Pediatr Transplant*. 2013;17:99-111.
46. Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2016 Annual Data Report: Heart. *Am J Transplant*. 2018;18 Suppl 1:291-362.
47. Tjang YS, Stenlund H, Tenderich G, Hornik L, Körfer R. Pediatric Heart Transplantation: Current Clinical Review. *J Card Surg*. 2008;23:87-91.
48. Riggs KW, Giannini CM, Szugye N, et al. Time for evidence-based, standardized donor size matching for pediatric heart transplantation. *J Thorac Cardiovasc Surg*. 2019;158(1097-685X (Electronic)):8.
49. Alsaied T, Khan MS, Rizwan R, et al. Pediatric Heart Transplantation Long-Term Survival in Different Age and Diagnostic Groups: Analysis of a National Database. *World J Pediatr Congenit Heart Surg*. 2017;8:337-345.
50. Raissadati A, Pihkala J, Jahnukainen T, Jokinen E, Jalanko H, Sairanen H. Late outcome after paediatric heart transplantation in Finland. *Interactive Cardiovasc Thorac Surg*. 2016;23:18-25.
51. Vanderlaan RD, Manlhiot C, Edwards LB, Conway J, McCrindle BW, Dipchand AI. Risk factors for specific causes of death following pediatric heart transplant: An analysis of the registry of the International Society of Heart and Lung Transplantation. *Pediatr Transplant*. 2015;19:896-905.
52. Calne RY, Thiru S, McMaster P, et al. CYCLOSPORIN A IN PATIENTS RECEIVING RENAL ALLOGRAFTS FROM CADAVER DONORS. *The Lancet*. 1978;312:1323-1327.
53. *Pediatric solid organ transplantation*. 2nd ed ed. Malden, Mass: Blackwell; 2007.
54. Li L, Zhao H, Chen B, et al. FXR activation alleviates tacrolimus-induced post-transplant diabetes mellitus by regulating renal gluconeogenesis and glucose uptake. *J Transl Med*. 2019;17:418-418.
55. Pflugrad H, Schrader A-K, Tryc AB, et al. Longterm calcineurin inhibitor therapy and brain function in patients after liver transplantation. *Liver Transplant*. 2018;24:56-66.
56. Maripuri S, Kasiske BL. The role of mycophenolate mofetil in kidney transplantation revisited. *Transplant Rev*. 2014;28:26-31.
57. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2016 Annual Data Report: Kidney. *Am J Transplant*. 2018;18 Suppl 1:18-113.
58. Staatz CE, Tett SE. Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. *Arch Toxicol*. 2014;88:1351-1389.

59. Bergmann TK, Barraclough KA, Lee KJ, Staatz CE. Clinical Pharmacokinetics and Pharmacodynamics of Prednisolone and Prednisone in Solid Organ Transplantation. *Clin Pharmacokinet*. 2012;51:711-741.
60. Ganschow R, Pape L, Sturm E, et al. Growing experience with mTOR inhibitors in pediatric solid organ transplantation. *Pediatr Transplant*. 2013;17:694-706.
61. Nguyen LS, Vautier M, Allenbach Y, et al. Sirolimus and mTOR Inhibitors: A Review of Side Effects and Specific Management in Solid Organ Transplantation. *Drug Safety*. 2019;42:813-825.
62. Min S, Papaz T, Lafreniere-Roula M, et al. A randomized clinical trial of age and genotype-guided tacrolimus dosing after pediatric solid organ transplantation. *Pediatr Transplant*. 2018;22:e13285.
63. Allegri L, Baldan F, Vallone C, et al. Tacrolimus Therapeutic Drug Monitoring in Stable Kidney Transplantation and Individuation of CYP3A5 Genotype. *Transplant Procs*. 2019;51:2917-2920.
64. World Health O. Constitution of the world health organization. 1995.
65. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? *PharmacoEconomics*. 2016;34:645-649.
66. Dua AB, Touma Z Fau - Toloza S, Toloza S Fau - Jolly M, Jolly M. Top 10 recent developments in health-related quality of life in patients with systemic lupus erythematosus. *Curr Rheumatol Rep* 2013;15:380.
67. Jay CL, Butt Z, Ladner DP, Skaro AI, Abecassis MM. A review of quality of life instruments used in liver transplantation. *J Hepatol*. 2009;51:949-959.
68. Ju A, Chow BY, Ralph AF, et al. Patient-reported outcome measures for life participation in kidney transplantation: A systematic review. *Am J Transplant*. 2019;19:2306-2317.
69. Parmar A, Vandriel SM, Ng VL. Health-related quality of life after pediatric liver transplantation: A systematic review. *Liver Transpl*. 2017;23:361-374.
