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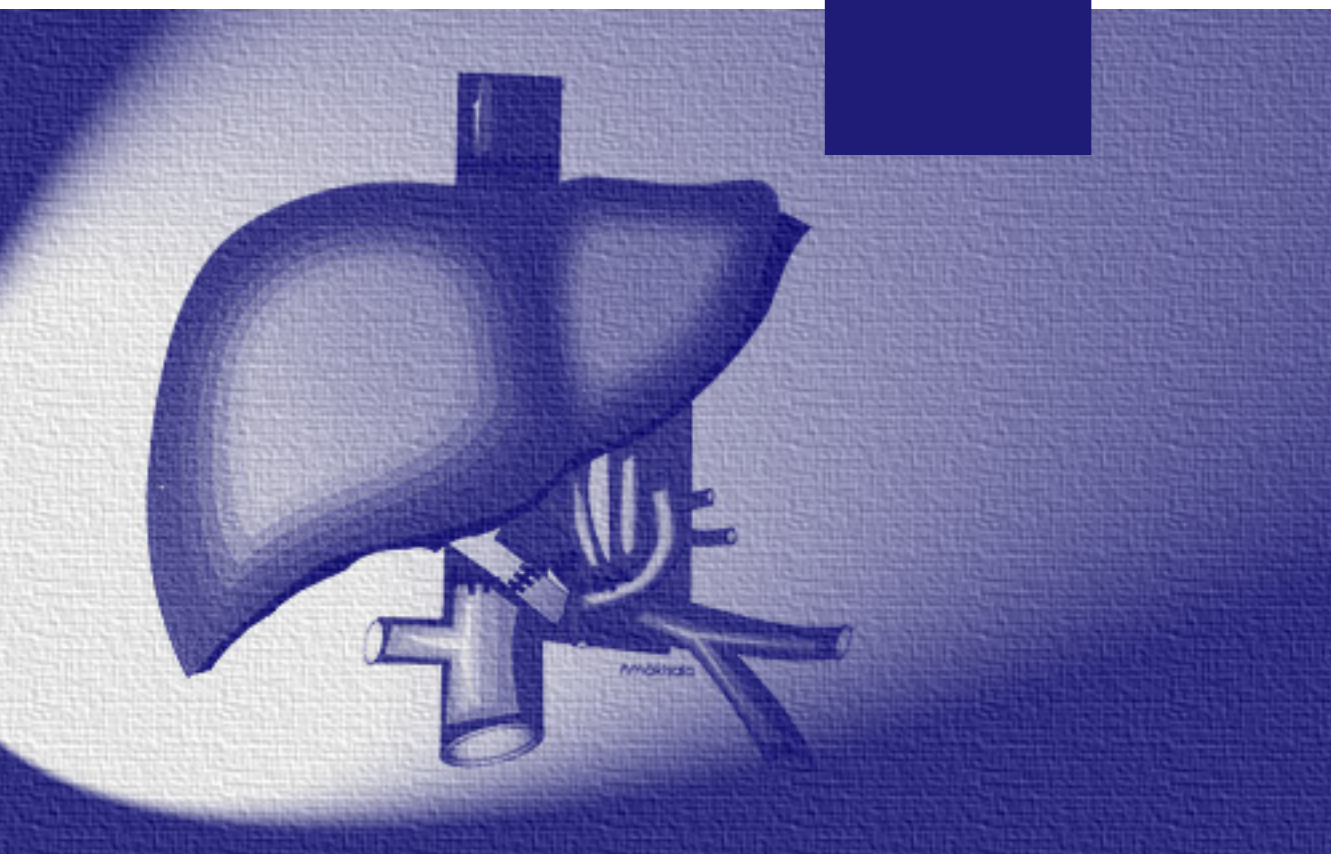
Long-term clinical outcome after liver transplantation

FREDRIK ÅBERG



Transplantation and Liver Surgery Clinic, Department of Surgery

Helsinki University Central Hospital
Faculty of Medicine, University of Helsinki

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FREDRIK ÅBERG

Academic dissertation

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Supervisor
Docent Helena Isoniemi
Transplantation and Liver Surgery Clinic
Department of Surgery
Helsinki University Central Hospital
University of Helsinki
Helsinki, Finland

Reviewers
Docent Martti Färkkilä
Division of Gastroenterology
Department of Medicine
Helsinki University Central Hospital
University of Helsinki
Helsinki, Finland

Docent Rauli Leino
Department of Medicine
Turku University Central Hospital
University of Turku
Turku, Finland

Opponent
Professor Bo-Göran Ericzon
Division of Transplantation Surgery
CLINTEC, Karolinska Institutet
Karolinska University Hospital Huddinge
Stockholm, Sweden

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Contents

Abstract

With transplant rejection rendered a minor concern and survival rates after liver transplantation (LT) steadily improving, long-term complications are attracting more attention. Current immunosuppressive therapies, together with other factors, are accompanied by considerable long-term toxicity, which clinically manifests as renal dysfunction, high risk for cardiovascular disease, and cancer.

This thesis investigates the incidence, causes, and risk factors for such renal dysfunction, cardiovascular risk, and cancer after LT. Long-term effects of LT are further addressed by surveying the quality of life and employment status of LT recipients.

The consecutive patients included had undergone LT at Helsinki University Hospital from 1982 onwards. Data regarding renal function – creatinine and estimated glomerular filtration rate (GFR) – were recorded before and repeatedly after LT in 396 patients. The presence of hypertension, dyslipidemia, diabetes, impaired fasting glucose, and overweight/obesity before and 5 years after LT was determined among 77 patients transplanted for acute liver failure.

The entire cohort of LT patients (540 patients), including both children and adults, was linked with the Finnish Cancer Registry, and numbers of cancers observed were compared to site-specific expected numbers based on national cancer incidence rates stratified by age, gender, and calendar time.

Health-related quality of life (HRQoL), measured by the 15D instrument, and employment status were surveyed among all adult patients alive in 2007 (401 patients). The response rate was 89%. Posttransplant cardiovascular risk factor prevalence and HRQoL were compared with that in the age- and gender-matched Finnish general population.

The cumulative risk for chronic kidney disease increased from 10% at 5 years to 16% at 10 years following LT. GFR up to 10 years after LT could be predicted by the GFR at 1 year. In patients transplanted for chronic liver disease, a moderate correlation of pretransplant GFR with later GFR was also evident, whereas in acute liver failure patients after LT, even severe pretransplant renal dysfunction often recovered. By 5 years after LT, 71% of acute liver failure patients were receiving antihypertensive medications, 61% were exhibiting dyslipidemia, 10% were diabetic, 32% were overweight, and 13% obese. Compared with the general population, only hypertension displayed a significantly elevated prevalence among patients – 2.7-fold – whereas patients exhibited 30% less dyslipidemia and 71% less impaired fasting glucose.

The cumulative incidence of cancer was 5% at 5 years and 13% at 10. Compared with the general population, patients were subject to a 2.6-fold cancer risk, with non-melanoma skin cancer (standardized incidence ratio, SIR, 38.5) and non-Hodgkin lymphoma (SIR 13.9) being the predominant malignancies. Non-Hodgkin lymphoma was associated with male gender, young age, and the immediate posttransplant period, whereas old age and antibody induction therapy raised skin-cancer risk.

HRQoL deviated clinically unimportantly from the values in the general population, but significant deficits among patients were evident in some physical domains. HRQoL did not seem to decrease with longer follow-up. Although 87% of patients reported improved working capacity, data on return to working life showed marked age-dependency: Among patients aged less than 40 at LT, 70 to 80% returned to work, among those aged 40 to 50, 55%, and among those above 50, 15% to 28%. The most common cause for unemployment was early retirement before LT. Those patients employed exhibited better HRQoL than those unemployed.

In conclusion, although renal impairment, hypertension, and cancer are evidently common after LT and increase with time, patients' quality of life remains comparable with that of the general population.

Original publications

I Åberg F, Koivusalo A-M, Höckerstedt K, Isoniemi H. Renal dysfunction in liver transplant patients: comparing patients transplanted for liver tumor or acute or chronic disease. *Transpl Int* 2007;20:591-9.

II Åberg F, Pukkala E, Höckerstedt K, Sankila R, Isoniemi H. Risk of malignant neoplasms after liver transplantation: a population-based study. *Liver Transpl* 2008;14:1428-36.

III Åberg F, Rissanen AM, Sintonen H, Roine RP, Höckerstedt K, Isoniemi H. Health-related quality of life and employment status of liver transplant patients. *Liver Transpl* 2009;15:64-72.

IV Åberg F, Jula A, Höckerstedt K, Isoniemi H. Cardiovascular risk profile of patients with acute liver failure after liver transplantation when compared with the general population. *Transplantation* 2010;89:61-8.

The original publications are referred to in the text by their roman numerals. The articles are reproduced with the kind permission of the copyright holders. In addition, some unpublished data are presented.

Abbreviations

ALF, acute liver failure
ALG, antilymphocyte globulin
ATG, antithymocyte globulin
BMI, body mass index
CI, confidence interval
CKD, chronic kidney disease
CLD, chronic liver disease
CMV, cytomegalovirus
CNI, calcineurin inhibitor
CV, cardiovascular
EBV, Epstein Barr virus
EC-MPS, enteric-coated mycophenolate sodium
ESRD, end-stage renal disease
GFR, glomerular filtration rate
HbA1c, glycated hemoglobin
HCC, hepatocellular carcinoma
HCV, hepatitis C virus
HDL, high-density lipoprotein
HRQoL, health-related quality of life
IFG, impaired fasting glucose
IL-2, interleukin-2
INR, international normalized ratio
LDL, low-density lipoprotein
LT, liver transplantation
MELD, Model for End-Stage Liver Disease
MMF, mycophenolate mofetil
MTOR, mammalian target of rapamycin
PBC, primary biliary cirrhosis
PSC, primary sclerosing cholangitis
PTLD, posttransplant lymphoproliferative disorder
SIR, standardized incidence ratio
SPR, standardized prevalence ratio

Introduction

Thomas Starzl and colleagues, working in Denver, Colorado, attempted the first human liver transplantation (LT) in 1963, but had to wait until 1967 for their first clinically successful LT.[1,2] Their success was a year later reinforced by the initiation of the first European clinical liver transplant program in Cambridge, UK, led by Roy Calne.[1,3-5] With an immunosuppression largely based on steroids and azathioprine, however, many patients were subject to fatal graft rejection; following transplantation less than 30% survived more than one year.[1]

In the early 1980s, the discovery of the potent immunosuppressant cyclosporine revolutionized the field by rendering graft loss due to rejection infrequent.[1] This success consequently enabled LTs to begin a transformation from a rather experimental procedure to a definitive therapy for end-stage liver disease. Shortly hereafter, with knowledge acquired by the Finnish surgeon Krister Höckerstedt at Calne's center in Cambridge, and through a joint team effort, the Finnish liver transplant program commenced. In 1982, the first Nordic LT was carried out in Helsinki.[6]

Since then, numerous advances in surgical technique, organ preservation, perioperative anesthesia, postoperative care, and clinical immunosuppression, as well as improved recipient selection and donor management have together gradually defeated the initial enemies of long-term survival – as evidenced by a current 10-year survival rate of roughly 60%, and at some centers of above 70%.[1,7-10] Concurrently, annual numbers of LTs performed in Europe alone have steadily increased from 25 in 1980 to 5531 in 2007.[8] By 2008, more than 80 000 LTs had been performed in Europe.[8] In Finland, the figure has stabilized at around 50 LTs annually.[7]

With fatal rejection made rare, the transplant community is now increasingly confronted by a new challenge: long-term complications.[11,12] Such complications – including especially renal dysfunction, malignancies, and cardiovascular disease – frequently contribute to late mortality.[8,12-17] Whereas toxicity from the life-long use of cyclosporine and the more recent agent tacrolimus, together with side-effects from concomitant immunosuppressants, are primarily implicated in the pathogenesis of these long-term complications, other potential causative factors are recognized as well.[12,16,18-20] The relative significance of each factor, however, remains vague, and the full extent of the problem in the setting of LT has, thus far, been scantily addressed. Vast research in the field has, moreover, yielded numerous new immunosuppressive agents, such as mycophenolate, sirolimus, and everolimus, which, through their distinct side-effect profiles, now offer transplant physicians the possibility to tailor immunosuppressive therapy.

The regular occurrence of long-term complications has naturally inspired enormous interest in developing strategies to prevent such complications, identifying the optimal degree of immunosuppression, recognizing regimens with less adverse effects, characterizing means to tailor immunosuppression, implementing appropriate follow-up screenings, and uncovering proper forms of therapy for complications once they occur. Essential for such achievements is, on the other hand, that the incidences, causes, and risk factors for the late complications first be accurately recognized. Until recent years, large-scale efforts to obtain such data have been restricted by rather small numbers of long-term survivors.

In Finland, data on the occurrence of long-term complications has been lacking. Results from different centers may, furthermore, differ, likely because of differing patient characteristics and immunosuppression regimens. Moreover, because crude survival times now show an impressive rise, the quality of life of long-term survivors – likely impacted by complications – is emerging as an important outcome measure.[21] To date, quality-of-life issues have, however, been poorly explored.[22]

This thesis addresses the issue of long-term nonhepatic complications following LT by exploring the incidence of renal dysfunction, malignancies, and cardiovascular risk. The influence of time after LT and the impact of transplantation-related factors such as immunosuppression on the appearance of these complications also deserved investigation. Finally, overall outcome is evaluated by means of posttransplant quality of life and working capacity assessment. These findings may aid in developing means to use the currently available tools to maximize favorable outcome.

Review of the literature

LIVER TRANSPLANTATION ACTIVITY

Indications

Change over time in indications. Recent years reveal a changing pattern of liver transplant indications. According to international liver registries, various liver tumors – in the early days constituting up to 50% of all indications – have gradually given way to cirrhosis, which, nowadays accounts for the majority of LTs performed in Europe and the USA.[7-9] Table 1 depicts the main indications in Europe and Finland.

Table 1. Indications for liver transplantation in Europe and Finland 1988-2008

Primary disease	Europe (n=70 288)	Finland (n=667)
Cirrhosis	**58%**	**40%**
Virus-related	38%	6%
Alcoholic	33%	25%
Viral + alcoholic	4%	0%
Primary biliary cirrhosis	11%	41%
Unknown causes	8%	16%
Autoimmune	4%	6%
Other	2%	6%
Liver tumor	**14%**	**8%**
Hepatocellular carcinoma	84%	65%
Cholangiocellular carcinoma	3%	2%
Other	13%	33%
Cholestatic disease	**10%**	**22%**
Primary sclerosing cholangitis	43%	69%
Biliary atresia	41%	26%
Other biliary diseases	16%	6%
Acute liver failure	**9%**	**21%**
Metabolic and other diseases	**9%**	**9%**

Nonbolded percentages are proportions of the respective main groups.
Data from references 8 and 23.

Whereas primary biliary cirrhosis (PBC) had been the main underlying condition, alcoholic cirrhosis and viral hepatitis (mostly hepatitis C, HCV) have now become the two most common forms of cirrhosis leading to LT, representing 33% and 38% of LTs performed for cirrhosis in Europe.[8] In Finland, however, alcoholic cirrhosis and viral hepatitis account for only 10% and 3% of all LTs, with the predominant chronic conditions being PBC and primary sclerosing cholangitis (PSC).[23] These account for 15% and 16% of all LTs performed in Finland, where PSC has in recent years surpassed PBC as the single most common indication. Acute liver failure (ALF) is a more common indication for LT in Finland (21% of all LTs) than in Europe (9%) or

in the USA (6-9%).[8,9] Liver tumors, representing 14% of LTs performed in Europe [8] and 8% in Finland,[23] currently consist mainly of hepatocellular carcinoma (HCC); other tumor types are rarely considered suitable for LT.[1] In children, the leading indication for transplantation is cholestatic liver disease.[8,9]

Timing of LT in current indications. In general, any patient with a liver disease resulting in life-threatening complications and a prognosis of one year of life or less, or with the inability to sustain a normal quality of life should be considered for LT.[1,24,25] The modern approach is to pursue optimal timing of LT: when the patient will derive maximum survival benefit from transplantation.[24,26,27] In practice, chronic liver disease (CLD) patients are usually considered for LT when they begin to show signs of hepatic decompensation (refractory ascites, hepatic encephalopathy, recurrent variceal hemorrhage, jaundice, coagulopathy, hypoalbuminemia, recurrent infections, or hepatorenal syndrome), or when they exhibit unbearable or disabling symptoms such as intractable pruritus.[25,27,28]

In PSC, LT is also considered in the case of recurrent cholangitis, rapid disease progression (as indicated by symptoms, biochemical markers, or cholangiographic findings), or a strong suspicion of progression to hepatobiliary malignancy (as indicated by tumor markers, radiology, or significant dysplasia in repeated biliary brush cytology).[29,30]

In the case of alcoholic cirrhosis, concern for relapsing alcohol abuse after LT has produced a widely adopted prerequisite of a 6-month abstinence period before consideration for LT.[1,11,17,31,32] The underlying rationale is to identify candidates with higher risk for recidivism, to allow time for adequate therapy for addiction, but also to identify cases where liver function may recover to a level that makes LT unnecessary.[1,11,17,31,32] The 6-month rule is, however, criticized as being based on no solid evidence, and hence, many experts recommend replacing such fixed periods with a more careful evaluation of each patient by addiction specialists.[1,17,31,32]

In asymptomatic cirrhosis and viral hepatitis, an additional motive for LT is concomitant HCC.[1] According to the widely adopted Milan criteria,[33] LT is a therapeutic option for HCC when one solitary HCC lesion ≤ 5 cm is evident or one to three HCC lesions, with none exceeding 3 cm.

Although the Kings College criteria [34] and Clichy criteria [35] are widely used, no universally standardized criteria dictate when ALF requires LT.[1,36] In Finland, the Kings College criteria are chiefly employed in the decision to proceed to LT.

Pretransplant evaluation. Liver transplant candidates undergo thorough evaluation in a multidisciplinary setting, including not only accurate assessment of liver pathology and severity of liver disease, but also evaluation of cardiopulmonary and renal function, screening for significant infections, possible infection foci, and co-morbidities, as well as comprehensive psychosocial evaluation.[1,17]

Contra-indications

Because of the universal shortage of organs for transplantation, LTs are performed only in patients for whom a reasonable prognosis is predicted.[1,25] Medical advances, however, continuously reduce the list of contra-indications. Currently, absolute contra-indications include recent or active malignancy – with exceptions such as HCC and basal cell carcinoma – uncontrolled infection, active alcohol- or drug abuse,

inability to comply with a complex posttransplant medical regimen and follow-up, and physical illnesses curtailing life expectancy such as advanced cardiopulmonary disease or major irreversible cerebral injury.[1,17,27,37]

The many conditions recognized as relative contra-indications differ among transplant centers.[1,11,17,27,38] As some are manageable, they often are regarded more as risk factors for adverse outcome and are always weighed on a case-by-case basis.[27]

Organ donors

In Western countries, the clear majority of LTs involve liver grafts from brain-dead donors.[11] This is, furthermore, the only form of LT practiced in Finland.[7] Most allocation policies also involve this type of LT.[27] The continuing organ shortage has, however, motivated efforts to increase the organ pool by awareness programs to increase donation rates, by expanding medical criteria for acceptable organs (extended-criteria donors), by employing organ donation after cardiac death (non-heart-beating donors), by splitting a liver for two recipients, and by accepting living partial-liver donors.[1,11,38,39]

Although this choice currently makes up a mere 3% to 4% of LTs in the USA and Europe, many Asian countries are, for cultural reasons, using living donors almost exclusively.[11,39]

An ideal brain-dead donor is aged less than 50 to 60, presenting with normal liver and kidney values and stabilized hemodynamics, is devoid of hepatobiliary disease, severe abdominal trauma, systemic infection, or malignancy.[37] Use of extended-criteria donors – including older donors, steatosed grafts, prolonged intensive care, elevated serum sodium, positive viral serology, and history of malignancy – is, together with use of non-heart-beating donors, associated with more postoperative complications and increased mortality.[11,37-39]

Organ allocation

The scarcity of donated organs relative to patients' need for them forces society to generate allocation policies, prioritizing scarce organs for those needing them most urgently. In most transplant programs, an available donor liver is, among compatible candidates, prioritized to the patient exhibiting the highest degree of medical urgency.[27,37] In LT, compatibility refers to ABO blood group compatibility as well as donor and recipient size and age similarity.[24,40,41] The role of other histocompatibility factors is negligible.[42] Although ALF and high-urgency retransplantation-necessitating conditions are universally given the highest priority, criteria of medical urgency for CLD differ.[27,37]

The US Model. The United States has, since 2002, allocated liver grafts according to candidate risk scores derived from the Model for End-Stage Liver Disease (MELD), a scoring system based on INR, creatinine, and bilirubin; MELD predicts waiting-list mortality and thus parallels disease severity.[9,43-45] Some conditions may merit additional points,[27] and a modification of this model serves for pediatric patients.[9,45]

European models. In Europe, allocation policies of the six main organ exchange organizations differ, with some inter-organizational collaboration regarding surplus

organs. While Spain, France, Italy, and the UK administer their own national organizations, Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands, and Slovenia collaborate in the agency Eurotransplant.[1,27] The Nordic countries, including Finland, cooperate in Scandiatransplant.[7] In 2006, Eurotransplant adopted a MELD-based allocation system similar to that in the USA.[27] The UK has recently developed and implemented a different scoring system: the United Kingdom Model for End-stage Liver Disease (UKELD), with its algorithm adding sodium level to the factors included in MELD.[25,27]

Scandinavian model. Within Scandiatransplant, high-urgency candidates are entitled to the first available liver graft from any member country within 3 days, whereas, in elective cases, donor organs are offered to collaborating centers only if not needed locally.[1,7]

Finnish model. Finland has avoided competition for organs between centers by having all LTs centralized in Helsinki. This, together with overall relatively small-scale LT activity and a short waiting-list, enables the allocation of donor livers based on careful clinical judgement – comprehensively balancing donor and recipient risks individually – instead of allocation based on rigorous mathematical algorithms.