70. Annunziato RA, Parbhakar M, Helcer J, Kapoor K, Henkel K, Arnon R. Strategies for Measuring Quality of Life among Pediatric Solid-Organ Transplant Recipients. *Prog Transplant*. 2014;24:247-256.
71. Barrera M, Hancock K, Atenafu E, et al. Quality of life in pediatric oncology patients, caregivers and siblings after psychosocial screening: a randomized controlled trial. *Support Care Cancer*. 2020;28:3659-3668.
72. Weissberg-Benchell J, Zielinski TE, Rodgers S, et al. Pediatric health-related quality of life: Feasibility, reliability and validity of the PedsQL transplant module. *Am J Transplant*. 2010;10:1677-1685.
73. Tong A, Tjaden L, Howard K, Wong G, Morton R, Craig JC. Quality of Life of Adolescent Kidney Transplant Recipients. *J Pediatr*. 2011;159:670-675.e672.
74. Buyan N, Türkmen MA, Bilge I, et al. Quality of life in children with chronic kidney disease (with child and parent assessments). *Pediatr Nephrol*. 2010;25:1487-1496.
75. Dobbels F, Decorte A, Roskams A, Van Damme-Lombaerts R. Health-related quality of life, treatment adherence, symptom experience and depression in adolescent renal transplant patients. *Pediatr Transplant*. 2010;14:216-223.
76. Rotella AAF, Nascimento RAd, Camargo MFCd, Nogueira PCK. EMOTIONAL REPERCUSSIONS AND QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS UNDERGOING HEMODIALYSIS OR AFTER KIDNEY TRANSPLANTATION. *Rev Paul Pediatr*. 2019;38:e2018221-e2018221.
77. Diseth TH, Tangeraas T, Reinfjell T, Bjerre A. Kidney transplantation in childhood: mental health and quality of life of children and caregivers. *Pediatr Nephrol*. 2011;26:1881-1892.
78. Adamczuk D, Roszkowska-Blaim M, Leszczynska B, Panczyk-Tomaszewska M. Life activity, disease acceptance and quality of life in patients treated with renal replacement therapy since childhood. *Adv Clin Exp Med* 2019;28:871-878.

79. Tozzi AE, Mazzotti E, Di Ciommo VM, Dello Strologo L, Cuttini M. Quality of life in a cohort of patients diagnosed with renal failure in childhood and who received renal transplant. *Pediatr Transplant*. 2012;16:840-845.
80. Tjaden LA, Vogelzang J, Jager KJ, et al. Long-Term Quality of Life and Social Outcome of Childhood End-Stage Renal Disease. *J Pediatr*. 2014;165:336-342.e331.
81. Thorsteinsdottir H, Diseth TH, Lie A, et al. Small effort, high impact: Focus on physical activity improves oxygen uptake (VO2peak), quality of life, and mental health after pediatric renal transplantation. *Pediatr Transplant*. 2018;22:e13242.
82. Vandekerckhove K, Coomans I, De Bruyne E, et al. Evaluation of Exercise Performance, Cardiac Function, and Quality of Life in Children After Liver Transplantation. *Transplantation*. 2016;100:1521-31.
83. Mohammad S, Hormaza L, Neighbors K, et al. Health status in young adults two decades after pediatric liver transplantation. *Am J Transplant*. 2012;12:1486-1495.
84. Kosola S, Lampela H, Lauronen J, et al. General health, health-related quality of life and sexual health after pediatric liver transplantation: a nationwide study. *Am J Transplant*. 2012;12:420-427.
85. Duffy JP, Kao K, Ko CY, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Ann Surg*. 2010;252:652-661.
86. Uzark K, Griffin L, Rodriguez R, et al. Quality of life in pediatric heart transplant recipients: A comparison with children with and without heart disease. *J Heart Lung Transplant*. 2012;31:571-578.
87. Barron L-C, Haas N, Hagl C, et al. Motor outcome, executive functioning, and health-related quality of life of children, adolescents, and young adults after ventricular assist device and heart transplantation. *Pediatr Transplant*. 2020;24:e13631.
88. Hollander SA, Chen S, Luikart H, et al. Quality of life and metrics of achievement in long-term adult survivors of pediatric heart transplant. *Pediatr Transplant*. 2015;19:76-81.
89. Petroski RA, Grady KL, Rodgers S, et al. Quality of Life in Adult Survivors Greater Than 10 Years After Pediatric Heart Transplantation. *J Heart Lung Transplant*. 2009;28:661-666.
90. Cavalli C, Tarzia V, Marini M, et al. A comparison of quality of life and psychological distress in heart transplantation patients at adult and pediatric ages. *Clin Transplant*. 2019;33:e13335.
91. Mellerio H, Alberti C, Labèguerie M, et al. Adult Social and Professional Outcomes of Pediatric Renal Transplant Recipients. *Transplantation*. 2014;97:196-205.
92. Haavisto A, Jalanko H, Sintonen H, Holmberg C, Qvist E. Quality of life in adult survivors of pediatric kidney transplantation. *Transplantation*. 2011;92:1322-1326.
93. Lind RC, Sze Y-K, de Vries W, et al. Achievement of developmental milestones in young adults after liver transplantation in childhood. *Pediatr Transplant*. 2015;19:287-293.
94. Rajchert J, Rosa M, Pawlowska J, Parczewski M, Wawrzynowicz-Syczewska M. Follow-Up of Pediatric Liver Transplant Patients After Reaching Adulthood. *Ann Transplant*. 2016;21:644-648.
95. Mitchell T, Gooding H, Mews C, et al. Transition to adult care for pediatric liver transplant recipients: the Western Australian experience. *Pediatr Transplant*. 2017;21:e12820.
96. Grady KL, Hof KVt, Andrei A-C, et al. Pediatric Heart Transplantation: Transitioning to Adult Care (TRANSIT): Baseline Findings. *Pediatr Cardiol*. 2018;39:354-364.

97. Svt. Väestön koulutusrakenne. 2016.
98. Thammana RV, Knechtle SJ, Romero R, Heffron TG, Daniels CT, Patzer RE. Racial and socioeconomic disparities in pediatric and young adult liver transplant outcomes. *Liver Transplant.* 2014;20:100-115.
99. Svt. Siviilisäädyn muutokset. 2016.
100. Svt. Perheet. 2016.
101. Hayashi MT. Telomere biology in aging and cancer: early history and perspectives. *Genes Genet Syst.* 2018;92:107-118.
102. Turner KJ VV, Griffin DK. Telomere Biology and Human Phenotype. *Cells.* 2019;8:73.
103. Zvereva MI, Shcherbakova Dm Fau - Dontsova OA, Dontsova OA. Telomerase: structure, functions, and activity regulation. *Biochemistry.* 2010;75:1563-1583.
104. Blackburn EH, Epel ES, Lin J. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science.* 2015;350:1193.
105. Rizvi S, Raza T, Mahdi F. Telomere Length Variations in Aging and Age-Related Diseases. *Curr Aging Sci. 2014;* 7:161-167.
106. Steenstrup T, Hjelmborg Jv Fau - Mortensen LH, Mortensen Lh Fau - Kimura M, Kimura M Fau - Christensen K, Christensen K Fau - Aviv A, Aviv A. Leukocyte telomere dynamics in the elderly. *Eur J Epidemiol.* 2013;28:181-187.
107. Willeit P, Raschenberger J, Heydon EE, et al. Leucocyte telomere length and risk of type 2 diabetes mellitus: new prospective cohort study and literature-based meta-analysis. *PLoS One.* 2014;9:e112483.
108. Brouilette SW, Whittaker A, Stevens SE, van der Harst P, Goodall AH, Samani NJ. Telomere length is shorter in healthy offspring of subjects with coronary artery disease: support for the telomere hypothesis. *Heart.* 2008;94:422-425.
109. Dei Cas A, Spigoni V, Franzini L, et al. Lower endothelial progenitor cell number, family history of cardiovascular disease and reduced HDL-cholesterol levels are associated with shorter leukocyte telomere length in healthy young adults. *Nutr Metab Cardiovasc Dis.* 2013;23:272-278.
110. Xu X, Hu H, Lin Y, et al. Differences in Leukocyte Telomere Length between Coronary Heart Disease and Normal Population: A Multipopulation Meta-Analysis. *Biomed Res Int.* 2019;2019:5046867-5046867.
111. Shen Q, Zhao X, Yu L, et al. Association of leukocyte telomere length with type 2 diabetes in mainland Chinese populations. *J Clin Endocrinol Metab.* 2012;97:1371-1374.
112. Strandberg TE, Saijonmaa O, Tilvis RS, et al. Association of telomere length in older men with mortality and midlife body mass index and smoking. *J Gerontol A Biol Sci Med Sci.* 2011;66:815-820.
113. Rode L, Nordestgaard BG, Weischer M, Bojesen SE. Increased body mass index, elevated C-reactive protein, and short telomere length. *J Clin Endocrinol Metab.* 2014;99:E1671-1675.