Surgical procedures

Conventional technique. As detailed reviews of surgical techniques involved in LT operations and principles of graft preservation and perioperative anesthesia are available elsewhere,[1,37,41] only some basic aspects need be discussed here. Following the exposure and dissection of relevant structures, ligation and cutting of the bile duct, crossclamping and cutting of the hepatic artery, portal vein, and infra- and suprahepatic caval vein, as well as removal of the diseased liver, the donor liver is usually placed in the same location (orthotopically).[41] Implantation of the liver in another location (heterotopically) is linked to inferior outcome and during the last two decades has been performed in less than 2/1000 recipients in Europe.[8,41]

Anhepatic phase. Clamping of both the inferior caval vein and the portal vein poses a hemodynamic challenge which can be overcome either by an extracorporeal, pump-driven veno-venous bypass or by caval-vein-sparing surgery (Piggyback).[1,37,41] Both techniques offer some potential complications such as thrombosis.[41] At Helsinki University Central Hospital, the veno-venous bypass is not in use, and a modified Piggyback method is practiced mainly in patients with compromised cardiac function.

Reconstructive techniques. The subsequent reconstruction of the vasculature and bile ducts are often by end-to-end anastomoses, but variations exist.[1,37,41] In Helsinki, end-to-end biliary anastomosis is without a T-tube, whereas PSC patients undergo reconstruction of the biliary tract by anastomosis of the donor bile duct to a small bowel loop (Roux-en Y).[37,41] Overall, several technical modifications of and variations in the transplantation procedure exist. Which of these are applied depends on characteristics of the recipient and the routine practice of the center, as well as the preference of the surgeon.[41]

Alternative surgical approaches. Size-reduction of a graft permits adult-donor livers to be used in children. An alternative, efficiently preserving the limited organ supply, is splitting a liver graft for two recipients – a method constituting approximately 3% to 5% of LTs performed in the USA and Europe.[8,9] Domino LT,

another innovative strategy, refers to a rather unusual situation where a patient with a particular disease, most frequently familial amyloid polyneuropathy, undergoes conventional LT, but simultaneously donates his or her native liver to some other patient awaiting LT.[46,47]

An evolving approach in ALF is to resect the patient's liver and transplant a partial graft adjacent to the resected diseased liver (auxiliary LT).[1] The advantage of such a procedure is the potential option to discontinue immunosuppression if the native liver, despite its poor prognosis, recovers. To date in Europe, auxiliary LT has been performed in less than 2% of all urgent LTs.[8] Despite the alternative surgical innovations, in Europe, LTs still performed with full-sized liver grafts from brain-dead donors amount to more than 80%.[8]

As evident in this overview, variations presently exist between nations and centers in their LT activity. Such variations, in addition to the effect of immunosuppression to be discussed, may influence the outcome following LT, the occurrence of complications, and patients' quality of life.

IMMUNOSUPPRESSION

The immune response in liver transplantation

Following LT, the recipient's immune system recognizes the implanted liver as foreign and consequently launches an immune response resulting in graft rejection. The underlying mechanisms by which such an immune response is mediated are complex, and despite intense research, remain incompletely understood.[1,48-51] According to current understanding, cellular reactions, mainly mediated by T-lymphocytes, play the predominant role, with the role of antibody-mediated responses apparently trivial.[1,48-51] As more thoroughly outlined in Figure 1, the rejection response can be divided into four phases: antigen recognition, lymphocyte activation, lymphocyte proliferation, and graft inflammation.[1]

Antigen recognition in recipient lymphoid tissue occurs either when recipient T lymphocytes recognize donor major-histocompatibility-complex-molecules expressed on donor-derived antigen-presenting cells (direct pathway), or when recipient T lymphocytes recognize donor-derived antigens in the context of self-major histocompatibility-complex-molecules expressed on recipient antigen-presenting cells (indirect pathway).[1,48,50] Some propose that, with a massive migration of graft-derived donor hematolymphoid cells (such as antigen-presenting cells) into recipient lymphoid tissue, the direct pathway predominates as a cause for acute rejection early posttransplant, whereas indirect pathways may predominate later on when donor antigen-presenting cells have slowly died out.[48,50] This phenomenon helps explain why rejection risk gradually decreases with time.[48,50] Moreover, the large component of liver graft-derived immunocompetent-mature donor T lymphocytes, together with a weakened recipient immune system, permits the highly unusual event of graft-versus-host disease.[52] The other phases of the immune response are depicted in Figure 1.

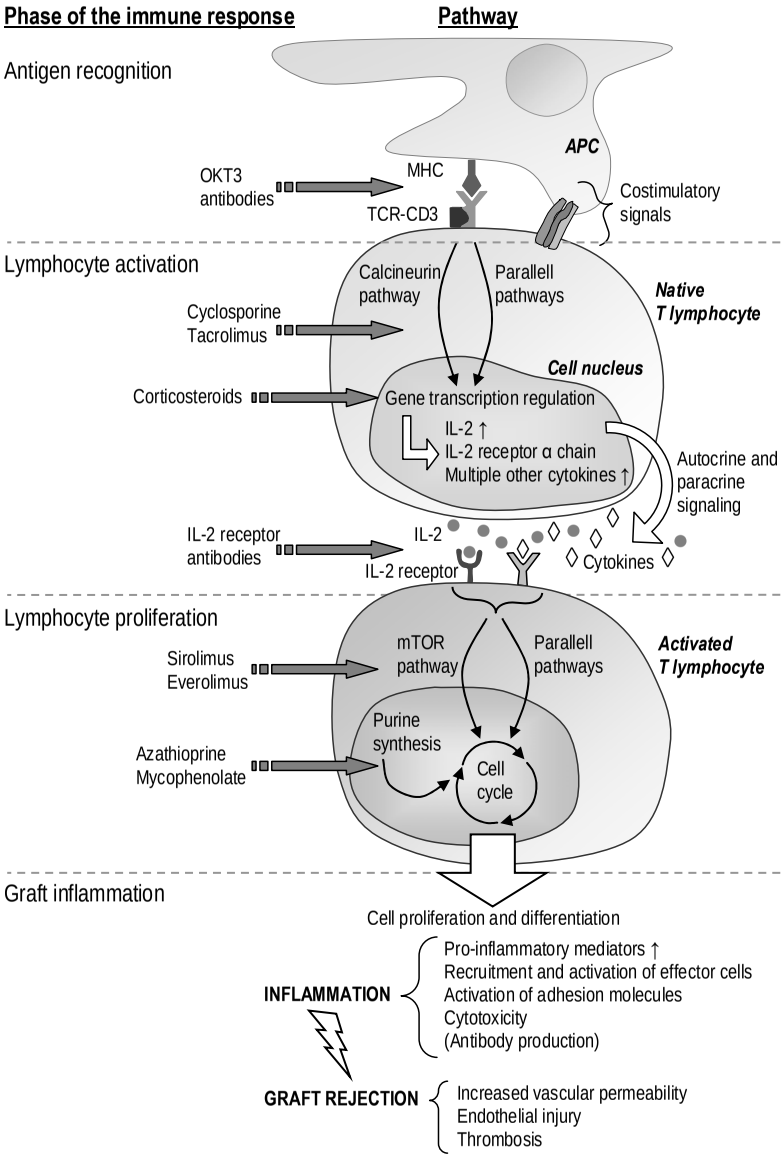

Figure 1. Phases and basic pathways of liver graft rejection according to current understanding. Cell-surface interactions between the major histocompatibility complex (MHC) on antigen-presenting cells (APC) and the T-cell receptor-CD3 (TCR-CD3) complex on native T lymphocytes, when coinciding with other costimulatory interactions between these cells, launch cytoplasmic signal cascades in the T lymphocyte. These cascades are mediated by the calcineurin pathway and other pathways, resulting in activation of the T lymphocyte. Activation hereby involves transcription of several genes, resulting in the expression of multiple cytokines (most noticeably interleukin-2 [IL-2]), IL-2 receptor α chain, and other mediators. By binding to the IL-2 receptor on activated T lympocytes, IL-2 delivers growth signals through the mammalian target of rapamycin (mTOR) pathway and other pathways. Similar autocrine and paracrine cytokines activate other receptors, which also initiate these pathways. Such pathways initiate the lymphocyte cell cycle, which, in the presence of adequate purine synthesis, results in proliferation and differentiation of lymphocytes. These reactions, along with a burst of cytokines, upregulation of adhesion molecules, and possible parallel pathways, recruit other proinflammatory cells, thus generating an inflammatory milieu in the liver graft. Graft damage arises from various immunological effector mechanisms, with humoral reactions likely playing only a minor role. The net effect – which histologically is characterized by portal inflammation, venular endothelial inflammation, and bile duct injury – is clinically manifested as acute graft rejection. The sites of actions of various immunosuppressive agents are also shown (horizontal gray arrows) but described only in the text.
The figure is created based on mechanisms depicted in references: 1, 48-51, 54, 72.

Principles of immunotherapy

To prevent graft rejection following LT, life-long immunosuppression therapy is, in the vast majority of patients, necessary.[11,14,53-55] In practice, successful posttransplant care relies on a continuous balance in immunosuppressive therapy between too mild – leading to rejection, and too intense – resulting in toxicity. Adding to the challenge is the variation in optimal degree of immunosuppression from patient to patient. This degree generally decreases with time; along with rejection risk.[54] Although some anecdotal cases of complete tolerance have been reported, no means to identify such cases yet exist.[56]

Standard regimens usually consist of a combination of three types of agents: a calcineurin inhibitor (CNI) – the mainstay of immunosuppressive therapy – is typically combined with antimetabolites and corticosteroids.[1,11,37,53,54] The advantage of such diversified therapy is that it increases efficacy while simultaneously allowing lower doses of each drug and, hence, minimizing drug-specific toxicity.[14,54] The most common drugs currently in clinical use, the era of their clinical introduction, and their side-effect profiles are summarized in Table 2.[14,57-71]

Calcineurin inhibitors

CNIs, comprising cyclosporine and tacrolimus, are thought to achieve their immunosuppressive effect primarily by inhibiting the activation of T lymphocytes (Figure 1).[48,51,72] Cyclosporine binds to the cytosolic protein cyclophilin, whereas tacrolimus, a macrolid compound exhibiting 100-fold greater potency than cyclosporine, binds to a corresponding protein called the FK506-binding protein 12.[1,48,51,54,72] These protein-drug complexes competitively block signal transduction through the calcineurin pathway, which in turn results in inhibition of the transcription of several genes, including genes for interleukin-2 (IL-2), critical for the activation of T lymphocytes (Figure 1).[1,48,51,54,72] CNIs selectively suppress lymphocyte reactions, while other cell lines are not significantly inhibited.[1]

Both CNIs are primarily metabolized in the liver via the cytochrome P450 3A4 system, which renders them able to function in multiple clinically important drug interactions.[14,55] Accordingly, as small differences in blood concentration can cause therapeutic failure or adverse effects, drug levels require regular monitoring.[14]

Following an initial weight-based dosage twice daily, subsequent dosage is guided by trough levels as well as by signs of adverse effects. Target levels vary between centers and depend also on concomitant medications.[1] Presently a newer microemulsified formulation of cyclosporine is available which is less dependent on biliary flow for absorption and exhibits more consistent bioavailability.[1] More recently, a prolonged-release formulation of tacrolimus has also been developed, allowing once-daily dosing.

Several adverse effects common to both CNIs are recognized, most notably nephrotoxicity and neurotoxicity, but with noteworthy differences, such as that tacrolimus is more diabetogenic, and cyclosporine causes more dyslipidemia and hypertension (Table 2).

Table 2. Compilation of the most frequent side-effects of immunosuppressive drugs, as used in the setting of liver transplantation.

	Cyclosporine	Tacrolimus	Corticosteroids	Azathioprine	Mycophenolate	mTOR inhibitors [a]
Era of clinical introduction	1980s	1990s	1960s	1960s	1990s	2000s
Adverse effect						
Alopecia	-	+	-	-	+	-
Bone marrow suppression	+	+	-	+++	++	+
Skin / mucosal lesions	-	+ (rash, pruritus)	++	- (?)	+	++ (oral ulceration, acne)
Gastrointestinal toxicity	+	++	++	+	+++ [b]	+
Hepatotoxicity	+	+	-	++	-	+
Hirsutism / gingival hyperplasia	+	-	-	-	-	-
Hyperglycemia / diabetes	+	++	+++	-	-	+ (?)
Hyperlipidemia	++	+	++	-	-	+++
Hypertension	+++	++	+++	-	-	+
Impaired wound healing	-	-	+	-	-	++
Myalgia / arthralgia	-	-	-	-	+	++
Nephrotoxicity	+++	+++	-	-	-	+ (proteinuria)
Neurotoxicity	++ [c]	++ [c]	+ (psychiatric)	-	+ (cephalalgia)	-
Osteoporosis	+	+	+++	-	-	-
Peripheral edema	-	-	++	-	-	++
Pneumonitis	-	-	-	-	-	+

Each drug also possesses specific side-effects in addition to those listed in the table.

-, not reported; +, rarely reported; ++, commonly reported; +++, very frequently reported; ?, data scarce or discordant

[a] The side-effect profile of everolimus may differ from that of sirolimus (limited data available)

[b] Enteric-coated mycophenolate sodium may have fewer gastrointestinal side-effects than mycophenolate mofetil

[c] Peripheral neuropathy, cephalalgia, tremor, convulsions; Tacrolimus reported to be somewhat more neurotoxic than cyclosporine (especially when administered intravenously)

Abbreviation: mTOR, mammalian target of rapamycin (sirolimus and everolimus)

Sources are references 14, 57-71.

CNI nephrotoxicity. Acute CNI nephrotoxicity is characterized by acute, dose-related, reversible afferent arteriolar vasoconstriction and hence a decrease in kidney function.[73,74] This effect is exaggerated by intravenous administration, and usually resolves within 1 to 2 days of dose reduction.[73] Acute CNI nephrotoxicity is also suggested to include acute tubular dysfunction, and vasoconstriction-associated ischemia may also injure the endothelium, hence contributing to thrombotic microangiopathy in the glomeruli.[73,74] Possible prothrombotic properties of CNI may further enhance such processes.[74] In contrast, chronic CNI nephrotoxicity involves several complex and partly undefined mechanisms which lead to the development of chronic irreversible functional impairment with associated morphological and histological changes to all compartments of the kidneys.[1,74] In contrast to the acute form, the development of chronic CNI nephrotoxicity, which often develops

gradually over some years, seems not to be directly related to the degree of systemic CNI exposure.[74] CNIs may also harm the kidneys indirectly by inducing hypertension and diabetes.[12]

Corticosteroids

Corticosteroids have, since the start of their use, been a critical component of posttransplant immunotherapy.[1] Their mechanisms of action are diverse, as they interact with intracellular receptors expressed in almost every cell of the body, subsequently regulating gene transcription.[48,51,54,72] This explains the substantial list of frequently observed, well-documented side-effects: insulin resistance, weight gain, sodium and fluid retention, hypertension, hyperlipidemia, osteoporosis, aseptic bone necrosis, myopathy, cataracts, glaucoma, cushingoid appearance, peptic ulcer, cosmetic changes (acne, hirsutism, skin fragility), susceptibility to infections, impaired wound healing, neuropsychiatric symptoms (depression, mania, psychosis, insomnia), amenorrhea in women, and growth retardation in children (Table 2).[1,48,51,54,72]

Corticosteroids also express a broad spectrum of immunosuppressive properties. Primarily, the steroid-receptor complex targets particular transcription factors, reducing the synthesis of multiple immunomodulating cytokines essential for T lymphocyte activation (Figure 1).[1,48,72] Other properties of key significance in the setting of LT include suppressing antibody and complement binding, inhibiting macrophage responses to alloantigens, suppressing eicosanoid production, and down-regulating adhesion molecules, as well as causing increased expression of transforming growth factor-β.[1,48,51,54,72]

Antimetabolites

Antimetabolites, including azathioprine and mycophenolate (mycophenolate mofetil, MMF, and enteric-coated mycophenolate sodium, EC-MPS), interfere with purine nucleotide synthesis and metabolism, thereby blocking the differentiation and proliferation of lymphocytes (Figure 1).[1,48,54,72] Azathioprine, an imidazole derivative of mercaptopurine that is rapidly metabolized to 6-mercaptopurine, acts as a purine analogue antagonizing purine synthesis unselectively with consequences for various cell types, although those cell types dividing rapidly, such as lymphocytes, are most susceptible.[1] In contrast, mycophenolate, a 2-morpholinoethyl ester of mycophenolic acid, has a relatively selective effect on lymphocytes.[1,72] Specifically, MMF and MPS inhibit inosine monophosphate dehydrogenase II, leading to suppression of the de novo purine synthesis pathway, which, unlike in other cell types, is a vital pathway for lymphocyte proliferation.[1,51,72]

The most common side-effects of antimetabolites are dose-dependent bone marrow suppression and gastrointestinal symptoms (Table 2).[1,51,72] Dosage is weight-based and adjusted by effect and signs of toxicity.[1] The EC-MPS preparation was originally developed with the aim of reducing gastrointestinal side-effects from MMF, but the results from initial trials, as to demonstrating any such advantage, are contradictory.[54,75]

Mammalian target of rapamycin inhibitors

Sirolimus (rapamycin), a macrolid compound structurally similar to tacrolimus, also mediates its action by binding to the FK506-binding protein 12.[48,51,72] The sirolimus-protein complex does not, however, inhibit the calcineurin pathway. Instead, it is suggested that this complex inhibits the mammalian target of rapamycin (mTOR) pathway, thereby blocking signals from a variety of cell surface receptors (including IL-2), with resultant suppression of cytokine-driven T lymphocyte proliferation (Figure 1).[48,51,72] Other mechanisms of action have also been described.[48] Recently this drug class has also included everolimus, a compound derived from sirolimus and differing structurally by only one molecule. Dosage of both compounds is targeted based on blood levels. Metabolism occurs through the cytochrome P450 3A4 system, with concomitant potential drug interactions. Primary side-effects include dyslipidemia, cytopenias, rash, oral ulcerations, arthralgia, diarrhea, and occasionally pneumonitis (Table 2).[1,51]

Concern regarding impaired wound healing and suspicion of a higher rate of hepatic artery thrombosis in early randomized trials have thus far limited the use of mTOR inhibitors in LT.[51,54] More recently, even mTOR inhibitor-induced proteinuria has been described in renal transplant patients.[76-78] Nevertheless, supported by results from experimental studies suggesting that mTOR inhibitors may promote graft tolerance and may exhibit antitumor activity, a number of potential roles for mTOR inhibitors in LT are projected, and intense research is underway.[54,79]

Antibody therapies

Intravenously administered antibodies target either specific T lymphocyte cell-surface antigens (monoclonal antibodies) or multiple cell-surface molecules (polyclonal antibodies), subsequently exerting their effects through lymphocyte depletion, modulation of lymphocyte function, or a combination of both (Table 3).[1,48,51,54,72,80] Following initial doses, flu-like symptoms may occur, ones related to intravascular release of cytokines by collapsing lymphocytes (cytokine-release syndrome), especially during treatment with animal-derived antibodies (antithymocyte globulin, ATG, antilymphocyte globuli, ALG, and OKT3).[1,51] The symptoms, including fever, headache, diarrhea, nausea, bronchospasm, and fluctuations of blood pressure, can be blocked by pre-treatment with corticosteroids, antihistamines, and antipyretics.[51]

Table 3. Antibodies - mechanisms and side-effects

	Target antigen	Principal immunologic effect	Mechanisms involved	Cytokine release syndrome	Comment
Polyclonal (ATG, ALG)	Various T lymphocyte cell-surface antigens	Lymphocyte depletion and multifaceted lymphocyte function modulation	● Complement-mediated cell lysis. ● Reticuloendothelial uptake of opsonized T lymphocytes. ● Apoptosis following binding to certain receptors. ● Masks, activates, or inactivates essential cell surface antigens.	Yes	● Preparations contain a mixture of antibodies with diverse specificity, and may thus produce adverse reactions with cell surface molecules on cells other than lymphocytes, causing for instance cytopenias. ● May express variable potency.
Monoclonal					
Muromonab-CD3 (OKT3)	CD3 antigen expressed in conjunction with the T cell receptor on the surface of native T lymphocytes	Lymphocyte depletion, (lymphocyte function modulation)	● Inhibits TCR-CD3-activated intracellular cascades, thus blocking T lymphocyte activation. ● Following binding, TCD-CD3 complex is lost from cell surface and the cell subsequently removed from circulation. ● Blocks function of T killer cells.	Yes	Anti-OKT3 antibodies may develop, with resultant loss of the immune-suppressive effect of OKT3.
Interleukin-2 receptor antibodies (basiliximab, daclizumab)	Alpha chain of interleukin-2 receptor (expressed only on activated T lymphocytes)	Lymphocyte modulation (and depletion of activated T lymphocytes)	Inhibits interleukin-2-mediated T lymphocyte proliferation.	No	● Low side-effect profile. ● Specific immunosuppressant (targets only activated T lymphocytes).
Alemtuzumab	CD52 antigen (present on most peripheral blood lymphocytes, thymocytes, monocytes, and macrophages)	Lymphocyte depletion	Antibody/complement-mediated cell lysis.	Yes, but less severe	● Recently introduced, limited clinical experience. ● Spares plasma cells and memory cells.

Adverse effects of immunosuppression

In addition to these drug-specific side-effects, immunosuppression itself is, regardless of regimen, associated with increased risk for two adverse effects: infection and malignancy.[81]

Immunosuppression and infections. Suppression of the immune system, the main task of which is to eradicate foreign pathogens, is, by its nature, accompanied by an

increased susceptibility to infections. Because therapies mainly suppress T lymphocyte function, this increased susceptibility involves pathogens whose eradication under normal circumstances fundamentally necessitates T lymphocyte responses.[81,82] Such pathogens include cytomegalovirus (CMV) and the Epstein Barr (EBV), varicella zoster, and herpes simplex viruses, *Pneumocystis jiroveci* (formerly *carinii*), and aspergillus, as well as other opportunistic microbes.[81,82] The degree of overall infection risk is determined by the dosage, duration, and chronological sequence of immunosuppressive therapy.[1,82] In addition to promoting susceptibility to various opportunistic pathogens, immunosuppression typically also enables common non-opportunistic pathogens to cause more aggressive infections, and often reduces signs and symptoms of infection.[1,82] In clinical reality, however, not only does pharmacological immunosuppression predispose transplanted patients to infections, but so also does impairment in pre-transplant health, complex surgical procedures, disrupted integrity of mucocutaneous barriers (catheters, intubation, drains), hospitalization, possible graft-transmitted pathogens, infection with immunomodulatory viruses, and latent infection in the recipient.[1,82] In the long-term, corticosteroids, for instance, predispose to microbe invasion by causing mucocutaneous fragility and impairing wound healing.[1,82]

Oncogenic effects of immunosuppression. The link between immunosuppression and increased cancer occurrence was, through epidemiological awareness, recognized decades ago.[83,84] In general, the risk for malignancy seems closely to correlate with cumulative exposure to immunosuppression.[85] Underlying oncogenic mechanisms remain incompletely elucidated, but the literature provides several hypotheses. First, chronic immunosuppression depresses certain components of the host immune system such as the natural killer cells involved in antitumor surveillance and in early destruction of arising neoplastic cells.[85] The resultant impaired surveillance may aggravate the oncogenic effects of environmental and genetic carcinogenic factors, enabling neoplasms to appear.[85]

Second, many of the cancer types common after transplantation are related to oncogenic viruses: lymphomas linked to Epstein Barr virus, nonmelanoma skin malignancies possibly associated with papillomaviruses, and Kaposi sarcoma related to human herpes virus 8.[85,86] In an immunocompromised state with depressed antiviral immune activity, such viruses may play an important catalytic role in progression towards malignancy.[85]

Third, many of the immunosuppressive agents may also have intrinsic drug-specific oncogenic properties unrelated to their immune-suppressive effect.[79,87] For instance, cyclosporine inhibits DNA repair mechanisms, induces cancer-cell invasiveness, and promotes angiogenesis.[87-90] Similarly, tacrolimus also promotes tumor progression,[91,92] and azathioprine can cause chromosome breaks and nuclear abnormalities.[87] On the other hand, mostly based on preclinical studies but increasingly also based on clinical evidence, mTOR inhibitors and MMF may themselves exhibit some antitumor activity.[79,85,90]

Together with these oncogenic factors, chronic antigen attack from the graft and local inflammatory processes stimulate a partially depressed immune system, and with impaired feedback mechanisms, control over the degree of immune response

may fail. This, in turn, may lead to abnormal lymphoid proliferation, resulting in post-transplant lymphoproliferative disorder (PTLD).[1,85]

PTLD is the designation of a heterogenic group of lymphoproliferative conditions (most frequently of B lymphocyte origin) with EBV in 80% of cases present in the malignant tissue.[85,93] The term comprises a spectrum of states, ranging from benign polyclonal mononucleosis-resembling conditions to malignant monoclonal non-Hodgkin lymphoma, in which benign forms may progress to malignancy.[93] The key underlying mechanism is an immunosuppression-induced inhibition of critical T lymphocytic control of B lymphocyte proliferation, which, in the setting of EBV reactivation, results in unrestricted lymphoid proliferation.[93] Lymphomas of T lymphocyte origin are, however, also possible.[93]

Clinical regimens and trends

Induction therapy. In contrast to other solid-organ transplantation, in which induction therapy with antibodies is frequently used to enhance immunosuppression immediately after transplantation, antibody induction therapy in LT mainly serves for delayed initiation of nephrotoxic CNIs in pre-existing renal failure.[19,51,53,94] Induction therapies are, moreover, increasingly being evaluated as part of CNI- or corticosteroid-avoidance protocols, and antibody induction may facilitate reduction in the subsequent maintenance immunosuppression required.[18,53,80,94-96] Some findings also point towards antibody induction as leading to a reduction in HCV recurrence.[94]

Although European statistics on immunosuppression trends are unavailable, US data indicate increasing use of antibody induction (7% in 1994 and 21% in 2004), possibly reflecting US allocation policies which tend to favor LT candidates with pre-existing renal dysfunction.[53] In the USA, IL-2 receptor antibodies are today the favored preparations (11% of overall use), followed by polyclonal antibodies, while use of OKT3 [37] and alemtuzumab is minimal.[53] In Finland, various induction therapies have been used in randomized multicenter studies. In patients with hepatorenal syndrome, IL-2 receptor antibodies are now the preferred agents, and are used in conjunction with a CNI delay.

Maintenance therapy. Although variations exist between centers regarding the specific agents used as well as the precise timing of their tapering and discontinuation, the standard maintenance regimen almost universally consists of either cyclosporine or tacrolimus, combined with corticosteroids and typically one of the antimetabolites.[11,18,37,38,53,55] The standard Finnish protocol comprises cyclosporine, corticosteroids (methylprednisolone), and MMF (azathioprine until 2006).

Due to their well-known side-effects, the large doses of corticosteroids in the first postoperative days and weeks are usually rapidly tapered, with complete withdrawal generally attempted during the first year.[37,55] In 2004, 80% of recipients were discharged on corticosteroids in the USA, with only 49% on steroids after 1 year and 33% after 2 years.[53] Although steroid withdrawal proves safe in terms of survival and rejection, and beneficial in relation to reducing metabolic effects and cardiovascular complications,[96] the emerging trend, evident in 20% of USA recipients,[53] is toward completely steroid-free regimens. This, however, remains controversial.[11,38,96] Patients transplanted for autoimmune conditions often need

higher doses of steroids, and HCV recipients benefit from steroid withdrawal in the long-term.[1]

Based on US statistics and European single-center experience, the most recent decades demonstrate a gradual shift from cyclosporine+azathioprine-based combinations to tacrolimus+MMF-based protocols at many centers.[11,37,53] The percentage of patients discharged from the hospital with an antimetabolite in the USA in 2004 was 58%, and 55% were using them at one year (52% MMF, 3% azathioprine).[53] MMF seems as safe as azathioprine, and appears superior in preventing acute rejection.[11,60] Although antimetabolites may be discontinued within 1 year after LT,[55] evidence is compelling that continuation of MMF reduces rejection rates, allows for lower doses of CNI, and may improve renal function and facilitate steroid withdrawal.[11,37,60,96-99]

In the USA, 97% of recipients were discharged with a CNI (89% tacrolimus, 8% cyclosporine), and more than 90% were using CNIs at one year after LT.[53] Debate is still ongoing and data somewhat conflicting regarding the optimal CNI agent. In cyclosporine- and tacrolimus-treated LT patients, survival appears comparable.[57,66-70,100] Tacrolimus appears to offer the benefit of slightly lower rates of early rejection and early graft loss, less hypertension and hyperlipidemia, and less need for steroids, but study results are not entirely unanimous.[57,66-70,100] The recently introduced prolonged-release form of tacrolimus, allowing once-daily dosing, will probably be superior in terms of patient compliance.[101] Cyclosporine, on the other hand, has the advantage of being less diabetogenic and causing less gastrointestinal toxicity and may be more beneficial in HCV-infected patients.[57,66-68,70,100,102]

As mentioned, the use of mTOR inhibitors in LT is still under evaluation. Emerging results, however, show their great potential, especially in reducing posttransplant cancer risk.[61,65,103,104] The mTOR-inhibitor-based regimens, therefore, appear as an attractive alternative for HCC-transplanted patients.[105,106] US data reveal that 5% of recipients had received sirolimus at the time of discharge in 2004, but, possibly reflecting the diminishing significance of wound-healing issues and hepatic artery thrombosis risk in later periods, up to 12% received sirolimus at one year.[53]

In response to the toxicity in current regimens, a number of modified immunosuppression protocols have been and presently are being attempted, with particular emphasis placed on minimizing corticosteroids and CNIs.[18,96] Novel approaches include modified regimens to reduce or avoid adverse effects, attempts to individualize therapy, and new drug-monitoring methods.[11,12,14,18,54,55,96] The long-desired possibility of inducing graft tolerance by selectively stimulating instead of suppressing the immune reaction, however, still remains a distant goal.[49]

Antirejection therapy. More than 90% of acute rejection episodes, affecting 18% of recipients in the USA, are reversed by either augmenting baseline immunosuppression or by employing a short course of corticosteroids, with no resultant detrimental effect on outcome.[11,38,53,69,72] Steroid-resistant rejection is typically treated with antibodies, with ATG and OKT3 most frequently used in 2004 in the USA.[53] In Finland, mainly OKT3 is the choice in steroid-resistant rejection.

Survival rates

Outcome after an intervention such as LT have a number of endpoints. The traditional endpoints: short-term patient survival (time from transplantation to death) and graft survival (time from transplantation to graft loss) now exhibit impressive lengthening (Figure 2 and 3). Among LT recipients, risk of death relative to that of the general population is, however, high, and although diminishing with longer follow-up, it remains elevated; a study from Birmingham[107] reported standardized mortality ratios of 13.6 at 0 to 4 years, 3.7 at 5 to 9 years, 2.6 at 10 to 14 years, and 1.5 beyond 15 years after LT.

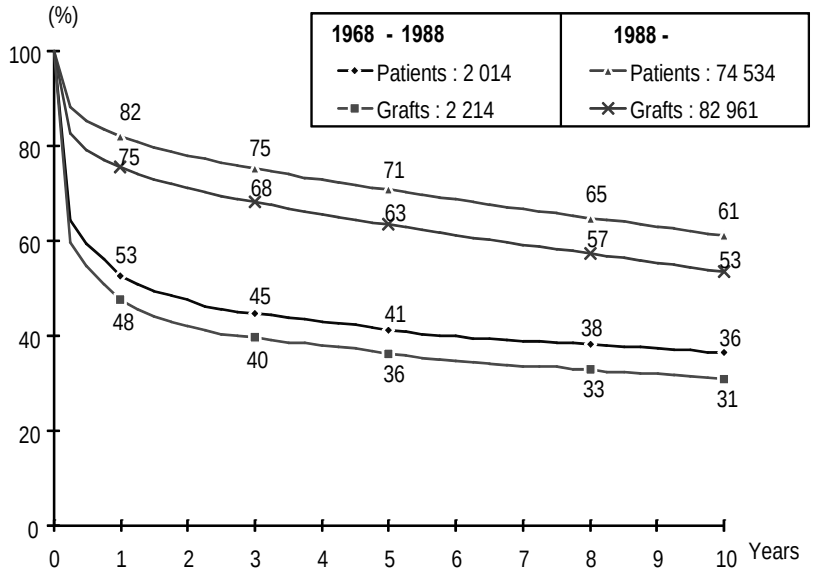

Figure 2. *Patient and graft survival following liver transplantation in Europe. Reproduced by permission of the copyright owner (European Liver Transplant Registry).*

During recent decades, survival improvement has occurred particularly for patients transplanted because of hepatic malignancy, cirrhosis, or ALF, as well as for pediatric patients.[11] The indications currently with the best survival rates in Europe are benign tumors and metabolic diseases, whereas malignant tumors, ALF, and HCV still generally show less good results.[11]

Causes of mortality vary with time after LT; typically graft dysfunction and general causes predominate in the early period, infections gain importance in the intermediate period, and de novo and recurrent tumors, in addition to general causes, then become key contributors (Figure 4).

Retransplantation due to graft loss – necessary in 10% to 15% of recipients – is in the first month chiefly the result of graft dysfunction or technical complications (hepatic artery thrombosis) and later mostly of disease recurrence or, infrequently, of chronic rejection.[1,8]

Another endpoint of increasing interest, particularly in the context of allocation policies, is “transplant benefit,” a measure of life-years gained from LT.[27]

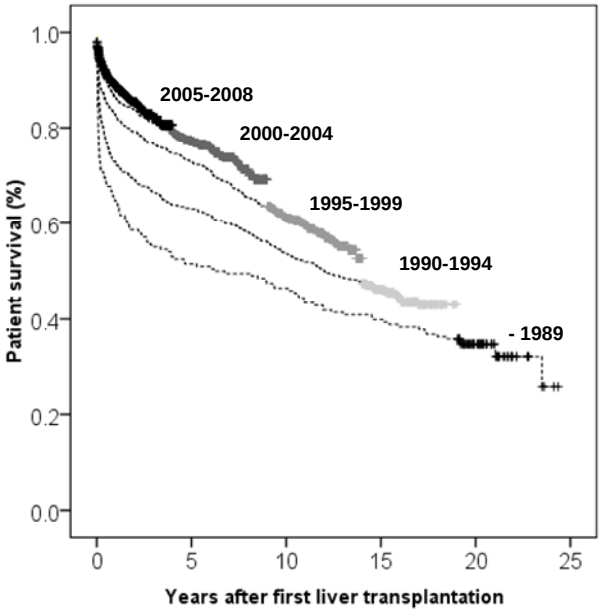

Figure 3. *Patient survival by era of liver transplantation in the Nordic countries. Reproduced by permission of the copyright owner (Scandiatransplant).*

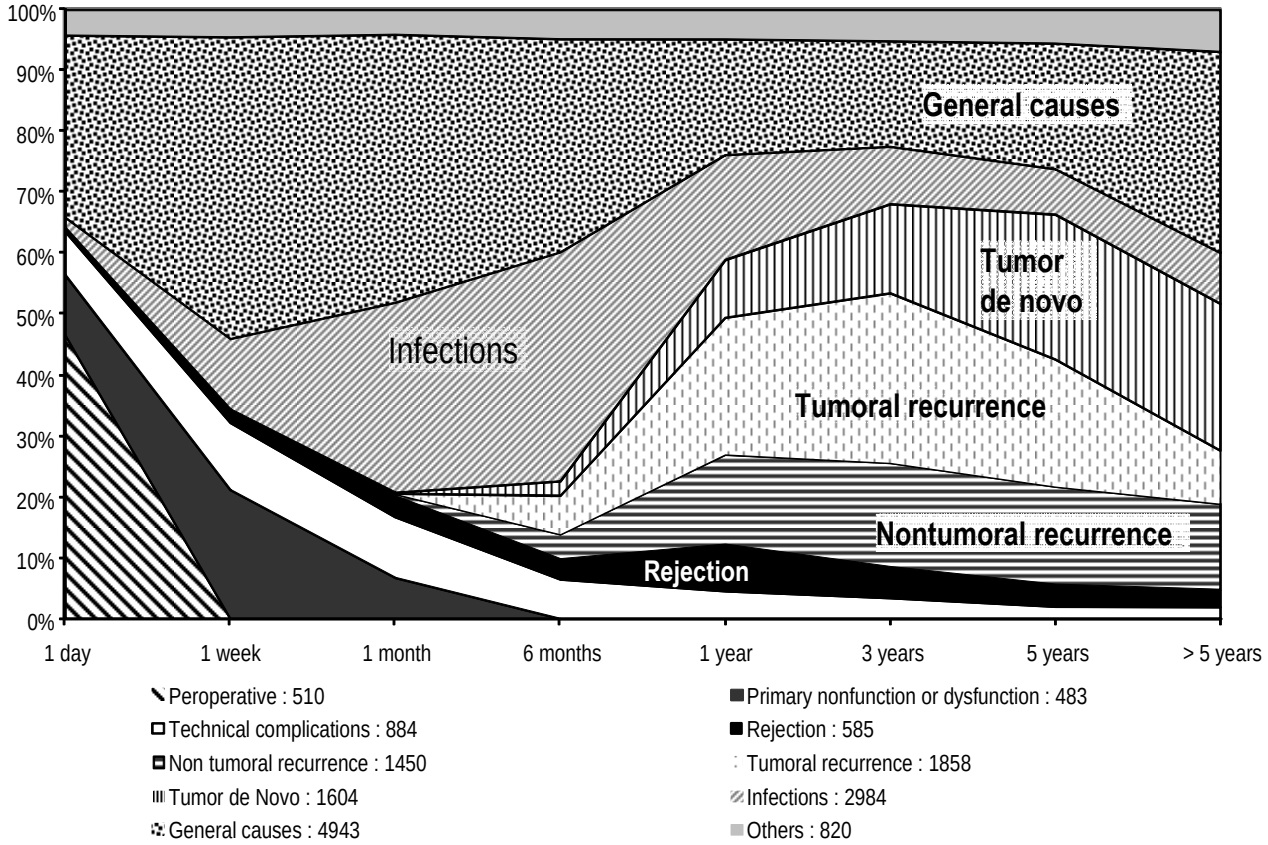

Figure 4. *Causes of mortality in relation to time after liver transplantation in Europe 1988 to 2008. Adapted with permission of the copyright owner (European Liver Transplant Registry).*

Quality of life

With more and more patients surviving past their first few posttransplant years, outcome evaluation has increasingly emphasized employment and quality of life.[11,21,22,108-111] Many immunosuppression-related side-effects and other LT-associated chronic medical conditions with little or no impact on survival may markedly impair quality of life.[11,21,112] This is of particular importance in pediatric patients, who are expected to survive for decades and who, at the time of LT, are still undergoing developmental processes.[108,112,113]

Methodology. Quality of life in medical research generally refers to health-related quality of life (HRQoL), a multidimensional construct reflecting the physical, psychological, and emotional dimensions of health.[109-111,113] HRQoL may be measured by a variety of generic (non-disease-specific) instruments, including psychometric and utility measures, as well as disease-specific instruments.[110] About 100 HRQoL studies on LT patients exist, but meta-analyses and reviews in this area indicate that methodological differences severely limit comparison of results across studies.[22,108-111,113] Single-center studies, on the other hand, are usually small, and subject to bias introduced by variable population characteristics.[108] Quality of life studies are, furthermore, constrained by some inherent limitations; they exclude deceased patients and patients in very poor condition (such as ALF patients prior to LT), and quality of life is affected by cultural, economic, and social factors.[22]

Impact of LT on HRQoL. Despite these limitations, several longitudinal studies note that the universally poor HRQoL of LT candidates significantly improves after LT at all ages.[22,108-111,113-116] The largest gains are in physical functioning, with domains related to psychological health, social functioning, and sexual functioning, although generally improving, showing more discrepancies across studies.[22,109-111,115]

Comparisons to healthy controls. The few studies comparing the HRQoL of LT recipients with that of healthy controls mostly indicate that the vast majority of patients experience a poorer HRQoL.[22,109-113,117] In a recent meta-analysis, such inferiority was evident in all domains except for mental health and bodily pain.[22] Data on HRQoL of long-term LT survivors are scarce,[22,118-121] but indicate similar results as for shorter-term survivors.