114. Sanders JL, Newman AB. Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? *Epidemiol Rev.* 2013;35:112-131.
115. Haapanen MJ, Perälä M-M, Salonen MK, et al. Telomere Length and Frailty: The Helsinki Birth Cohort Study. *J Am Med Dir Assoc.* 2018;19:658-662.
116. Vatanen A, Hou M, Huang T, et al. Clinical and biological markers of premature aging after autologous SCT in childhood cancer.*Bone Marrow Transplant* 2017;52:600-605.
117. Kooman J, Dekker M, Usvyat LA, et al. Inflammation and premature aging in advanced chronic kidney disease. *Am J Physiol Renal Physiol.* 2017;313;938-950.

118. Stefanidis I, Voliotis G, Papanikolaou V, et al. Telomere Length in Peripheral Blood Mononuclear Cells of Patients on Chronic Hemodialysis Is Related With Telomerase Activity and Treatment Duration. *Artif Organs*. 2015;39:756-764.
119. Crépin T, Legendre M, Carron C, et al. Uraemia-induced immune senescence and clinical outcomes in chronic kidney disease patients. *Nephrol Dial Transplant*. 2020;35:624-632.
120. Luttropp K, Nordfors L, McGuinness D, et al. Increased Telomere Attrition After Renal Transplantation-Impact of Antimetabolite Therapy. *Transplantation direct*. 2016;2:e116.
121. Crepin T, Carron C, Roubiou C, et al. ATG-induced accelerated immune senescence: clinical implications in renal transplant recipients. *Am J Transplant*. 2015;15:1028-1038.
122. Uziel O, Laish I Fau - Bulcheniko M, Bulcheniko M Fau - Harif Y, et al. Telomere shortening in liver transplant recipients is not influenced by underlying disease or metabolic derangements. *Ann Transplant*. 2013;21:567-575.
123. Welzl K, Welzl K, Kern G, et al. Effect of Different Immunosuppressive Drugs on Immune Cells from Young and Old Healthy Persons. *Gerontology*. 2014;60:229-238.
124. Meijers RW, Litjens NH, de Wit EA, Langerak AW, Baan CC, Betjes MG. Uremia-associated immunological aging is stably imprinted in the T-cell system and not reversed by kidney transplantation. *Transplant Int*. 2014;27:1272-1284.
125. Serrano OK, Bangdiwala AS, Vock DM, et al. Post-Transplant Malignancy after Pediatric Kidney Transplantation: Retrospective Analysis of Incidence and Risk Factors in 884 Patients Receiving Transplants Between 1963 and 2015 at the University of Minnesota. *J Am Coll Surg*. 2017;225:181-193.
126. Park B, Yoon J, Choi D, et al. De novo cancer incidence after kidney and liver transplantation: Results from a nationwide population based data. *Sci Rep*. 2019;9:17202-17202.
127. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the Incidence of Malignancy in Recipients of Different Types of Organ: A UK Registry Audit. *Am J Transplant*. 2010;10:1889-1896.
128. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011;306:1891-1901.
129. Serrano OA-O, Bangdiwala AS, Vock DA-O, et al. Incidence and magnitude of post-transplant cardiovascular disease after pediatric kidney transplantation: Risk factor analysis of 1058 pediatric kidney transplants at the university of Minnesota. *Pediatr Transplant* 2018; 22:e13283.
130. Wareham NE, Li Q, Sengeløv H, et al. "Risk of de novo or secondary cancer after solid organ or allogeneic haematopoietic stem cell transplantation". *J Cancer Res Clin Oncol*. 2019;145:3125-3135.
131. Hsu C-T, Chang M-H, Ho M-C, et al. Post-transplantation lymphoproliferative disease in pediatric liver recipients in Taiwan. *J Formos Med Assoc*. 2019;118:1537-1545.
132. L'Huillier AG, Dipchand AI, Ng VL, et al. Posttransplant lymphoproliferative disorder in pediatric patients: Survival rates according to primary sites of occurrence and a proposed clinical categorization. *Am J Transplant*. 2019;10:2764-2774.
133. Francis A, Johnson DW, Craig JC, Wong G. Incidence and Predictors of Cancer Following Kidney Transplantation in Childhood. *Am J Transplant*. 2017;17:2650-2658.
134. Jäämaa-Holmberg S, Salmela B, Lemström K, Pukkala E, Lommi J. Cancer incidence and mortality after heart transplantation – A population-based national cohort study. *Acta Oncol*. 2019;58:859-863.

135. Smith Jodi M, Martz K, McDonald Ruth A, Harmon William E. Solid tumors following kidney transplantation in children. *Pediatr Transplant*. 2013;17:726-730.
136. Åberg F, Isoniemi H, Pukkala E, et al. Cancer After Liver Transplantation in Children and Young Adults: A Population-Based Study From 4 Nordic Countries. *Liver Transplant*. 2018;24:1252-1259.
137. Cahoon EK, Linet MS, Clarke CA, Pawlish KS, Engels EA, Pfeiffer RM. Risk of Kaposi sarcoma after solid organ transplantation in the United States. *Int J Cancer*. 2018;143:2741-2748.
138. Debray D, Baudouin V, Lacaille F, et al. De novo malignancy after solid organ transplantation in children. *Transplant Proc*. 2009;41:674-675.
139. Bhat M, Mara K, Dierkhising R, Watt KDS. Immunosuppression, Race, and Donor-Related Risk Factors Affect De novo Cancer Incidence Across Solid Organ Transplant Recipients. *Mayo Clinic Proceedings*. 2018;93:1236-1246.
140. Asleh R, Clavell AL, Pereira NL, et al. Incidence of Malignancies in Patients Treated With Sirolimus Following Heart Transplantation. *J Am Coll Cardiol*. 2019;73:2676-2688.
141. Thimonier E, Guillaud O, Walter T, et al. Conversion to everolimus dramatically improves the prognosis of de novo malignancies after liver transplantation for alcoholic liver disease. *Clin Transplant*. 2014;28:1339-1348.
142. Rademacher S, Seehofer D, Eurich D, et al. The 28-year incidence of de novo malignancies after liver transplantation: A single-center analysis of risk factors and mortality in 1616 patients. *Liver Transplant*. 2017;23:1404-1414.
143. Carenco C, Assenat E, Faure S, et al. Tacrolimus and the Risk of Solid Cancers After Liver Transplant: A Dose Effect Relationship. *Am J Transplant*. 2015;15:678-686.
144. Herman-Edelstein M, Rozen-Zvi B, Zingerman B, et al. Effect of immunosuppressive drugs on DNA repair in human peripheral blood mononuclear cells. *Biomed Pharmacother*. 2012;66:111-115.
145. Tsai YF, Chen HP, Liu FC, et al. Nationwide population-based study reveals increased malignancy risk in taiwanese liver transplant recipients. *Oncotarget*. 2016;7:83784-83794.
146. Ma MKM, Lim WH, Turner RM, Chapman JR, Craig JC, Wong G. The Risk of Cancer in Recipients of Living-Donor, Standard and Expanded Criteria Deceased Donor Kidney Transplants: A Registry Analysis. *Transplantation*. 2014;98:1286-93.
147. Hsiao C-Y, Lee P-H, Ho C-M, Wu Y-M, Ho M-C, Hu R-H. Post-Transplant Malignancy in Liver Transplantation: A Single Center Experience. *Medicine*. 2014;93:e310.
148. Brattström C, Granath F, Edgren G, Smedby KE, Wilczek HE. Overall and Cause-Specific Mortality in Transplant Recipients with a Pretransplantation Cancer History. *Transplantation*. 2013;96:297-305.
149. Hayashida MZ, Fernandes VMC, de Melo Fernandes DR, Ogawa MM, Tomimori J. Epidemiology and clinical evolution of non-melanoma skin cancer in renal transplant recipients: a single-center experience in São Paulo, Brazil. *Int J Dermatol*. 2015;54:e383-e388.
150. Ploos van Amstel S, Vogelzang JL, Starink MV, Jager KJ, Groothoff JW. Long-Term Risk of Cancer in Survivors of Pediatric ESRD. *Clin J Am Soc Nephrol*. 2015;10:2198-2204.
151. Sprangers B, Nair V, Launay-Vacher V, Riella LV, Jhaveri KD. Risk factors associated with post–kidney transplant malignancies: an article from the Cancer-Kidney International Network. *Clin Kidney Jl*. 2018;11:315-329.
152. Kiberd BA, Rose C, Gill JS. Cancer Mortality in Kidney Transplantation. *Am J Transplant*. 2009;9:1868-1875.

153. D'Arcy ME, Coghill AE, Lynch CF, et al. Survival after a cancer diagnosis among solid organ transplant recipients in the United States. *Cancer*. 2019;15:933-942.
154. Koukourgianni F, Harambat J, Ranchin B, et al. Malignancy incidence after renal transplantation in children: a 20-year single-centre experience. *Nephrol Dial Transplant*. 2010;25:611-616.