Predictors of HRQoL. Factors most consistently associated with impaired posttransplant HRQoL include pretransplant disease-severity, HCV, de novo disease (such as posttransplant diabetes), length of exposure to immunosuppression; the impact of age, gender, alcoholic liver disease, and ALF (etiologies other than ALF and alcoholic liver disease scantily studied) remains contradictory.[22,108,112,113,116,121]

Economic aspects. Utility-based HRQoL measures allow calculation of quality-adjusted life-years, in order to include HRQoL in cost-effectiveness analyses.[109,110] Cost and cost-effectiveness issues receive increasing emphasis nowadays, but such data on LTs are scanty.[109,110]

Employment

With an average age at LT of less than 50, adult recipients would be spending their days working. However, only 26 to 57% of recipients return to work.[22,110,111,117,119,122,123] This wide range may depend on differing definitions of "employed," on use of non-validated instruments, and on disparity in patient

population, sample size, and length of follow-up.[22,109-111,122] Proposed predictors of post-LT employment include younger age, pretransplant employment and high income, private insurance, absence of pretransplant diabetes, good physical functioning, and higher general health score.[22,117,122,123] Data on appropriate interventions to encourage return to work especially after LT, are unavailable.

Short-term complications

Improvement in survival times largely mirrors a reduction in common short-term complications such as vascular problems, acute rejection, biliary strictures and leaks, infections, and early toxicity from immunosuppressive agents (Table 4).[1,10,14,17,37,38,41,55,124-134]

Infections. The majority of LT recipients experience one or more infections by a broad spectrum of pathogens. Infection is also a major cause of death in the first 6 months (Figure 4).[1,82] A predictable pattern of infection, has, in recent years, been drastically altered and its overall incidence reduced by antimicrobial prevention strategies and more judicious use of immunosuppressive agents.[82] Common prevention protocols include vaccination, perioperative antibiotics and antifungals, antiviral prophylaxis or preemptive therapy, and anti-pneumocystis prophylaxis.[1,17,37,55,82]

During the first postoperative month, surgery-related and postoperative care-associated bacterial and fungal infections predominate (wound infections, intra-abdominal infections, pneumonia, catheter infections, anastomotic leak- and stricture-induced infections, clostridium colitis), but immunosuppression-induced exacerbation of a recipient's pre-existing smoldering infection, herpes simplex infection, or donor-derived infection (uncommon) may also occur.[1,37,82]

Months 1 to 6 are typically characterized by residual effects of technical problems and earlier infections, infections with immunomodulatory viruses (CMV, EBV, HCV), and many opportunistic fungi (Candida, aspergillus, Cryptococcus) and bacteria.[1,82] The widespread use of trimethoprim-sulfamethoxazole as anti-pneumocystis prophylaxis has not only made pneumocystis infection rare, but has also reduced the occurrence of toxoplasmosis and many listeria and nocardia infections.[17,82,135] Most transplant centers employ some form of prevention for CMV,[17,82,136] and antiviral prophylaxis is associated with its 58 to 80% reduction.[136] Overall incidence of CMV disease within the first year is approximately 5%, a rate highly dependent on donor and recipient serologic status. Prophylaxis may delay its onset.[136] Donor-acquired or reactivated CMV may manifest as fever, malaise, and cytopenias (CMV syndrome), or as tissue-invasive disease (most often involving the gut), but may also, through complex immunomodulatory properties, predispose to and interrelate with acute and chronic rejection, accelerated HCV recurrence, EBV-associated PTLD, other opportunistic infections – and thus with reduced survival.[82,136]

Risk for infection begins to diminish at 6 months after LT, and infections in the long term resemble those of the general population; with community-acquired viral respiratory infections constituting up to 80%.[82] Recurrent chronic viral hepatitis infection also becomes increasingly relevant.[82]

Table 4. The main noninfectious complications in early post-liver transplantation (LT).

	Incidence in modern literature	Typical time of occurrence after LT	Impact on outcome
Biliary complications (10-15% in large series)			
Anastomotic strictures	3-9%	<8 months	When treated → usually no negative impact.
Nonanastomotic strictures	3-15%	Any time, on average 3-6 months in large series	Frequent need for repeated interventions. 50% graft loss.
Leakages	2-15%	Predominantly <1 month	If untreated → infection and abscess formation.
Rarities: biloma, hemobilia, biliary abscess, papillary dyskinesia/ampullary dysfunction, bile stones, mucocele			
Vascular complications			
Early postoperative bleeding	7-15%, ~5% require surgery	≤2 days	Variable. Site of bleeding found in 50% of surgically explored cases
Hepatic artery thrombosis	~3% (0-7%) in adults, ~8% (1-20%) in children	~30% <1 month (typically ≤ 1.week), ~70% >1 month	Mortality rate: ~33% (12-60%) in adults, ~25% (0-80%) in children. Biliary complications common. Early-onset → usually reoperation + reanastomosis; 50-70% require re-LT.
Hepatic artery stenosis	~3-5% (difficult to ascertain)	<6 months	If untreated → 50% rate of obstruction and thrombosis.
Portal vein stenosis	<3%	Within weeks, but may occur at any time.	If untreated → portal vein thrombosis and graft failure possible.
Portal vein thrombosis	<3%	2/3 within 1 month	Variable.
Vena cava/hepatic vein occlusion	0-2%	Within weeks	Variable.
Rarities: aneurysms, vascular rupture, steal syndrome			
Rejection			
Acute	20-50% (heterogenous diagnostic criteria). Clinical rejection: ~30%	Peak incidence 2.week, predominantly <3 months	Histological severity an important prognosticator. Mostly mild episodes with graft / patient survival generally unimpaired (even associated with improved long-term survival).
Hyperacute	Extremely rare	Within hours	Mortality approaching 100%.
Graft-versus-host disease	<1%	<2 months	Mortality rate: >70% in adults, ~35% in children. Graft not affected.
Graft dysfunction Note: variously defined			
Primary nonfunction	4-7%	Typically <3 days, by definition <7-10 days	Urgent retransplantation necessary, otherwise death.
Initial poor function	15-30%	As above, but more elongated	May recover with supportive therapy. Urgent retransplantation in progression to extrahepatic complications (hemodynamic instability, renal failure, other organ dysfunction).
Small-for-size syndrome [a]	Depends on the setting	Immediately	50% mortality (sepsis) within 6 weeks.
Other: Complications related to postoperative intensive care (cardiorespiratory problems, hemodynamic complications, electrolyte alterations, renal dysfunction, neurological complications)			

[a] Graft dysfunction due to insufficient functional liver mass
Data from references 1,10,14,17,37,38,41,55, and 124-134.

LONG-TERM COMPLICATIONS

In contrast to the short-term complications, for which incidences, risk factors, and treatment options are generally well known, corresponding data for long-term problems are only now emerging.

Renal dysfunction

Alhough renal dysfunction in the long-term usually manifests as chronic kidney disease (CKD), with gradually deteriorating renal function over months to years, acute kidney injury in the perioperative period may leave residual dysfunction as well.[19] Although CKD occurs more frequently as follow-up lengthens, its precise incidence varies (4% to 80%) due to differing definitions, variable follow-up time, and differing methodology, population characteristics, and therapy.[19,73,137-144] In a large population-based study comprising more than 36 000 LT patients, incidence of CKD – defined as a glomerular filtration rate (GFR) < 30 mL/min – rose from 8% at 1 year to 18% at 5 years, and rose above 25% at 10 years.[139]

Etiology of CKD. Causes and risk factors for posttransplant CKD are partly intertwined and can be divided into pre-, peri-, and posttransplant conditions. In the pre-LT period, renal function may be impaired by kidney disease independent of the liver disease (as in the nontransplant setting), by disease-entities affecting both the liver and kidney (such as viral hepatitis-related glomerulonephritis, various toxins, and alcoholic cirrhosis-associated IgA nephropathy), or as a consequence of end-stage liver disease (hepatorenal syndrome type I and II).[145] In the perioperative period, acute kidney injury is reported in 17% to 95% of patients, and a severe form requiring renal-replacement therapy in 5% to 35%.[1,19,73] Although in many cases renal function is subsequently regained, in other instances a variable degree of residual dysfunction may persist; hence contributing significantly to CKD.[19,73,139]

Established risk factors for acute kidney injury in the LT setting include these pretransplant factors, severity of liver disease, hemodynamic instability, intraoperative bleeding, lack of use of the Piggyback technique, graft dysfunction, prolonged vasopressor use, infections, re-laparotomy, and drug toxicity (including CNIs).[19]

Following the immediate posttransplant period, CKD may be attributed to CNIs via primary chronic nephrotoxicity as well as being secondary to CNI-induced hypertension and diabetes.[1,12] Use of other nephrotoxic agents (certain antibiotics), drug interactions, and HCV recurrence may also contribute to CKD development.[1,19,73] Risk factors that clinical studies most consistently note as associated with impaired long-term renal function, especially in the LT population, include high doses of CNI, pre-LT hepatorenal syndrome, pre-existing renal insufficiency, duration of pre-LT renal dysfunction, hypertension, diabetes, use of nephrotoxic drugs, postoperative acute kidney injury, postoperative renal-replacement therapy, HCV infection, and older age.[19,137-140,142-144,146-148]

The relative importance of these causes and risk factors, however, remains somewhat obscure. Few studies have assessed etiology by means of renal biopsy.[141,149,150] Whereas Fisher and colleagues,[141] studying biopsies in severe renal dysfunction (creatinine > 250 μM/L), concluded that 77% of cases showed

histological findings suggestive of CNI nephrotoxicity, Pillebout and colleagues,[149] investigating 26 patients with GFR < 60 mL/min, noted lesions of a more multifactorial origin: CNI-related lesions were present in 46% of cases, but these often coincided with pathological changes attributable to other etiologies. More recently, O'Riordan and colleagues[150] demonstrated results very similar to those of Pillebout.

Measurement and definition of CKD. In a clinical setting, direct measurement of GFR – the gold standard for assessing renal function – is impractical and expensive.[151] Creatinine concentrations are routine, but are increasingly being replaced by estimations of GFR through equations such as the Cockcroft-Gault equation or Modification of Diet in Renal Disease Study equations.[151,152] Estimations of GFR in the cirrhotic patient are, however, usually inaccurate,[152] and also in the LT recipient only ~65% of GFR estimates fall within 30% of the GFR measured directly.[151] Recent National Kidney Foundation guidelines define CKD as GFR below 90 mL/min or kidney damage, and end-stage renal disease (ESRD) as the need for renal-replacement therapy.[153]

Impact of renal impairment on outcome. Renal dysfunction, whether pre-existing or in the form of acute kidney injury or CKD, is associated with increased post-LT mortality and graft loss.[19,73,139,154] Ojo and colleagues[139] noted, among patients developing CKD after transplantation, a 4.55-fold mortality risk.

Management. Assessing the degree of reversibility of pretransplant renal dysfunction is imperative, because irreversible renal impairment may require combined liver-kidney transplantation.[145,155] This may, however, be difficult since the generally reversible hepatorenal syndrome, for instance, can also become partially irreversible if prolonged, and the exact duration during which this transformation occurs remains unknown.[145] Following LT, CKD-preventive strategies include appropriate management of hypertension and diabetes, as well as avoidance of nephrotoxic drugs.[12] Antibody induction (mostly IL-2 or ATG) with delayed introduction of CNI is becoming established for patients with significant preexisting renal dysfunction[18,19,53] and is undergoing trials as preemptive therapy in LT recipients with normal renal function.[99] Following CKD, CNI reduction, with or without introduction of other immunosuppressants, is generally considered safe and efficient.[18,19] In contrast, complete CNI avoidance, with conversion to (or initial) MMF- or mTOR inhibitor-based immunosuppression, appears to elevate risk for rejection.[18,19] In advanced CKD, CNI reduction may not improve renal function.[156] Furthermore, both the optimal timing of CNI-reduction measures and means to identify those who will respond to such measures remain undefined.[19]

Malignancy

Posttransplant cancer may arise from donor-transmitted malignant cells – with different malignancies bearing different tumor-transmission rates[1] – from recurrence of the recipient's earlier malignancy, or from de novo cancer, the most common type. HCC leading to LT may, moreover, be related to posttransplant malignancy.[1] The reported frequency of de novo cancer after LT ranges from 2 to 26%, depending mainly on follow-up but also on patients and methodology (as also for renal

dysfunction).[12,157] Cumulative cancer incidence, taking into account unequal follow-up times, increases to over 20% at 10 years (Table 5).[158-165]

Table 5. Studies reporting cumulative incidences of post-liver transplantation cancers

Cancer	Author, year, country	Patients	Years				Proportion of cancers	
			5	10	15	20	Nonmelanoma skin	Lymphoma
Any cancer	Jonas et al,[158] 1997, Germany	458	15%				24%	21%
	Haagsma et al,[159] 2001, The Netherlands	174	6%	20%	55%		52%	4%
	Xiol et al,[160] 2001, Spain	137	13%	26% at 8 years			70%	10%
	Herrero et al,[161] 2005, Spain	187	25%	39%			56%	11%
	Finkenstedt et al,[162] 2009, Austria	779	10%	24%	32%	42%	17%	11%
	Watt et al,[165] 2009, USA	798	12%	22%			54%	9%
Nonskin cancer	Haagsma et al,[159] 2001, The Netherlands	174	2%	10%	33%			
	Xiol et al,[160] 2001, Spain	137	5%	9% at 8 years				
	Herrero et al,[161] 2005, Spain	187	11%	22%				
	Jiang et al,[163] 2008, Canada	2034		9%				
	Marqués Medina et al,[164] 2009, Spain	528	9%	18%	25%			
	Watt et al,[165] 2009, USA	798	7%	14%				

Few series compare cancer incidences with age- and gender-matched controls, but those that do, report a 2.1- to 4.3-fold overall greater cancer incidence among LT patients (Table 6).[107,159,161-163,166-168] Comparison with the normal population corrects some bias stemming from ethnic and demographic differences.[157] Whereas nonmelanoma skin cancer and lymphoma (PTLD) are clearly the most common types, up to 70% and 45% of posttransplant cancers, uncertainty remains as to the incidence of other tumors.[16,157]

Risk factors. Risk factors independently associated with overall de novo cancer development include age and underlying alcoholic liver disease.[159-162,165,169-172] In addition, some have noted increased cancer risk related to ulcerative colitis or PSC,[107,165] prolonged pre-LT immunosuppression,[159] azathioprine (vs cyclosporine monotherapy),[172] and rejection episodes.[172] Such risk factors may, however, not apply for to tumor types, and some risk factors may predispose only to specific cancers.[12] Ulcerative colitis and PSC, for instance, predispose to colon cancer, and alcoholic liver disease to upper aerodigestive tumors.[157] Data are inadequate regarding the influence of history of extrahepatic malignancy on its posttransplant recurrence.[14,157]

PTLD. Most research focuses on the more neoplastic end of the PTLD spectrum (lymphoma), so that incidences of early benign processes which may progress to malignancy are seldom reported. One large registry study noted a cumulative 5-year incidence of post-LT lymphoma of approximately 1.5%.[173] Pediatric populations show higher incidences – up to 15% – which mainly reflects children's more frequent EBV-seronegativity.[14] More than 80% of PTLDs are EBV-positive, and these occur predominantly during the first posttransplant year, comprise about half of all PTLDs,

Table 6. Studies comparing post-liver transplantation cancer incidences with those in the general population by standardized incidence ratios (SIRs)

Author, year, country	Patients	Overall SIR (95% CI)	Nonmelanoma skin, SIR (95% CI)	Lymphoma, SIR (95% CI)	Other statistically significant SIRs	Not statistically significant SIRs
Jain et al,[166] 1998, USA	1000	Not reported	Not reported	Not reported	Oropharynx 7.6	Melanoma, lung, gastrointestinal system, prostate, kidney, bladder, gynecological tract, thyroid, brain
Sheiner et al,[167] 2000, USA	121	3.9 (2.1-6.7) (nonmelanoma skin cancer excluded)	3.2 (estimated)	28.6 (7.7-73.1)	Not reported	Not reported
Haagsma et al,[159] 2001, The Netherlands	174	4.3 (2.4-7.1); 2.7 (1.2-5.2 skin/lip cancer excluded)	70.0 (28.1-144)	Not reported	Colon 12.5, kidney 30.0	Breast, lung, Kaposi sarcoma
Oo et al,[107] 2005, UK	1778	2.1 (1.7-2.4)	5.8 (4.3-7.6)	10.3 (6.1-16.2)	Colon 4.9, lung 2.0	Breast, cervix, rectum
Herrero et al,[161] 2005, Spain	187	3.2 (2.2-4.7) (nonskin cancer excluded)	16.9 (11.8-23.5)	Not reported	Not reported	Not reported
Jiang et al,[163] 2008, Canada	2034	2.5 (2.1-3.0) (nonmelanoma skin cancer excluded)	Not reported	20.8 (14.9-28.3)	Colon and rectum 2.6	Oral, pancreas, lung, kidney, leukemia, prostate, breast
Baccarani et al,[168] 2009, Italy	417	2.6 (1.9-3.6) (nonmelanoma skin cancer excluded)	Not reported	13.8 (6.3-26.2)	Kaposi sarcoma 144, esophagus 23.4, cervix 30.7, head and neck 7	Colon, stomach, lung, melanoma, breast
Finkenstedt et al,[162] 2009, Austria	779	1.9 (1.5-2.3) (nonmelanoma skin cancer excluded)	Not reported	8.0 (4.0-14.2)	Lung 3.1, esophagus 8.3, oropharynx 4.8	Colon and rectum, stomach, pancreas, prostate, kidney, breast, bladder

more often localize in the graft, and are the dominant type in children.[85,174] Conversely, EBV-negative PTLD is distributed more evenly throughout a 10-year follow-up and may be related to higher mortality; some authors argue that this type may actually be a separate disease entity.[85,174,175] The best established contributors to PTLD development are EBV-seronegative recipients (especially with EBV-seropositive donors) and intense immunosuppression (especially use of OKT3 or ATG antibodies).[93,157,173,175-177]

A high viral load of EBV, HCV, or CMV infection, autoimmune liver disease, or alcoholic cirrhosis have also been implicated as predisposing to PTLD.[176] The clinical presentation is broad – frequently with nonspecific symptoms – and extranodal involvement is common (up to 90% of PTLDs).[85,93,173] Diagnosis requires histopathologic examination, and work-up includes extensive blood chemistry and serologic and radiologic assessment.[17,85,93] Reducing immunosuppression is an integral part of treatment and is often sufficient for early lesions. Antiviral therapy

may be applied in EBV-positive PTLD, and in some cases anti-CD20 antibodies (rituximab), radiation, or chemotherapy.[14,55,93] The ideal regimen, however, remains undefined. Furthermore, some evidence exists that anti-CMV immunoglobulin such as CMV prophylaxis may prevent early PTLD.[178]

Skin cancers. In LT recipients, the most frequent cutaneous malignancies are squamous cell and basal cell carcinoma.[157,179] Squamous cell carcinoma tends to develop at a younger age, be more aggressive, and more often show multiple lesions than in the general population.[14] Risk factors include intensity of immunosuppression, PSC, and hepatocarcinoma, and as also for the nontransplant population: older age, previous skin cancer, sun exposure, and fair skin.[14,85,157,160,165,179] Treatment follows conventional practice, and re-evaluation of immunosuppression is, due to high risk for recurrence, also advisable.[179]

Other cancer types often observed with high frequency include colorectal, pulmonary, and oropharyngeal, plus Kaposi sarcoma (Table 6). Some series have, however, observed no such cases.[157] Although cancer types common in the general population (breast, cervix, prostate) appear no more frequently in LT recipients, such cancers may occur at an earlier age, be more aggressive, and be linked to poor survival.[157,162,180] The value of immunosuppression adjustment following the occurrence of nonskin, non-PTLD malignancies is unclear.[55]

Impact on outcome. Haagsma and colleagues[159] reported an overall cancer-related risk of death of 2% at 5 years, 5% at 10, and 15% at 15 years. Survival is, however, closely related to tumor type; nonmelanoma skin cancer has little influence on survival (2-year survival after diagnosis close to 90%), whereas internal malignancies contribute significantly to mortality.[12,15,159,161,162,181] Mortality from PTLD reaches 50%.[173,175]

Prevention and screening. The effect of avoiding risk factors such as smoking and sun exposure is accentuated in the LT population.[12,55] CNI reduction or conversion to mTOR inhibitors may reduce cancer risk,[182,183] but ensuing rejection episodes requiring heavy immunosuppression may eradicate any such benefit.[85] Which immunosuppression regimen is optimal in patients at high risk for posttransplant cancer remains unclear.[85] Furthermore, no evidence-based screening protocol is defined for the LT population, although annual skin exams and strict adherence to standard screening guidelines are general recommendations.[12,14,17,85] EBV viral-load monitoring may aid in identification of patients at risk for PTLD.[175] Recent data reveal that the introduction of intensified posttransplant surveillance (including annual CTs and urologic, gynecologic, and dermatologic screening) improved survival.[162]

Risk for cardiovascular disease

By 10 years, LT recipients face a cardiovascular (CV) disease event rate of 24%,[184] and CV disease emerges as one leading cause of late mortality.[8,185] Comparison with a matched general population confirms that LT patients have a 3-fold risk for CV events and a 2.6-fold risk for CV death.[186] Apparently accelerated atherosclerosis may result mainly from an excess of traditional CV risk factors after LT;[12,185,187,188] recent studies report a post-LT prevalence of hypertension ranging from 49 to 77%, that of dyslipidemia from 27 to 62%, obesity from 22 to 47%, and diabetes from 9 to

57%.[167,186,189-192] Glucose levels, blood pressure, and lipid levels are often transiently elevated in the early posttransplant period,[193] but Sheiner and colleagues [167] observed that, among LT patients surviving more than 5 years, the standardized prevalence ratio (SPR), as compared with that of the nontransplant population, was 3.1 for hypertension, 6.0 for diabetes, 1.2 for obesity (non-significant), and 0.9 for hypercholesterolemia (non-significant). Other series have shown 22% of nonobese patients' becoming obese within 2 posttransplant years.[194] Numerous and partially interrelated variables contribute to this elevated CV risk-factor prevalence, including those of the nontransplant population and ones more specific to those with LT. The latter include immunosuppressive drugs for all risk factors, HCV and CMV infection for diabetes, and cholestatic liver disease for dyslipidemia.[12,185,195]

Diabetes. The pretransplant cirrhotic state may itself induce hepatogenous diabetes, via peripheral and hepatic insulin resistance as well as via impaired insulin secretion.[196] Such a form of diabetes – estimated to affect up to 60% of cirrhotics[196] – has resolved in up to 67% following LT.[197] In the early posttransplant period, surgery-related stress, high-dose corticosteroid and CNI therapy, infection, and parenteral nutrition often elicit transient hyperglycemia,[185,198,199] which is also associated with elevated risk for overt diabetes later.[195] On the other hand, as many as 80% of diabetes cases sustained past the early post-LT period develop within 1 month post-LT.[192]

Corticosteroids promote diabetes primarily by elevating both peripheral insulin resistance and gluconeogenesis stimulation, and to a lesser extent by impairing insulin secretion.[200,201] This diabetogenicity appears to be dose-dependent; steroid dose reduction improves insulin sensitivity, although complete withdrawal from a low dose (prednisolone 5 mg/day) may perhaps offer no further benefit.[201]

CNIs, on the other hand, predispose to diabetes through multiple mechanisms mutually resulting in suppression of pancreatic insulin secretion.[200] These effects, which are more intense with tacrolimus,[64] may in part reverse themselves following dose reduction.[200,201] Diabetes has been associated with poorer post-LT prognosis: increased CV morbidity and mortality, more fatal infections, higher rejection rates, and impaired graft survival.[192]

Immunosuppression-induced hypertension and dyslipidemia. Mechanisms underlying corticosteroid-induced hypertension include activation of the renin-angiotensin system, increased responsiveness to catecholamines and angiotensin II, and reduced activity of vasodepressor systems.[12] CNIs may cause hypertension through increased sympathetic and renin-angiotensin system activity, increased endothelin synthesis, and reduced nitric oxide-mediated vasodilatation, the net effect being vasoconstriction.[12] CNIs promote dyslipidemia by inhibiting bile acid 26-hydroxylase, thereby reducing bile acid synthesis from cholesterol and reducing the subsequent transport of cholesterol into the intestine. Moreover, cyclosporine binds to the LDL receptor, resulting in an elevated serum LDL level (Table 2).[202]

Other CV risk factors. Of LT recipients, 17% in one series were active smokers.[203] Renal failure has been recognized as an independent CV risk factor,[188] but little data exist on other CV risk factors in this population.

Management. The efficacy of conventional CV risk-reducing interventions has not been specifically confirmed in the LT population, but given the convincing data

from the nontransplant population, many authors advise the extrapolation of common guidelines to LT recipients.[12,14,55,185] The recommended management of posttransplant diabetes follows the same principles as for type 2 diabetes.[12,204] Assessment of overall CV risk using scoring systems such as SCORE or Framingham has been applicable to the LT population.[205] Evidence points to the particular benefit of calcium-channel blockers, as they may counteract CNI-induced renal vasoconstriction, and also to the benefit of drugs suppressing the renin-angiotensin system, which is activated by CNIs.[74] Hypercholesterolemia may, in addition to accelerated atherosclerosis, be associated with chronic graft rejection,[185] and likewise the possibilty exists that statins have a rejection-opposing effect.[206]

Adjustment in immunosuppression. Steroid-free regimens safely improve glycemic control, blood pressure levels, and the lipid profile, and they support weight-loss efforts.[12,55,96,207] A similar benefit is achieved by introducing mycophenolate in conjunction with CNI dose reduction.[12] Regarding other modifications, substituting one agent with another often modifies the risk-factor profile in favorable and unfavorable directions (Table 2).[12,185]

Other nonhepatic complications

Osteoporosis. In addition to risk factors recognized in the nontransplant population, end-stage liver disease (especially of cholestatic origin), corticosteroids, and CNIs contribute to posttransplant bone-mass loss, which is most profound 3 to 6 months after LT.[12,208] By 2 years after LT, the cumulative incidence of fracture is 24% to 55%; thereafter the fracture risk diminishes, because average bone mineral density typically improves.[12,208,209] The recommended management parallels that in the nontransplant population.[12,55]

Other long-term complications. Pharmacotherapy after LT conveys the potential for a wide spectrum of chronic conditions and symptoms in the long term. Among long-term survivors, the reported prevalence of neurologic complications (mostly polyneuropathies) ranges from 6 to 11% and of cataract from 8 to 24%, and occurrence of peptic ulcer disease is approximately 5%.[167,184,210]

Nonadherence. Long-term complications, side-effects, and the high cost of medication, as well as attitudes of adolescents pose a threat to adherence to the medical regimen, which may subsequently worsen outcome.[211] Poor adherence may be difficult to detect and even more difficult to manage.[211]

Hepatic complications

Disease recurrence. Recurrence of the primary liver disease is a leading cause of graft failure following the first posttransplant year,[8] even though diseases tend to recur with highly variable frequency. HCV and HCC recurrence have the highest clinical relevance (Table 7).[14,17,55] Detection of recurrence is often hampered by coexistence of overlapping histological changes attributed to transplant-related factors such as rejection or ischemic biliary complications, and by the poor diagnostic utility of standard blood tests.[212]

Table 7. Recurrence of the primary liver disease after liver transplantation

	Likelihood of histological recurrence	Likelihood of progression to cirrhosis or graft failure	10-year graft survival in Europe, 1988-2008[8]	10-year graft survival in Finland, 1982-2008[23]
Primary biliary cirrhosis	++	+	71%	78%
Primary sclerosing cholangitis	++	++	70%	83%
Autoimmune hepatitis	++	+	66%	90%
Alcoholic liver disease	+	+	61%	63%
Hepatitis C	+++	+++	55%	82%[a]
Hepatitis B	+ (with prophylaxis)	+	69%	N.A.
Hepatocellular carcinoma	+ (when within Milan criteria)	-	47%	44%

[a] 7-year survival (n=13)
Abbreviations: N.A., not available

Chronic rejection. Chronic rejection injures the vascular endothelium and bile ducts, manifesting clinically as increasing cholestasis.[212] Occurring at any time after LT, it is overall considered a rare event – with current incidence estimates of less than 3% among adults and approximately 10% in children. It is almost always preceded by acute rejection.[213] Early chronic rejection may respond to additional immunosuppression; other cases require retransplantation.[55,213]

Biliary complications. Although late biliary complications, sometimes resulting in chronic graft dysfunction, may be the sequelae of earlier biliary problems, nonanastomotic biliary strictures in particular may also emerge during longer-term follow-up in as many as 15% of recipients.[14,126,127] Any injury to the biliary epithelium, including hepatic artery thrombosis, preservation injury, and prolonged ischemia, can contribute to the development of such strictures, but immunologic factors entailing rejection, CMV, and PSC, predominate as the cause for strictures appearing in the long term.[126,127] Strictures – frequently discovered by cholestatic liver tests or recurrent cholangitis – may often be treated by endoscopic dilatation and stenting.[14,126,127] Occasionally they require surgery, however, and if graft failure develops, retransplantation.[14,126,127]

Other complications. Chronic graft dysfunction may, in addition to those conditions above, occasionally result from chronic hepatitis, de novo fibrosis or cirrhosis, and various vascular, drug-induced, and viral causes.[214] The clinical relevance of such complications remains uncertain.[214]

Aims of the study

The overall aim of this thesis was to investigate the long-term effects of liver transplantation on major long-term nonhepatic complications and on quality of life as compared with an age- and gender-matched Finnish general population, and also its effects on employment status.

The specific objectives were to evaluate:

1. In adult patients after liver transplantation, their renal function and the cumulative incidence of chronic kidney disease (I).

2. In adult patients transplanted for acute liver failure, their prevalence of cardiovascular risk factors (IV).

3. Among all Finnish liver transplant patients, the occurrence of cancer (II).

4. Among all adult Finnish liver transplant patients alive, their quality of life and employment status (III).

Patients and methods

PATIENTS AND GENERAL STUDY DESIGN

Consecutive patients undergoing LT at Helsinki University Hospital were included (Table 8). With commencement of the Finnish LT program in 1982, all adult liver transplantations in Finland have been performed at the Surgical Hospital of Helsinki University Hospital. The patients also make regular scheduled follow-up visits at the same clinic. In addition, if any graft problems ensue, investigations and treatment are performed at the clinic, with follow-up data from local hospitals sent to the transplant center at least twice annually.

End-points of follow-up were the end of each study. In Study I, the other end-points were development of ESRD or retransplantation. In Study IV, is was the fifth posttransplant year. Children (aged under 17) were included only in Study II. For other exclusion criteria, see Table 8.

Table 8. Features of study design

	I	II	III	IV
Issue addressed	Renal dysfunction	Malignancy	Quality of life, employment	Cardiovascular risk
Time-period for transplantation	1982-2004	1982-2005	1982-2007	1987-2004
Number of patients included	396	540	353	77
Method of patient recruitment	Consecutive	Consecutive	Consecutive	Consecutive
Retransplanted patients included	No	Yes	Yes	Yes
Children included	No	Yes	Adults transplanted as children	No
Other exclusions	Prior organ transplantation (1 kidney) Combined liver-kidney transplants (n=8)	-	Deceased patients (n=273) Nonresponders (n=45) Incomplete questionnaires (n=3)	Other than acute liver-failure patients
Control group	No	Finnish Cancer Registry; matched for age, gender, and calender time	National Health 2000 Health Examination Survey; matched for age, gender, and residence area	National Health 2000 Health Examination Survey: sample weighted to reflect age and gender distribution
Follow-up endpoints	June 2004 Dialysis or kidney transplantation Retransplantation Death	December 2005 Death	June/July 2007	5 years after transplantation (February 2009)

Ethical approval for Study III came from the ethics committee of the Helsinki and Uusimaa Hospital district, and all patients also signed an informed consent form. Studies II and IV received approval from the National Institute for Health and Welfare.

Study I assessed renal function at different posttransplant time-points, as well as possible changes in renal function after LT and the frequency distribution of different stages of renal dysfunction. Subgroup analyses were performed by indication group (CLD, ALF, or liver tumor), and further according to renal function at listing for LT, according to time period of LT, and according to the MELD score at LT. Patients who developed CKD or ESRD underwent a more detailed review.

Study II evaluated the cumulative incidence of malignancies after LT, with occurrence of malignancies compared to an age-, gender-, and calendar-time-matched Finnish general population. Potential LT-related risk factors for development of cancer also assessed comprised transplant indication, initial CNI agent, acute rejection, antibody therapy, retransplantation, and CMV status. Identical analyses were performed separately for development of lymphoma, skin cancer, and other cancer types. Among patients who developed any posttransplant malignancy, assessment included method of cancer detection and outcome after cancer.

Study III sought to reveal the HRQoL and employment status of LT recipients, to compare the HRQoL of patients with that of the general population, and to investigate LT-related factors possibly influencing posttransplant HRQoL and employment.

Study IV evaluated incidence of hypertension, dyslipidemia, weight gain, and diabetes following LT for ALF, and compared the 5-year posttransplant CV risk factor prevalence with equivalent data from the general population. The accumulation of CV risk factors in relation to age, as well as possible LT-related predictors of CV risk were also relevant, as was occurrence of CV disease before or during the study period.

CLINICAL PARAMETERS AND DEFINITIONS

Background clinical, laboratory, and demographic data, comprising age, gender, time of LT, liver-disease diagnosis, and immunosuppression regimen came from the prospective Finnish liver transplant registry, patient records, and the hospital's laboratory database. In addition, Studies II and IV included data on acute rejection episodes and treatment with monoclonal or polyclonal antibodies. Study I, moreover, included data on waiting times for LT, preoperative renal-replacement therapies, and MELD score, while Study II incorporated data on CMV status, and Study IV on steroid use and degree of graft steatosis. This was defined as steatosis present in more than 30% of hepatocytes in time-zero liver biopsy before liver implantation. MELD scores were calculated according to the official equation[9] by use of laboratory parameters obtained on the day of transplantation (I); no diagnosis-based exception points were given, and in the case of a creatinine level exceeding 350 μmol/L dialysis, the creatinine level was, in the MELD equation, set at 350.

Renal function

Renal function was assessed as plasma creatinine and urea at the following time-points: at listing, day of transplantation, at worst value during the first postoperative week, and annually thereafter.

For a better estimation of GFR, creatinine clearances were calculated at these same time-points, with patients' weights also recorded. Creatinine clearance was calculated by the Cockcroft–Gault formula,[215] by which GFR = (140-age) × weight (kg) / *a* × plasma creatinine (μmol/L), where *a* is 0.8 for men and 0.95 for women. Renal function was classified into stages according to recommendations of the National Kidney Foundation.[153] According to these guidelines, stage 1 is GFR ≥90 mL/min (normal renal function), stage 2 is GFR 60 to 89 (mild decrease), stage 3 is GFR 30 to 59 (moderate decrease), and stage 4 is GFR ≤29 (severe decrease). In this study, ESRD was defined as either GFR <15, or initiation of dialysis, or need for kidney transplantation. CKD was defined as stage 4 renal dysfunction or ESRD lasting at least 6 months.

Malignancies

Data regarding cancers among patients and controls came from the Finnish Cancer Registry. The cohort of Study II was compared with the national population register. The correct personal identification number and data on vital status were achieved for every cohort member. All residents of Finland since 1 January 1967 have a unique personal identification code used in all the major registers in Finland. Follow-up for cancer through the files of the population-based Finnish Cancer Registry was automatic, via the personal identifier as a key. Follow-up for cancer started at the date of the first transplant, and ended at death or on 31 December 2005, whichever came first. A further division was time elapsed since LT. In sub-analysis among patients with acute rejection, follow-up for cancer started at the date of rejection.

The numbers of cases and person-years at risk were counted, by five-year age groups, separately for four calendar periods (1982-1987, 1988-1993, 1994-1999, and 2000-2005). The expected numbers of cases for all cancers combined and for specific cancer types were calculated by multiplying the number of person-years in each gender and age-group by the corresponding cancer incidence rate in all of Finland during the period of observation. The specific cancer types a priori selected for analysis included cancer sites with a known or suspected exceptional risk in earlier studies, and other common cancer types. This provides the entire picture of the cancer situation among Finnish LT patients.

Cardiovascular risk factors and disease

Data collected. CV risk factor variables collected were body mass index (BMI) and medications for hypertension, dyslipidemia, and diabetes, as well as history of coronary heart disease, cerebrovascular disease, and peripheral vascular disease. These data were collected at the time of listing to LT as well as at 5 years posttransplant. Furthermore, fasting plasma/serum concentrations of glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and glycated hemoglobin (HbA1c) were determined

at 5 years post-LT. No data on corresponding blood levels at the time of listing were collected; because ALF alters lipid and glucose levels considerably, these would have been unreliable markers of previous cardiovascular risk.[216]

Blood pressure levels were not recorded due to the lack of any prospectively planned and standardized protocol of blood pressure measurement. Blood pressure levels sporadically available in this retrospective setting involve multiple sources of error and were thus disregarded. Use of antihypertensive medication, conversely, was based on multiple measurements and clinical practice guidelines, and can therefore be regarded as a more reliable marker of hypertension. Antihypertensive drugs included were beta-blockers, diuretics, angiotensin-converting-enzyme inhibitors, angiotensin-II inhibitors, calcium-channel blockers, centrally acting antihypertensives, and a combination of these.

Antidiabetic drugs comprised insulin and oral antihyperglycemic agents. Lipid-lowering drugs comprised statins, fibrates, and cholesterol-absorption inhibitors. Data on cardiovascular diseases before and after LT as well as cause of death were collected for patients dying earlier than 5 years after LT.

Definitions of CV risk factors. In accordance with World Health Organization criteria,[217] diabetes was defined as a fasting plasma/serum glucose of 7.0 mmol/L (126 mg/dL) or above, or use of antidiabetic medication. Impaired fasting glucose (IFG) was defined as a fasting plasma/serum glucose between 6.1 and 6.9 mmol/L (110 and 125 mg/dL) and no antidiabetic medication.