155. Noone A-M, Pfeiffer RM, Dorgan JF, et al. Cancer-attributable mortality among solid organ transplant recipients in the United States: 1987 through 2014. *Cancer*. 2019;125:2647-2655
156. Karakoyun M, Önen Ş, Baran M, et al. Post-transplant malignancies in pediatric liver transplant recipients: Experience of two centers in Turkey. *Turk J Gastroenterol*. 2018;29:89-93.
157. Gajarski RJ, Blume ED, Urschel S, et al. Infection and malignancy after pediatric heart transplantation: The role of induction therapy. *J Heart Lung Transplant*. 2011;30:299-308.
158. Endén K, Tainio J, Nikkilä A, et al. Cancer morbidity and mortality after pediatric solid organ transplantation—a nationwide register study. *Pediatric Nephrology*. 2020;35:1719-1728.
159. Simard JF, Baecklund E, Kinch A, et al. Pediatric Organ Transplantation and Risk of Premalignant and Malignant Tumors in Sweden. *Am J Transplant*. 2011;11:146-151.
160. Yanik EL, Smith JM, Shiels MS, et al. Cancer Risk After Pediatric Solid Organ Transplantation. *Pediatrics*. 2017;139:e20163893.
161. Kitchlu A, Dixon S, Dirk JS, et al. Elevated Risk of Cancer Following Solid Organ Transplant in Childhood: A Population-based Cohort Study. *Transplantation*. 2018;103:588-596.
162. Jeong HJ, Ahn YH, Park E, et al. Posttransplantation lymphoproliferative disorder after pediatric solid organ transplantation: experiences of 20 years in a single center. *Korean J Pediatr*. 2017;60:86-93.
163. Barış Z, Özçay F, Yılmaz Özbek Ö, Haberal N, Sarıalioğlu F, Haberal M. A single-center experience of post-transplant lymphoproliferative disorder (PTLD) cases after pediatric liver transplantation: Incidence, outcomes, and association with food allergy. *Turk J Gastroenterol*. 2018;29:354-360.
164. Cleper R, Ben Shalom E, Landau D, et al. Post-transplantation lymphoproliferative disorder in pediatric kidney-transplant recipients – A national study. *Pediatr Transplant*. 2012;16:619-626.
165. Huebler M, Schubert S, Lehmkuhl HB, et al. Pediatric heart transplantation: 23-year single-center experience☆. *Eur J Cardio-Thorac Surg*. 2011;39:e83-e89.
166. Arshad A, Azeka E, Barbar S, et al. Long-Term Evaluation of Post-transplant Lymphoproliferative Disorders in Paediatric Heart Transplantation in Sao Paulo, Brazil. *Pediatr Cardiol*. 2019;40:1655-1662.
167. Chinnock R, Webber SA, Dipchand AI, Brown RN, George JF, the Pediatric Heart Transplant S. A 16-Year Multi-Institutional Study of the Role of Age and EBV Status on PTLD Incidence Among Pediatric Heart Transplant Recipients. *Am J Transplant*. 2012;12:3061-3068.
168. Wozniak LJ, Mauer TL, Venick RS, et al. Clinical characteristics and outcomes of PTLD following intestinal transplantation. *Clin Transplant*. 2018;32:e13313.
169. Andres AM, Ramos E, Hernandez F. Current status of pediatric intestinal transplant in Europe. *Curr Opin Organ Transplant*. 2020;25:183-188.
170. Gwon JG, Kim YH, Han DJ. Different causes of early and late-onset post transplant lymphoproliferative disorder in kidney transplantation patients after 2000. *Asian J Surg*. 2019;42:551-556.
171. Huang JG, Tan MYQ, Quak S-H, Aw MM. Risk factors and clinical outcomes of pediatric liver transplant recipients with post-transplant

lymphoproliferative disease in a multi-ethnic Asian cohort. *Transpl Infect Dis*. 2018;20:e12798.
172. Ishihara H, Shimizu T, Unagami K, et al. Post-Transplant Lymphoproliferative Disorder in Kidney Transplant Recipients: A Single-Center Experience in Japan. *Ther Apher Dial*. 2016;20:165-173.
173. Schober T, Framke T, Kreipe H, et al. Characteristics of Early and Late PTLD Development in Pediatric Solid Organ Transplant Recipients. *Transplantation*. 2013;95:240-6.
174. Hsu CT, Chang MH, Ho MC, et al. Post-transplantation lymphoproliferative disease in pediatric liver recipients in Taiwan. *J Formos Med Assoc*. 2019;118:1539-1545.
175. Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk Factors for Early-onset and Late-onset Post-transplant Lymphoproliferative Disorder in U.S. Kidney Recipients. *Am J Hem*. 2011;86:206-209.