For the purpose of this study, dyslipidemia was defined as a fasting plasma/serum cholesterol of 5.0 mmol/L (190 mg/dL) or above, or a LDL level of 3.0 mmol/L (114 mg/dL) or above, or a HDL level of 1.0 mmol/L (38 mg/dL) or less, or a triglyceride level of 2.0 mmol/L (176 mg/dL) or above, or medication for dyslipidemia.

Hypertension was defined as use of antihypertensive medication. Overweight was defined as BMI 25-30 kg/m² and obesity as greater than 30 kg/m². In analyses on difference in risk factor prevalence before and after LT, definitions of hypertension, dyslipidemia, and diabetes were based solely on use of medication at these two separate time-points.

HRQoL and employment assessment

HRQoL was assessed with the 15D questionnaire, mailed for self-administration to all patients alive in June 2007, along with a prepaid envelope for its return. Questionnaires were in each patient's native language, Finnish or Swedish, the two official languages in Finland. The letter also included a questionnaire for assessment of employment status and a consent form which the patients were asked to sign and return. A reminder went in July 2007 to those who did not respond to the first letter. Strict confidentiality was ensured, and in order to obtain truthful responses we stressed that their transplant physicians would have no access to answers from any individual patient. Letters were returned to a department unassociated with the transplantation center (Helsinki and Uusimaa Hospital Group, Group Administration) and responses were registered by persons uninvolved in analyses of the results.

15D. HRQoL was measured by the 15D instrument,[218] a generic, 15-dimensional, standardized and self-administered measure of HRQoL which can serve

both as a profile and a single-index score measure.[218,219] Its 15 health dimensions are: moving, seeing, hearing, breathing, sleeping, eating, speech, elimination (urination and defecation), usual activities (keeping up with work, studies, household activities, and leisure activities), mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity.

For each dimension, the respondent must choose from one of five levels that best describes his or her present health status (the best level being 1 and the worst, 5). The valuation system of the 15D is based on application of the multi-attribute utility theory. A set of utility or preference weights obtained from the general public through a 3-stage valuation procedure generates the utility score, i.e., the 15D score (single index number), over all the dimensions on a 0 to 1 scale (1 = no problems in any dimension, 0 = deceased), and dimension level values on a 0 to 1 scale.[219] The minimal clinically important difference in 15D score is ≥0.03.[219] In most of its important properties, the 15D compares favorably with similar instruments.[218,220]

If a respondent leaves up to three questions unanswered, the missing data may be imputed by regression models taking responses on the other dimensions as well as age and gender as explanatory variables, according to 15D instructions.[218]

Employment status and working capacity. A categorical and descriptive evaluation of patients´ current employment status and the subjective impact of LT on their working capacity was assessed with five questions:

1. Are you currently in working life (yes or no)?
2. If the answer to the previous question was no, then choose one of the following alternatives:
    a. Retired.
    b. Studying.
    c. Unemployed.
    d. Early retirement for a cause associated with my liver disease.
    d. Early retirement for a cause not associated with my liver disease.
    e. Other cause (what?).
3. How soon after your transplantation were you able to return to work?
    a. Less than 3 months.
    b. 3-6 months.
    c. 6-12 months.
    d. 1-2 years.
    e. >2 years.
    f. Work not resumed.
4. If the answer to the previous question was option f, then choose one of the following alternatives:
    a. Retirement at required age before transplantation.
    b. Retirement at required age shortly after transplantation.
    c. Studying before transplantation.
    d. Unemployed before transplantation.
    e. Early retirement after transplantation for a cause associated with my liver disease.
    f. Early retirement after transplantation for a cause not associated with my liver disease.
    g. Other cause (what?).
5. How do you estimate your current working capacity and functional capacity in everyday life compared to that at 1 week before transplantation? (The respondent must choose 1 to 5 options on a bipolar scale where 1 is “much better” and 5 is “much worse”).

CONTROL POPULATIONS

Control data from the Finnish general population for Studies III and IV came from the National Health 2000 Health Examination Survey. This survey, conducted in 2000 and 2001, is because of its careful study design and 93% participation rate considered to accurately and validly represent the entire adult Finnish population.[221] Those individuals in the age range of the LT recipients and for whom necessary comparison data were available were selected; in Study III controls comprised 6050 individuals and in Study IV 6483.

In Study III, the control sample was, for the purpose of analysis, weighted to reflect patients' age and gender distribution.

In Study IV, comparisons between patients and controls were adjusted for age, gender, and area of residence, because CV risk factor prevalence in the Finnish general population shows considerable variation in these factors.

Study II obtained control data from the Finnish Cancer Registry. The cancer registration system in Finland is virtually complete,[222] and the computerized record linkage procedure precise,[223] thus providing unbiased control data and accurate comparisons for the study.

IMMUNOSUPPRESSION

All patients received CNI–based initial immunosuppression. The majority received cyclosporine in combination with azathioprine and methylprednisolone. Only a few patients, those participating in controlled clinical trials, had tacrolimus-based initial immunosuppression. Furthermore, some immunologically unstable patients – particularly patients presenting with a recurrent early acute rejection episode after steroid-treated acute rejection, and patients with late acute rejection episodes – were converted from cyclosporine to tacrolimus. MMF was added for some patients with CNI-induced nephrotoxicity, and CNI doses were subsequently reduced or withdrawn. For a few patients participating in controlled studies, MMF during the study period also served as the initial antimetabolite, instead of azathioprine.

The initial target of cyclosporine concentration was 200 to 250 ng/mL, tapered over time to maintain a level of 70 to 150 ng/mL. For tacrolimus, respective values were 15 to 20 ng/mL and 5 to 10 ng/mL.

All acute rejection episodes were histologically confirmed. The initial treatment regimen included a 5-day steroid course (methylprednisolone 3 mg/kg/day) with steroid-resistant rejections treated with OKT3 monoclonal antibodies or in some cases with ATG polyclonal antibodies. Antibodies – consisting of ATG and, since 2000, with IL-2 receptor antibodies – were also administered to some patients as induction therapy when CNI-based initial immunosuppression was considered too risky.

STATISTICAL ANALYSIS

Data were analyzed with StatView for Windows (SAS Institute, Inc., Cary, NC, USA) statistical software (I), or SPSS statistical software version 14.0 (SPSS, Inc., Chicago, IL, USA) (II, III, IV). In general, the Chi-Square test served for categorical variables, whereas survival functions and cumulative incidence rates were calculated by the Kaplan-Meier method. Differences in survival between groups were tested by the log rank test.

Study I applied the unpaired t-test or Mann-Whitney test as appropriate for comparing two groups, with the Kruskal-Wallis test for comparing three groups. The paired t-test or when appropriate the Wilcoxon signed-rank test served to test differences within a group across time-points. Correlations between laboratory parameters were calculated with the Spearman correlation.

Study III analyzed differences in mean 15D score between groups by use of the independent samples t-test or a 1-way analysis of variance as appropriate. The same study reports the differences in means between groups as well as their 95% confidence intervals (CI) for the main results.

The standardized incidence ratio (SIR) for cancers was calculated by dividing observed number of cases by the expected number (II). Similarly, SPRs for CV risk factors were calculated as the observed case prevalence in the patient population at 5 years after LT divided by the expected cases in the general population (prevalence in general population x patient population size) (IV). The expected prevalence was counted in 5-year age groups adjusted for gender and the five university hospital districts according to patient's geographical area of residence. The 95% CIs for the SIRs and SPRs were calculated assuming a Poisson distribution of cases. The SPR was statistically tested by the z-test.

Potential LT-related risk factors for the development of cancer were considered in a Cox proportional hazards model adjusted for age, gender, and time since transplantation. The same analysis was also done separately for development of lymphoma, skin cancer, and other cancer.

In Study III, subgroup analyses were performed by age, gender, survival time, transplant number, and employment status. These subgroups were considered in separate linear regression models, with the 15D score as the dependent variable and age, gender, and the respective subgroup variable as independent variables. Another test was whether any linear or inverted U-shape relationship existed between HRQoL and survival time; this was tested by including both survival time and its square as explanatory variables in the respective linear regression model. The LT population was further combined with the age- and gender-standardized sample of the general population in order to test whether the HRQoL of the different transplant indication groups (CLD, ALF, or liver tumor) would deviate from that of the general population. This test computed a linear regression model adjusted for current age and gender, where each of the three LT indication groups were coded with a different indicator variable, and the general population served as the reference.

Relative risk ratios were calculated for variables possibly associating with CV risk factors (IV).

P values <0.05 were considered statistically significant. However, to test whether significant differences existed between LT patients and the general population on the individual 15D dimensions according to the independent samples t-test, and simultaneously adjusting for multiple testing, the Bonferroni correction was used (III). Here a P value <0.003 (0.05/15 = 0.003) was considered statistically significant (III).

Results

POPULATION CHARACTERISTICS AND SURVIVAL

Baseline and posttransplant characteristics of the patients included in the studies are shown in Table 9. Average age at LT was somewhat lower in Study II due to the inclusion of children, whereas the higher proportion of female patients was even more accentuated in the ALF population (IV).

Table 9. Patient characteristics

	I	II	III	IV
Study	Renal dysfunction	Malignancy	Quality of life, employment	Cardiovascular risk
Patients, n	396	540	353	77
Time period of transplantations	1982-2004	1982-2005	1982-2007	1987-2004
Age at transplantation, mean (SD)	48 (11)	43 (18)	48 (13)	46 (12)
Gender, male:female	42:58%	45:55%	42:58%	30:70%
Decade of transplantation				
1980s	9%	8%	6%	6%
1990s	54%	49%	36%	55%
2000s	37%	43%	58%	39%
Liver transplantation diagnoses				
Chronic liver disease	70%	73%	73%	
Primary biliary cirrhosis	34%	26%		
Primary sclerosing cholangitis	22%	19%		
Alcoholic cirrhosis	15%	14%		
Viral cirrhosis	3%	4%		
Other	26%	38%		
Acute liver failure	23%	18%	22%	100%
Unknown etiology	63%			62%
Other known etiology	12%			13%
Acute Budd-Chiari	10%			9%
Drug-related	10%			11%
Toxic (nondrug)	5%			5%
Liver tumor	7%	8%	5%	
Hepatocellular carcinoma and cirrhosis	45%			
Hepatocellular carcinoma without cirrhosis	35%			
Other liver malignancies	20%			
Preoperative dialysis	15%			
Days on preoperative dialysis, mean (SD)	10 (17)			
MELD score at transplantation, mean (SD)	20 (11)			
History of nonhepatic malignancy		2%		
Initial calcineurin inhibitor agent				
Cyclosporine		82%		86%
Tacrolimus		17%		14%
Acute rejection		52%		52%
Monoclonal/polyclonal antibody therapy		12%		20%
Retransplantation		9%	7%	16%
Steroid use at 5 years				42%
Methylprednisolone dose at 5 years, mean (SD)				2.9 mg (1.4)
Patients with graft steatosis				17%

Abbreviations: MELD, model for end-stage liver disease

Of 401 LT recipients still alive in 2007, 356 (89%) returned the HRQoL and employment questionnaires (III). Three of the responders were excluded because they omitted more than three answers on the 15D; thus 353 patients were included in the final analyses (Table 9). Patients who underwent LT as children were more likely to be nonrespondents than were older patients, as shown by 13% of nonresponders' belonging to this group versus 5% among responders. In other features, responders and nonresponders did not differ significantly.

During the period from 1982 to 2007, overall patient survival rates were 90% at 1 year, 82% at 5 years, 72% at 10, and 59% at 20. Corresponding graft survival rates were 85% at 1 year, 75% at 5 years, and 65% at 10 (Figure 5).

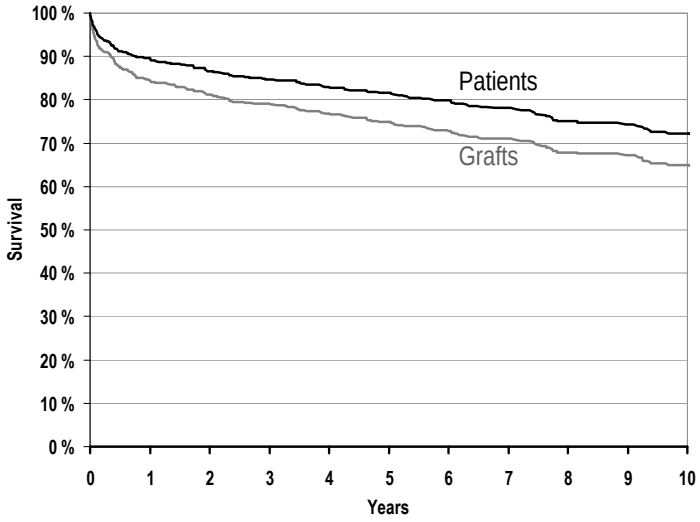

Figure 5. *Patient and graft survival after liver transplantation at Helsinki University Central Hospital between 1982 and 2007.*

Less than 10% of all LTs were performed during the 1980s (Table 9). With time, a noticeable improvement in survival rates emerged (Figure 6). Most of this improvement, however, occurred during patients' first posttransplant year.

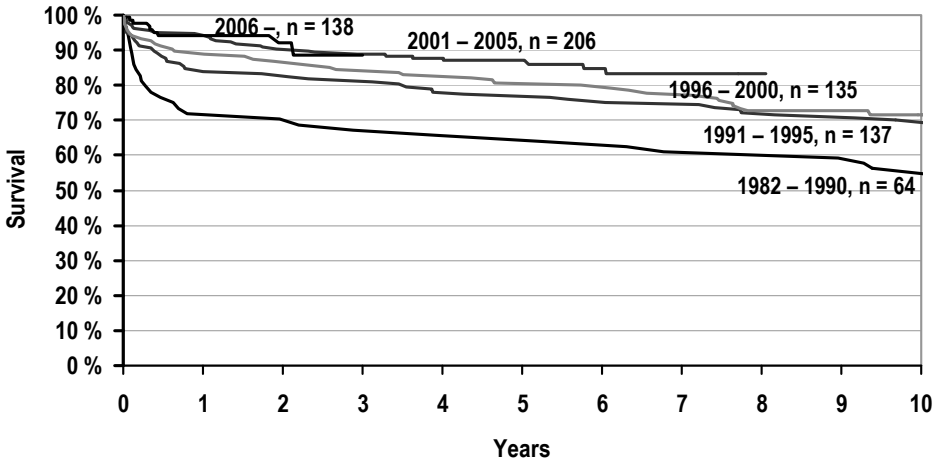

Figure 6. *Patient survival by time-period of liver transplantation in Finland.*

CLD and ALF patients displayed significantly better survival than did liver tumor patients (P = 0.001 between groups) (Figure 7).

Average waiting times for LT, as reported in Study I, were 42 days for the CLD group, 5 for the ALF group, and 31 for the liver tumor group. Of ALF patients, 40% required dialysis prior to LT, as compared to 8% of CLD patients and 3% of liver tumor patients.

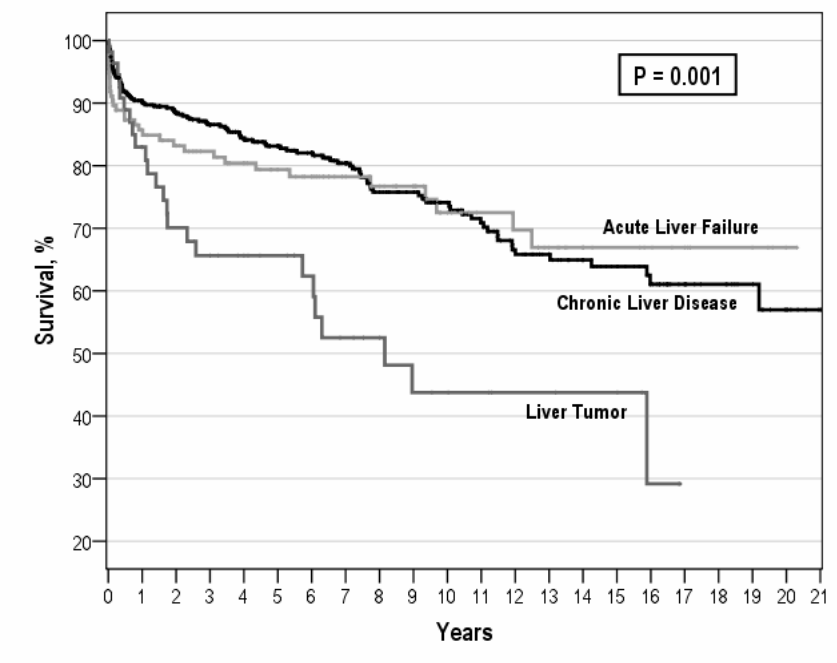

Figure 7. *Patient survival according to indication group in Finland.*

Compared with other indication- and age groups, retransplantation was more often necessary in ALF patients (see Study I, Table 1, p. 3) and in children (see Study III, Table 1, p. 1430).

RENAL FUNCTION

Pattern of renal function

Average blood concentrations of cyclosporine and tacrolimus decreased steadily during follow-up; mean (SD) cyclosporine levels in ng/mL were 184 (82) at 1 year, 159 (63) at 3 years, 143 (41) at 5, and 122 (35) at 10; mean tacrolimus levels were 10.7 (7.6) at 1 year, 9.2 (5.1) at 3 years, and 7.7 (3.9) at 5.

Average creatinine level increased slightly, but nonetheless statistically significantly, from that before LT to that at 1 year among all patients combined and among CLD patients (Table 10). Among liver tumor patients, the increase was even more pronounced, whereas ALF patients showed the opposite trend of a lower mean creatinine level after LT than before. During the first postoperative week, average creatinine levels were significantly higher than were pretransplant levels in all groups (P < 0.0001), except the tumor group. Creatinine levels at the first-week time-point also differed significantly between the three indication groups (P = 0.0002), with a

significant difference, moreover, appearing between the CLD and ALF groups at listing (P = 0.02).

Average GFR at different time-points demonstrated similar patterns of renal function (Table 10; see also Study I, Table 3, p. 3), except in the ALF group, where decreasing mean GFR levels, pre- to posttransplant, contradicted the improved renal function expressed by creatinine. Average GFR did not significantly differ among indication groups.

Table 10. Levels of creatinine (µmol/L) and estimated GFR (mL/min) at different time-points for all patients, and separately for chronic liver disease, acute liver failure, and liver tumor. Levels expressed as mean (SD).

	At listing	LT day	First week	1 y	10 y
All patients, n	396	395	394	327	52
Creatinine	100 (87) *	106 (81) *	166 (112)	109 (50)	102 (32)
Estimated GFR	99 (50) *	94 (55) *		76 (29)	70 (23)
Chronic liver disease, n	277	276	276	235	41
Creatinine	91 (73) *	96 (60) *	155 (104)	108 (48)	100 (33)
Estimated GFR	98 (46) *	91 (43) *		76 (30)	71 (23)
Acute liver failure, n	90	90	88	71	9
Creatinine	137 (122) N.S.	143 (126) N.S.	210 (131)	107 (55)	115 (32)
Estimated GFR	97 (62) ***	101 (86) ***		76 (28)	64 (23)
Liver tumor, n	29	29	29	21	2
Creatinine	75 (20) **	80 (25) **	145 (93)	121 (45)	87 (11)
Estimated GFR	111 (38) *	105 (35) *		75 (24)	70 (-)

Abbreviations: LT day, day of liver transplantation; First week indicates highest creatinine values recorded for each patient during the first posttransplant week.
* P<0.0001, ** P<0.001, *** P<0.01; N.S., non-significant (comparisons with 1-year levels).
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Stages of renal dysfunction over time. Figure 8 illustrates the relative frequency distributions of the stages of renal dysfunction at different times – excluding patients already on dialysis. The incidence of stage 4 (severe) renal dysfunction at listing was 4.8% among all patients, 2.2% for CLD, 14.6%, ALF, and 0% for the tumor group. During follow-up, a steadily increasing proportion of patients with either stage 3 or 4 (moderate or severe) dysfunction appeared among all patients and among CLD patients.

In the ALF group, a significant reduction (P = 0.005) occurred in the incidence of stage 4 renal dysfunction from the listing date to 1 year after LT. No other groups exhibited a similar reduction. In the tumor group, stage 4 renal dysfunction did not occur at listing or at 1 year, but at 3 years, an incidence of 10% had already emerged, and was followed at 5 years by 20%.

Incidence and etiology of renal disease

A total of 25 patients (6% of all patients) developed CKD. During the study period, of these 25, 7 progressed to ESRD. This resulted in a cumulative incidence of CKD of 1.8% at 1 year, 9.7% at 5 years, and 15.7% at 10. Likewise, the cumulative incidence of ESRD rose from 0.3% at 1 year to 1.8% at 5 years and 3.3% at 9. CKD appeared on average at 4.3 years after LT (range 0 to 10 years), whereas ESRD appeared on average at 5.6 years (range 0.2 to 9.6 years).

Overall, 20 (7%) of CLD patients developed CKD, compared with 4 (4%) of ALF patients and 1 (3%) of liver tumor patients. Of these, progression to ESRD occurred in 6 of 277 patients (2%) with CLD, and, of 90, in only 1 (1%) ALF patient.

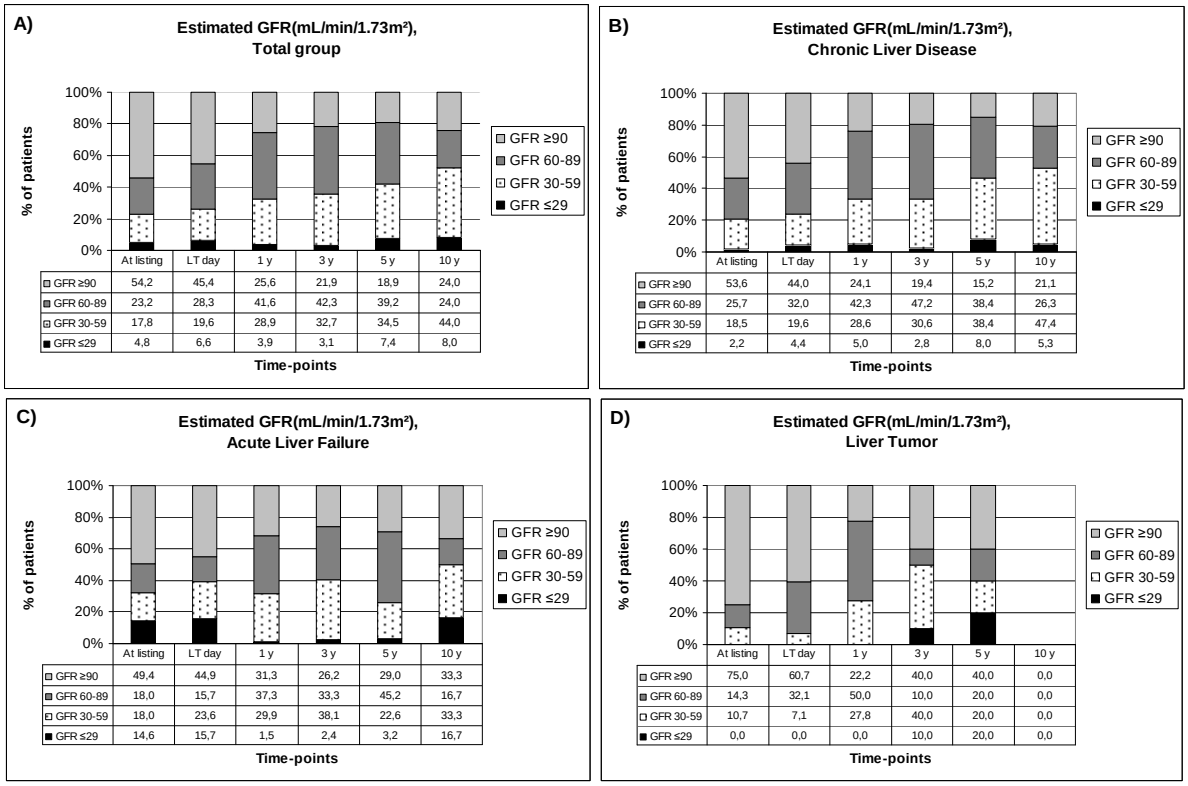

Figure 8. *Relative frequency distribution of estimated GFR at different time points among the total group (A), chronic liver disease (B), acute liver failure (C), and liver tumor (D) groups. Patients on continuous post-transplant dialysis excluded. Reproduced by permission of the publisher, John Wiley & Sons, Ltd.*

Four of the seven ESRD patients underwent renal biopsy; in other cases, renal diagnosis was based on clinical evaluation. In four cases (57%), the main cause for ESRD was chronic CNI toxicity (supported by biopsy results in three cases), and one patient each had pre-existing IgA nephropathy (biopsy confirmed), or polycystic kidney degeneration along with antibiotic toxicity, or an uncertain diagnosis due to multiple predisposing factors (diabetes mellitus, hypertension, and CNI toxicity). At the end of follow-up, two of the ESRD patients remained in dialysis, two had received a kidney transplant, and three had died without kidney transplantation. Dialysis commenced in all patients prior to kidney transplantation.

Influence of various factors on posttransplant renal function

Pre- and early posttransplant renal function. Patients were stratified in two subgroups based on their GFR at listing: either <60 (90 patients; 23%) or ≥60 (306 patients; 77%) mL/min (Figure 9). After LT, renal function deteriorated in patients with good pretransplant GFR; in contrast, it improved among patients with poor pretransplant estimated GFR. The difference between subgroups remained significant for up to 5 years after LT (Figure 9).

In the CLD population, the number of patients with a GFR <60 mL/min at listing was 57 of 277 (21%) and in the ALF population 30 of 90 (33%). Figure 10 illustrates posttransplant changes in mean GFR among the pretransplant GFR-stratified CLD and ALF groups. Patients in the tumor group were excluded from this stratification because they were too few. Of patients with a poor pretransplant GFR, 73% (32 of 44 patients) remained with a GFR less than 60 mL/min at 1 year in the CLD group. By contrast, only 35% (8 of 23) of ALF patients remained with a GFR less than 60 mL/min. The respective results at 5 years were 76% (19 of 25) of CLD patients and 15% (2 of 13) of ALF patients.

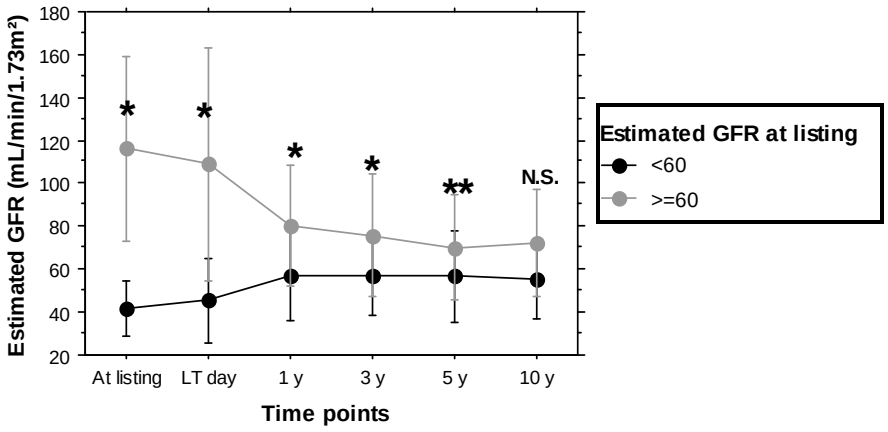

Figure 9. *Stratification of all patients based on GFR at listing (< or ≥60 mL/min), and subsequent mean GFR in these two subgroups. Vertical lines depict ± 1 standard deviation. * P < 0.0001, ** P = 0.003. Reproduced by permission of the publisher, John Wiley & Sons, Ltd.*

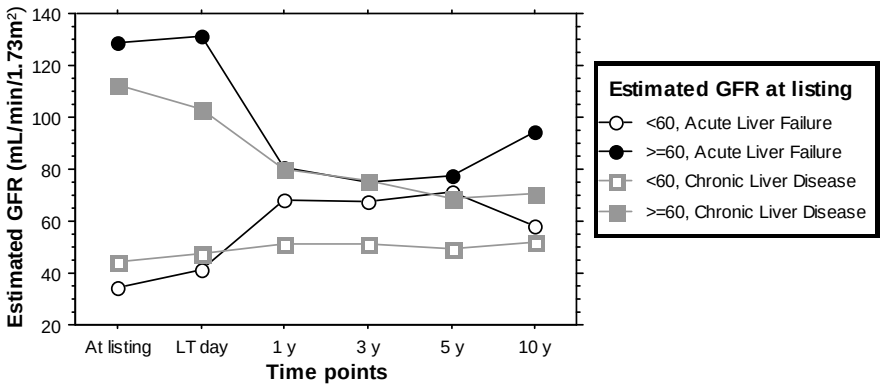

Figure 10. *Stratification of chronic liver disease and acute liver failure patients based on the GFR at listing (< or ≥60 mL/min), and subsequent mean GFR in these subgroups. Reproduced by permission of the publisher, John Wiley & Sons, Ltd.*

Parallel to these figures, the correlation between GFR at listing and later GFR was strongest in the CLD group, whereas GFR at 1 year correlated well with long-term renal function in all groups (Table 11).

Five of the 58 patients (9%) who had required pretransplant dialysis developed CKD posttransplant, resulting in a relative risk for CKD of 1.5 (95% CI 0.6-3.7). On average, CLD patients required longer renal-replacement therapies prior to LT than did ALF patients; mean time on pretransplant dialysis was 16 days for CLD and 5 days for ALF patients.

Table 11. Correlations between GFR at listing and at 1 year after transplantation with subsequent GFR levels.

GFR		1 year	3 years	5 years	10 years
At listing	All patients	0.54 *	0.51 *	0.43 **	0.50 **
	Chronic liver disease	0.63 *	0.62 *	0.54 **	0.63 **
	Acute liver failure	0.35 **	0.27 n.s.	0.26 n.s.	0.43 n.s.
	Liver tumor	0.49 ***	0.72 ***	0.31 n.s.	-
1 year	All patients		0.86 *	0.81 **	0.73 **
	Chronic liver disease		0.86 *	0.79 **	0.75 **
	Acute liver failure		0.85 *	0.88 **	0.79 ***
	Liver tumor		0.99 **	0.96 **	-

* $P < 0.0001$, ** $P < 0.01$, *** $P < 0.05$, n.s., non-significant

Of the 25 patients who later developed CKD, at listing 36% had stage 3 renal dysfunction and 12% stage 4. At 1 year, 84% had either stage 3 or 4.

MELD. The MELD score on the day of LT correlated rather poorly with later renal function (see Results in Study I, p. 6). Notably, however, among patients with a MELD score of 25 or less, renal function deteriorated more sharply following LT, approaching that of patients with MELD above 25 (see Study I, Figure 4, p. 7).

Era of transplantation. Patients transplanted in earlier eras of LT presented with poorer mean GFR, but steepness of loss of renal function posttransplant was greater among those more recently transplanted (see Study I, Figure 3, p. 6).

MALIGNANCIES

Cancer incidence

During a posttransplant follow-up of 3222 person-years in the cohort of 540 LT recipients, 39 de novo cancers developed in 36 patients. An additional 11 cases of de novo basal cell carcinoma of the skin also occurred. Of the 540 patients, 420 (74%) were alive at the end of follow-up.

The cumulative incidence of posttransplant de novo cancer was 3% at 1 year, 5% at 5 years, 13% at 10, and 16% at 20 (Figure 11). The respective cumulative risk for de novo cancer-related mortality was 0%, 1%, 2%, and 2%.

In comparison with the general population, the overall SIR was 2.59 (95% CI 1.84-3.53; Table 12). In addition to basal cell carcinoma – not included as cancer in overall SIR – non-Hodgkin lymphoma and non-melanoma skin cancer were the only cancer types to show significantly elevated SIRs (Table 12). Non-melanoma skin cancer included Kaposi sarcoma and squamous cell carcinoma. For nonsignificant SIRs see Study II, Table 2, p. 1432. In addition to the cancer types preselected for SIR analysis, we observed one each of urinary bladder, ovarian, and uterine cancers, and a fibrosarcoma.

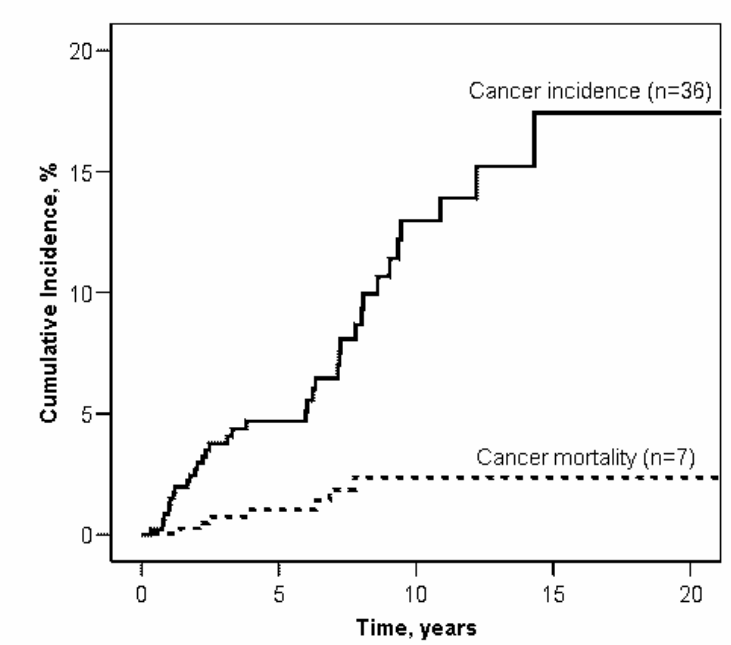

Figure 11. *Cumulative incidence of de novo cancer and de novo cancer mortality following liver transplantation. Recurrence of pretransplant cancer not included. Reproduced by permission of the publisher, John Wiley & Sons, Inc.*

Table 12. Standardized incidence ratio (SIR) with 95% confidence intervals (CI) for all cancer cases and cases with significant SIRs among Finnish liver transplant patients, 1982-2005.

Primary site	Observed	Expected	SIR	95% CI
ALL CANCERS	39	15.1	2.59	1.84-3.53 *
Non-Hodgkin lymphoma	8	0.57	13.9	6.01-27.4 *
Skin, nonmelanoma	10	0.26	38.5	18.5-70.8 *
Basal cell carcinoma of the skin	*11*	*2.97*	*3.70*	*1.85-6.62 **

* $P < 0.001$

Influence of various factors on posttransplant cancer occurrence

Gender. A higher SIR appeared in males (SIR 4.16, 95% CI 2.61-6.30) than in females (SIR 1.74, 95% CI 1.01-2.78). Furthermore, of eight non-Hodgkin lymphomas, six occurred in males, producing a markedly higher non-Hodgkin lymphoma SIR for males (SIR 26.7, 95% CI 9.79-58.1) than for females (SIR 5.72, 95% CI 0.69-20.7). Conversely, SIRs for nonmelanoma skin cancer were similar for males (SIR 36.2, 95% CI 9.87-92.7) and females (SIR 40.2, 95% CI 14.8-87.5).

Age. The SIR was more elevated in children (SIR 18.1, 95% CI 2.19-65.5) than in adults (SIR 5.77, 95% CI 1.87-13.5 for those aged 17-39 and SIR 2.27, 95% CI 1.55-3.20 for those ≥40). The SIR for non-Hodgkin lymphoma was 123 (95% CI 3.12-686) at ages <17, 55.7 (95% CI 6.74-201) at ages 17 to 39, and 9.42 (95% CI 3.06-22.0) at ≥40. Of 10 nonmelanoma skin cancer cases, nine occurred among the oldest transplant patients (≥40 at LT), the SIR for this group being 36.1 (95% CI 16.5-68.5).

Follow-up period. SIRs were further calculated according to posttransplant follow-up period, namely <2 years, 2 to 9 years and ≥10 years. Here, SIRs were higher in the earlier follow-up periods (see Study II, Table 3, p. 1432). All non-Hodgkin lymphomas and nervous system cancers (all meningeomas) detected occurred before 10 years posttransplant, whereas nonmelanoma skin cancers occurred quite uniformly during each of the follow-up periods.

Pretransplant cancer. Prior to LT, 55 patients each had a preexisting liver tumor, and another 11 had a history of nonhepatic malignancy. These 11 comprised 3 colon cancers, and 1 each of lymphoma, ventricle carcinoid, rectal cancer, pancreatic cancer, spinocellular skin cancer, medullar meningeoma, rectal carcinoid with metastasis to the liver, and thymoma with later HCC. None of these 11 patients developed de novo cancer posttransplant. The average time from detection of pretransplant malignancy to LT was 6.8 years (range 0.3-20.6 years).

Indication. The 113 ALF patients had somewhat higher SIR (3.35, 95% CI 1.61-6.16) than did patients with CLD (381 patients, SIR 2.39, 95% CI 1.58-3.48) or liver tumor (46 patients, SIR 2.47, 95% CI 0.30-8.92). This difference between groups was, however, not statistically significant in age-, gender-, and follow-up-adjusted hazards ratio statistics (Table 13, see also Study II, Table 4, p. 1433).

Immunosuppression. Cyclosporine was used in 441 patients (82%) as the initial CNI agent. In this group, 36 of the 39 cancers (92%) were detected after LT. The cyclosporine group also produced 10 times more patient-years of follow-up than did the tacrolimus group: 2938 patient-years versus 276 patient-years. The overall SIR for patients with cyclosporine as their initial agent, as compared to that of the general population, was 2.61 (95% CI 1.83-3.61). Cancer sites that showed significantly increased SIRs in this group were non-Hodgkin lymphoma (SIR 13.36, 95% CI 5.37-27.5), non-melanoma skin cancer (SIR 41.79, 95% CI 20.04-76.84), and basal cell carcinoma (SIR 4.06, 95% CI 2.03-7.26). The overall SIR for patients with tacrolimus as their initial agent was 2.32 (95% CI 0.48-6.79), compared to the general population's. In the tacrolimus group, no cancer site showed significantly increased SIRs.

Rejection. Those who had experienced one or more acute rejection episodes (276 patients) had a lower SIR (1.77, 95% CI 0.95-3.02) than did those who had

experienced no rejection (261 patients, SIR 3.52, 95% CI 2.39-5.27). Furthermore, compared to the group of patients without rejection, the group with a history of a non-antibody-treated acute rejection was associated with a relative cancer risk estimate of 0.41 (P = 0.02) (Table 13).

Antibody therapy. Antibody therapy for acute rejection did not alter cancer risk significantly. Of 276 patients with acute rejection, 47 (17%) had been treated with mono- or polyclonal antibodies. The SIR value for this group (1.71, 95% CI 0.35-4.98) was similar to the SIR value for those who had not been treated with antibodies (SIR 1.79, 95% CI 0.86-3.29). Antibody induction therapy, on the other hand, raised the relative risk for cancer 4.3-fold (P = 0.004) (Table 13) and the relative risk for skin cancer 6.0-fold (P = 0.01) as compared to that of patients not treated with antibodies (see Study II, Table 4, p. 1433).

Table 13. HRs for development of cancer after liver transplantation, according to Cox proportional hazard analysis adjusted for age, gender, and time since transplantation.

	HR (95% CI)
Liver transplant indication	
Chronic liver disease	1.00 (reference)
Acute liver failure	1.20 (0.54-2.66)
Liver tumor	0.79 (0.19-3.40)
Initial calcineurin-inhibitor agent	
Cyclosporine	1.00 (reference)
Tacrolimus	0.80 (0.24-2.66)
Acute rejection	
No	1.00 (reference)
Yes, no antibody	**0.41 (0.19-0.88)**
Yes, antibody treatment	0.45 (0.14-1.50)
Mono-/polyclonal antibody therapy	
No	1.00 (reference)
Yes, for acute rejection	0.72 (0.22-2.37)
Yes, induction therapy	**4.32 (1.61-11.6)**
Retransplantation	0.84 (0.25-2.78)
Cytomegalovirus status	
Donor - Recipient -	1.00 (reference)
Donor + Recipient -	1.81 (0.21-15.9)
Donor - Recipient +	0.97 (0.13-7.36)
Donor + Recipient +	0.77 (0.09-6.61)

Bold figures highlight significant levels ($P < 0.05$).

Abbreviations: CI, confidence interval; HR, hazard ratio.

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Cancer detection and outcome

Average time from LT to detection of cancer was 61 months (range 4-172 months), and 80% of posttransplant cancers were detected at ages 45 to 74 years. All 8 lymphomas appeared at less than 7 years from LT; on average at 3 years.