176. Perry AM, Aoun P, Coulter DW, Sanger WG, Grant WJ, Coccia PF. Early onset, EBV– PTLD in pediatric liver-small bowel transplantation recipients: a spectrum of plasma cell neoplasms with favorable prognosis. *Blood*. 2013;121:1377-1383.
177. Weintraub L, Weiner C, Miloh T, et al. Identifying Predictive Factors for Posttransplant Lymphoproliferative Disease in Pediatric Solid Organ Transplant Recipients With Epstein-Barr Virus Viremia. *J Pediatr Hematol Oncol*. 2014;36:e481-6.
178. Hyun H, Park E, Cho M, et al. Post-Transplant Lymphoproliferative Diseases in Pediatric Kidney Allograft Recipients with Epstein-Barr Virus Viremia. *J Korean Med Sci*. 2019;34:e203-e203.
179. Allen UD, Preiksaitis JK, the ASTIDCoP. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33:e13652.
180. Colombini E, Guzzo I, Morolli F, et al. Viral load of EBV DNAemia is a predictor of EBV-related post-transplant lymphoproliferative disorders in pediatric renal transplant recipients. *Pediatr Nephrol*. 2017;32:1433-1442.
181. Nocera A, Ghio L, Dall'Amico R, et al. De novo cancers in paediatric renal transplant recipients: a multicentre analysis within the North Italy Transplant programme (NITp), Italy. *Eur J Cancer*. 2000;36:80-86.
182. Thergaonkar RW, Bhardwaj S, Sinha A, et al. Posttransplant Lymphoproliferative Disorder: Experience from a Pediatric Nephrology Unit in North India. *Indian J Nephrol*. 2018;28:374-377.
183. Paolino G, Donati M, Didona D, Mercuri SR, Cantisani C. Histology of Non-Melanoma Skin Cancers: An Update. *Biomedicines*. 2017;5:71.
184. Ingvar Å, Smedby KE, Lindelöf B, et al. Immunosuppressive treatment after solid organ transplantation and risk of post-transplant cutaneous squamous cell carcinoma. *Nephrol Dial Transplant*. 2009;25:2764-2771.
185. Howard MD, Su JC, Chong AH. Skin Cancer Following Solid Organ Transplantation: A Review of Risk Factors and Models of Care. *Am J Clin Dermatol*. 2018;19:585-597.
186. Khosravi H, Schmidt B, Huang JT. Characteristics and outcomes of nonmelanoma skin cancer (NMSC) in children and young adults. *Journal of the American Academy of Dermatology*. 2015;73:785-790.
187. Vos M, Plasmeijer EI, van Bemmel BC, et al. Azathioprine to mycophenolate mofetil transition and risk of squamous cell carcinoma after lung transplantation. *J Heart Lung Transplant*. 2018;37:853-859.
188. Funk-Debleds P, Ducroux E, Guillaud O, et al. Subsequent nonmelanoma skin cancers and impact of immunosuppression in liver transplant recipients. *Journal American Academy of Dermatology*. 2018;79:84-91.

189. Phan K, Moloney FJ, Hogarty DT, Lenane P, McColl D, Yazdabadi A. Mammalian target of rapamycin (mTOR) inhibitors and skin cancer risk in nonrenal solid organ transplant recipients: systematic review and meta-analysis. *Int J Dermatol*. 2020;59:91-98.
190. Krynitz B, Edgren G, Lindelöf B, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—A Swedish population-based study. *Int J Cancer*. 2013;132:1429-1438.
191. Imko-Walczuk B, Roskosz-Stożkowska M, Szymańska K, Kadylak D, Dębska-Ślizień A. Skin cancer in children after organ transplantation. *Postepy Dermatol Alergol*. 2019;36:649-654.
192. Fattouh K, Ducroux E, Decullier E, et al. Increasing incidence of melanoma after solid organ transplantation: a retrospective epidemiological study. *Transplant Internat*. 2017;30:1172-1180.
193. Ascha M, Ascha MS, Tanenbaum J, Bordeaux JS. Risk Factors for Melanoma in Renal Transplant Recipients. *JAMA dermatology*. 2017;153:1130-1136.
194. Tainio J, Jahnukainen K, Nurmio M, Pakarinen M, Jalanko H, Jahnukainen T. Testicular function, semen quality, and fertility in young men after renal transplantation during childhood or adolescence. *Transplantation*. 2014;98:987-993.
195. Jahnukainen K, Heikkinen R, Henriksson M, Cooper TG, Puukko-Viertomies LR, Mäkitie O. Semen quality and fertility in adult long-term survivors of childhood acute lymphoblastic leukemia. *Fertil Steril*. 2011;96:837-842.
196. Vatanen A, Hou M, Huang T, et al. Clinical and biological markers of premature aging after autologous SCT in childhood cancer. *Bone Marrow Transplantation*. 2017;52:600.
197. Aalto A-M, Aro AR, Teperi J. *RAND-36 terveyteen liittyvän elämänlaadun mittarina Mittarin luotettavuus ja väestöarvot suomalaisessa aikuisväestössä : STAKES in sarja Tutkimuksia 1999*. Vol 1011999.
198. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of general psychiatry*. 1961;4:561-571.
199. Cawthon RM. Telomere measurement by quantitative PCR. *Nucleic Acids Res*. 2002;30:e47-e47.
200. Tjaden LA, Grootenhuis MA, Noordzij M, Groothoff JW. Health-related quality of life in patients with pediatric onset of end-stage renal disease: state of the art and recommendations for clinical practice. *Pediatr Nephrol*. 2016;31:1579-1591.
201. Montinaro V, Iaffaldano Gp Fau - Granata S, Granata S Fau - Porcelli P, et al. Emotional symptoms, quality of life and cytokine profile in hemodialysis patients. *Clin Nephrol*. 2010;73:36-43.
202. Spencer BWJ, Chilcot J, Farrington K. Still Sad after Successful Renal Transplantation: Are We Failing to Recognise Depression? An Audit of Depression Screening in Renal Graft Recipients. *Nephron Clin Pract*. 2011;117:106-112.
203. Kogon AJ, Stoep AV, Weiss NS, Smith J, Flynn JT, McCauley E. Depression and its associated factors in pediatric chronic kidney disease. *Pediatr Nephrol*. 2013;28:1855-1861.
204. Rodriguez Cuellar CI, García de la Puente S, Hernández Moraria J, Bojórquez Ochoa A, Filler G, Zaltzman Grishevich S. High depression rates among pediatric renal replacement therapy patients: A cross-sectional study. *Pediatr Transplant*. 2019;23:e13591.
205. Lee JM, Jung YK, Bae J-H, et al. Delayed transplantation may affect intellectual ability in children. *Pediatr Int*. 2017;59:1080-1086.
206. Lewis H, Marks SD. Differences between paediatric and adult presentation of ESKD in attainment of adult social goals. *Pediatr nephrol*. 2014;29:2379-2385.

207. Gunn ME, Lahteenmaki PM, Puukko-Viertomies LR, Henriksson M, Heikkinen R, Jahnukainen K. Potential gonadotoxicity of treatment in relation to quality of life and mental well-being of male survivors of childhood acute lymphoblastic leukemia. *J Cancer Surviv*. 2013;7:404-412.
208. Jordakieva G, Grabovac I, Steiner M, et al. Employment Status and Associations with Workability, Quality of Life and Mental Health after Kidney Transplantation in Austria. *Int J Environ Res Public Health*. 2020;17:1254.
209. Diseth TH, Emblem R. Long-term psychosocial consequences of surgical congenital malformations. *Sem Pediatr Surg*. 2017;26:286-294.
210. Koppelstaetter C, Kern G, Leierer G, Mair SM, Mayer G, Leierer J. Effect of cyclosporine, tacrolimus and sirolimus on cellular senescence in renal epithelial cells. *Toxicol in Vitro*. 2018;48:86-92.
211. Chebel A, Catallo R, Mabon C, et al. Rapamycin safeguards lymphocytes from DNA damage accumulation in vivo. *Eur J Cell Biology*. 2016;95:331-341.
212. Li P, Tian C, Ge N, et al. Premature senescence of T cells in long-term survivors of renal transplantation. *Biochem Biophys Res Commun*. 2011;407:599-604.
213. Koukourgianni F, Harambat J Fau - Ranchin B, Ranchin B Fau - Euvrard S, et al. Malignancy incidence after renal transplantation in children: a 20-year single-centre experience. *Neph Dial Transplant*. 2010;25:611-6.
214. Acuna SA, Fernandes KA, Daly C, et al. Cancer mortality among recipients of solid-organ transplantation in Ontario, Canada. *JAMA Oncology*. 2016;2:463-469.
215. Hall EC, Pfeiffer RM, Segev DL, Engels EA. Cumulative incidence of cancer after solid organ transplantation. *Cancer*. 2013;119:2300-2308.
216. Lai T-P, Wright WE, Shay JW. Comparison of telomere length measurement methods. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2018;373:20160451.
217. Pape L. State-of-the-art immunosuppression protocols for pediatric renal transplant recipients. *Pediatr Nephrol*. 2019;34:187-194.