Posttransplant noncutaneous cancer developed in 25 patients. In retrospective examination of their patient records, cancer was detectable during routine follow-up in only three of these cases. The one case of breast cancer was detected during routine mammography, the rectal cancer during protocol colonoscopy for the patient's ulcerative colitis, and the fibrosarcoma during a routine visit to the physician. The last patient underwent intensified follow-up due to unclear cause for hypersedimentation and hematuria. The remaining 22 patients had cancer detected after investigations of symptoms.

Of the 36 patients who developed posttransplant cancer, 14 died by the end of follow-up; of these 14 patients, 7 died due to de novo malignancy, 5 due to solid organ tumor (1 each, ovarian, pancreatic, rectal, brain lymphoma, and prostate), and 2 of PTLD. The 7 remaining patients died from causes not directly related to their cancer: one died of fungal infection 2 months after being diagnosed with Kaposi sarcoma, 2 died of kidney failure, and one each of cerebral infarction, myocardial infarction, noncompliance with pharmacotherapy, and one because of coronary disease.

CARDIOVASCULAR RISK FACTORS

Cardiovascular risk factor incidence

Of the 91 consecutive ALF patients, 14 died prior to the 5-year time point. Of these 14, 3 were on preexisting antihypertensive medication and 1 had preexisting diabetes, but none were diagnosed with pre- or posttransplant CV disease.

Final analyses, therefore, included 77 ALF patients. For prevalence of CV risk factors before and 5 years after LT see Table 14.

A general trend toward weight loss emerged at the two time-points. Hypertension increased 6-fold, and the proportion of patients on lipid-lowering medication or with diabetes more than doubled (Table 14). The 5-year post-LT incidence of new-onset hypertension was 68% (46 of 68 patients), of new-start use of lipid-lowering medication, 7% (5 of 74 patients), of new-onset diabetes, 7% (5 of 74 patients), and of new-onset obesity, 5% (3 of 59 patients). Furthermore, by 5 years after LT, 92% of patients presented with at least 1 of the 4 CV risk factors (overweight/obesity, hypertension, dyslipidemia, or IFG/diabetes); the average number of CV risk factors being 1.9 (SD 1.0). The sum of CV risk factors increased with age (see Study IV, Figure 2, p. 5).

In comparison to the age-, gender-, and residence area-adjusted Finnish general population, the prevalence of hypertension at 5 years after LT was 2.73-fold that expected (Figure 12). In contrast, the prevalence of dyslipidemia was 31% less than expected, while overweight and obesity deviated nonsignificantly from the expected.

Diabetes tended to be more prevalent among LT recipients, although not significantly so, whereas IFG was significantly less common. When added together, the number of observed cases (diabetes+IFG) was 10 and expected cases 11.

Table 14. Number of patients with cardiovascular risk factors present at listing to liver transplantation and 5 years after.

	Pretransplant	Posttransplant
	n (%)	n (%)
Overweight (BMI 25-30 kg/m²)	30 (39)	25 (32)
Obesity (BMI >30 kg/m²)	15 (19)	10 (13)
Antihypertensive medication	9 (12)	55 (71)
Lipid-lowering medication	3 (4)	7 (9)
Diabetes	3 (4)	8 (10)
Type 2 diabetes	2 (3)	7 (9)
Oral antihyperglycemic medication	1 (1)	1 (1)
Insulin	2 (3)	6 (8)
Combination of oral agents and insulin	0 (0)	1 (1)

Percentages are proportion among all 77 patients.

Abbreviation: BMI, body mass index.

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Cardiovascular disease incidence

Three patients of the study population had a history of preexisting CV disease before LT: two patients had coronary artery disease with a history of coronary artery bypass graft surgery, and one had a history of transient ischemic attack, an acute myocardial infarction, and paroxysmal atrial fibrillation. Within 5 years after LT, an additional two patients were diagnosed with CV disease, including one with atrial fibrillation. The other patient underwent percutaneous transluminal coronary angioplasty and stenting 6 months after LT, and coronary artery bypass graft surgery 3 years after LT, and, moreover, was diagnosed with non-ST-elevation myocardial infarction 5 years after LT. Both patients had hypertension and dyslipidemia post-LT, one was obese, but neither had diabetes.

Influences upon posttransplant cardiovascular risk

The initial CNI used (tacrolimus or cyclosporine), steroid use at 5 years, history of retransplantation, history of acute rejection, antibody therapy, and graft steatosis were individually tested by calculation of relative risk ratios, for any association with the appearance of new-onset hypertension, diabetes, dyslipidemia, or overweight/obesity. Of these variables, the only statistically significant associations were between antibody therapy and hypertension (relative risk 1.49, 95% CI 1.15-1.94) and between antibody therapy and diabetes (relative risk 6.43, 95% CI 1.18-34.9) (see Study IV, Table 3, p. 5).

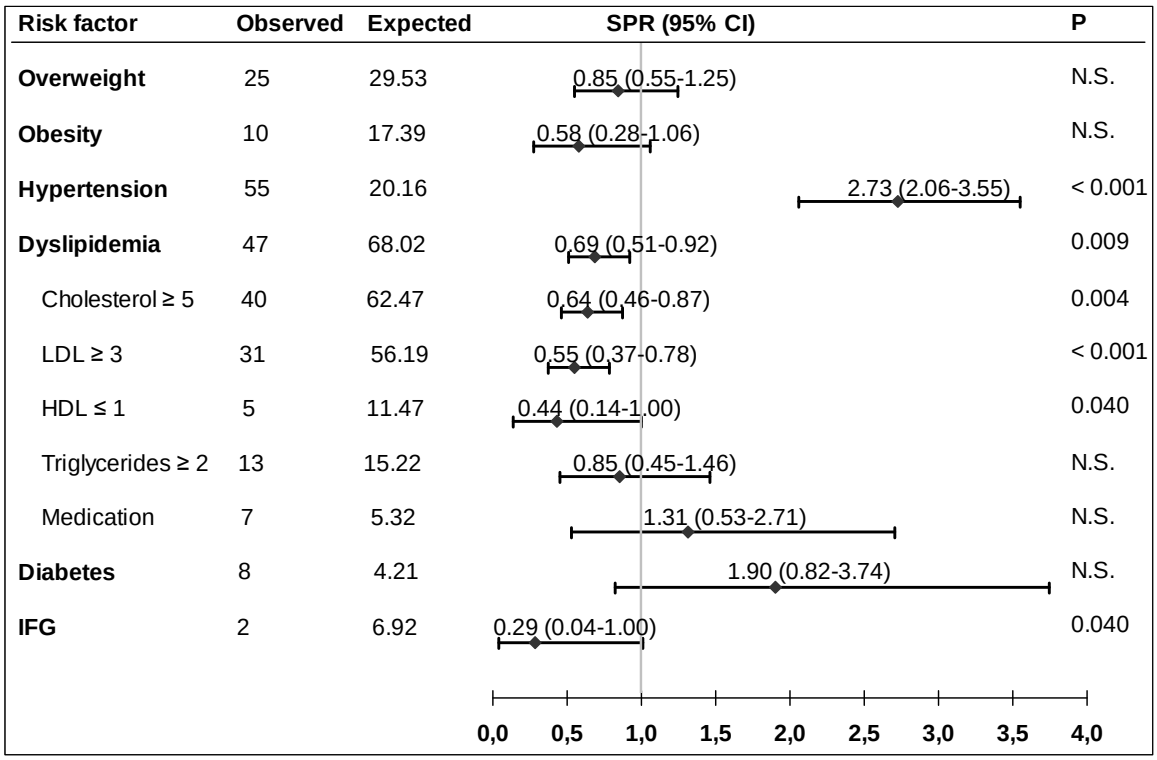

Figure 12. *Observed and expected numbers of cases with risk factor present, and standardized prevalence ratios (SPR) with 95% confidence intervals (CI), among the 77 patients 5 years after liver transplantation. N.S., not significant. Reproduced by permission of the publisher, Lippincott, Williams & Wilkins.*

QUALITY OF LIFE OUTCOMES AND EMPLOYMENT

HRQoL compared with that of the general population

On average, LT recipients demonstrated 15D scores similar to those of the matched general population (Table 15). Although this difference was statistically significant, it did not reach the level of 0.03 that is considered clinically relevant (Table 15). In the individual HRQoL dimensions, LT recipients exhibited statistically significantly lower 15D scores on the dimensions of moving, elimination (urination, defecation), usual activities (keeping up with work, studies, household activities, leisure activities), and sexual activity (Table 15; see also Study III, Figure 1, p. 68). Conversely, LT patients displayed higher 15D scores on the dimension of discomfort and symptoms. The groups did not differ significantly on the other dimensions.

Table 15. Significant differences in average 15D scores between liver transplant recipients and the Finnish general population.

	Liver transplant patients, mean (SD)	**General population**, mean (SD)	**Difference in mean levels between groups (95% CI)**
Overall 15D score	**0.889 (0.103)**	**0.907 (0.089)**	**0.018 (0.007-0.029)**
Lower mean scores for patients:			
Moving			0.040 (0.022-0.058)
Sleeping			0.029 (0.010-0.048)
Elimination			0.048 (0.027-0.069)
Usual activities			0.066 (0.044-0.088)
Sexual activity			0.045 (0.020-0.070)
Higher mean scores for patients:			
Discomfort and symptoms			0.037 (0.014-0.059)

A difference of 0.03 between groups regarding the mean 15D overall score is considered clinically relevant.

Various influences upon posttransplant HRQoL

Age and gender. When adjusted for patient's age at the time of the study, gender had no significant effect on 15D scores. Conversely, a small but statistically significant decline in 15D scores occurred by age (regression coefficient -0.001, 95% CI -0.002-0.000), when adjusted for gender. Age at LT, on the other hand, did not influence 15D scores significantly, when adjusted for current age and gender (regression coefficient -0.000, 95% CI -0.002 – 0.003).

Retransplantation. A history of retransplantation altered 15D scores nonsignificantly in age- and gender-adjusted analysis (regression coefficient -0.029, 95% CI -0.073 – 0.014).

Follow-up period. Patients who had undergone LT less than 1 year prior to the study reported worse 15D scores than did patients with a longer time since transplantation (see Study III, Figure 2, p. 67). Conversely, patients at 1 to 5 years since LT exhibited the highest 15D scores. Mean 15D scores did, however, subsequently decrease gradually over time (see Study III, Figure 2, p. 67). With current age and gender standardized, a slight inverted U-shape relationship between HRQoL and survival time after LT remained, but this relationship was insufficiently robust to be statistically significant (see Study III, Table 2, p. 68). Nor was the coefficient of linear survival time significant (-0.001, 95% CI -0.003-0.002).

Indication. On average, CLD-, ALF-, and liver-tumor patients exhibited similar 15D scores, respectively, 0.892 (SD 0.101), 0.883 (SD 0.102), and 0.877 (SD 0.131). When compared with the age- and gender-standardized general population, however, the ALF group deviated somewhat more from the expected 15D scores than did CLD- or liver-tumor patients (Table 16).

Employment status and working capacity

A third of all patients at the time of the study were employed (see Study III, Table 3, p. 69), and their proportions did not differ by indication: percentages were 36% in the CLD, 34% in the ALF, and 32% in the tumor groups. Among the 64% of patients unemployed, the majority (56%) were unemployed due to early retirement, whereas 31% were unemployed due to age-limit retirement (see Study III, Table 3, p. 69).

Table 16. Deviation in 15D scores by indication group from that expected in the age- and gender-adjusted Finnish general population. Analyses performed by linear regression.

	Linear regression coefficient (95% CI)	*P*
General population	reference	
Chronic liver disease	-0.011 (95% CI -0.021 to -0.001)	0.04
Acute liver failure	-0.024 (95% CI -0.042 to -0.005)	0.01
Liver tumor	-0.012 (95% CI -0.050 to 0.026)	0.54

At the time of the study, 268 patients were of working age (20 to 65 years old). Of these 268, 119 (44%) were employed, and these patients displayed both statistically and clinically significantly better 15D scores when adjusted for age and gender, than did working-age patients who were unemployed,. The difference in average 15D score between these two groups was 0.07 (95% CI 0.05-0.10).

Although 43% of patients had returned to work after LT (see Study III, Table 3, p. 69), a return to work displayed an apparent age-dependent trend, with younger LT patients being more likely to return to work (Figure 13). Younger patients were also more often able to return to work after LT in less than 6 months (Figure 13).

Comparison of indication groups revealed that a larger proportion of the 258 CLD patients returned to work in less than 6 months, 46 (18%), than of the 76 ALF patients, 8 (11%). The difference between these proportions (0.07, 95% CI -0.03-0.15) was, however, nonsignificant. Liver-tumor patients were excluded from analysis due to their small number.

Despite the finding that less than half the patients had returned to work after LT, 87% of recipients experienced better working/functional capacity than experienced one week before LT (Table 17). In CLD and ALF patients, proportions were similar: 90% and 81%, but in liver-tumor patients the proportion was significantly less: 72% (P = 0.012). None of the patients transplanted at ages 20 years or less reported that their working/functional capacity at the time of the study had deteriorated compared to that before LT. In the two other age-groups, proportions of patients reporting improved working/functional capacity were similar: among the 168 aged 20 to 50, 147 (88%), and among the 153 older than 50, 131 (86%).

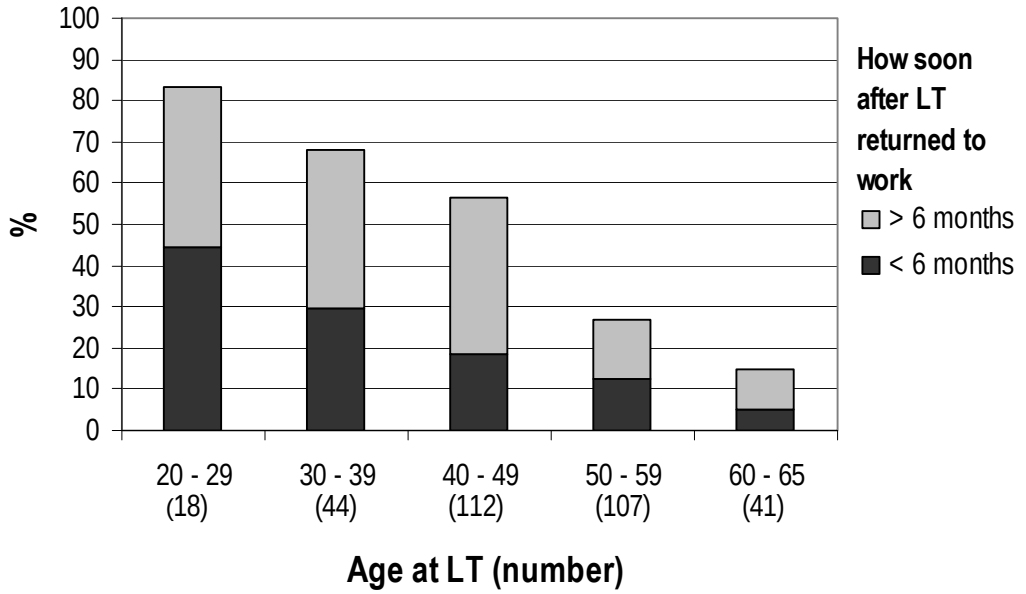

Figure 13. *Percentages of liver transplant (LT) patients who returned to work after LT according to age at time of LT. Only working-age patients included (20-65 at LT). Proportions inside the columns show how soon after LT they had returned to work. Reproduced by permission of the publisher, John Wiley & Sons, Inc.*

Table 17. Patients' estimation of their change in working/functional capacity from that at 1 week before liver transplantation to that at the time of the study.

	n	Answer
Much better	*258*	77%
Slightly better	*32*	10%
Unchanged	*19*	6%
Slightly worse	*15*	4%
Much worse	*9*	3%

Discussion

METHODOLOGY

Studies I to IV reveal, in a retrospective and partly cross-sectional fashion, the frequency of renal dysfunction, cancer, and cardiovascular risk, as well as the quality of life and employment status, following LT. These studies include virtually all LT patients transplanted in Finland and alive up to 25 years from LT, with only one patient lost to follow-up. The single-center setting, the intensive follow-up protocol by the transplant center, and the prospective national liver transplant registry, moreover, provide precise demographic and clinical data relevant for analyses. Major drawbacks, however, include the retrospective design, which does not allow reaching with certainty conclusions on the associations found. For instance, declining renal function or rising blood pressure, glucose, or lipid levels may call for adjustments in the patient's pharmacotherapy, but this is difficult to ascertain retrospectively. Subgroup analyses were, moreover, in part limited by inadequate statistical power, as evidenced by their width of confidence intervals. Where results were nonsignificant, the chance of a type II statistical error must be kept in mind.

The principal strengths of the studies include the precise data obtained from a comprehensive cohort of patients at many time-points. In Studies II, III, and IV, an additional advantage is the accurate comparisons with age- and gender-matched controls who accurately represent the Finnish general population as a whole.

Renal function measurement. Assessing renal function in end-stage liver disease patients and in LT recipients is challenging, due to the inaccuracy of all commonly used parameters.[151,152] Direct measurement of GFR by methods such as inulin clearance – the gold standard – is impractical and expensive and has not been used at our center. The most practical estimation of GFR is achieved by creatinine-based formulas. Although the Modification of Diet in Renal Disease Study equation has recently demonstrated slightly better accuracy than the Cockcroft–Gault equation [151] and has been used in many of the recent studies,[137,139,224,225] the latter was our choice in the present study due to its wide use in clinical practice.

Cardiovascular risk factors. In addition to the potential bias resulting from defining hypertension solely by use of medication, the study ignored some of the other CV risk factors such as tobacco use and family history.

HRQoL assessment. Any quantification of quality of life is noninformative if subjects are not compared to a reference population. To permit such a comparison, we chose a generic HRQoL instrument. The excellent availability of reference data from the Finnish general population made the 15D instrument best. The lack of studies utilizing this instrument, however, hampers comparison of HRQoL results to those in other series. With a response rate exceeding 88%, the representativeness of the patient population was excellent, and the sample is considered of a size achieving sufficient statistical power for reliable comparison with controls. As in all of the other series in this field, bias naturally results from the exclusion of deceased patients.

Employment assessment. The reliability of the employment results are limited by the ad hoc nature of the questionnaire as well as by definition issues: Part-time versus

full-time employment or whether patients returned to their original work and salary level were not distinguishable.

Cumulative incidence. Incidence of the complications studied is largely dependent on length of time after transplantation, so actuarial incidence rates among patients with differing follow-up times are noncomparable across studies. One means of enabling comparison across studies for dichotomous endpoints such as CKD and cancer is by calculating cumulative incidence rates. CV risk factors, however, are often transient, particularly in the early posttransplant period, and assessing cumulative incidence is thus less suitable. To adjust both for follow-up time and for early transient disruptions in blood pressure, glucose, and lipid levels, the point prevalence of CV risk factors at 5 years after LT required assessment.

Control data for the studies were generally precise and reliable. Study IV, however, risked bias because whereas patient data were collected during 1992 to 2008, control data were collected during 2000 to 2001. The results in that study therefore do not account for population trends in the prevalence of CV risk factors between 1992 and 2008.

Standardized ratios (SIR and SPR) and regression analyses allow for reliable comparison of two populations of markedly different size, and also compensate for any differences in gender- or age distribution between populations. In Study IV, comparison was further matched for area of residence, because the prevalence of CV risk factors in Finland exhibits considerable local variation. Prevalence of actual cardiovascular disease was not compared to that of the general population because reliable comparison would likely necessitate a follow-up longer than 5 years to avoid a falsely low disease prevalence among patients.

INCIDENCE OF LONG-TERM NONHEPATIC COMPLICATIONS

Renal dysfunction. Many studies have employed diverse definitions of renal dysfunction and CKD,[140,141,143,144] and this severely hampers interpretation and comparison of results. The Kidney Disease Outcomes Quality Initiative Guidelines have recently developed a widely acknowledged GFR-based classification,[153] the one adopted in the present study.

The cumulative incidence of CKD was 10% at 5 years and 16% at 10 years, almost half that observed by Ojo and colleagues[139] in their review of 36 849 LT patients in the USA. By applying an equivalent definition of CKD, they reported a cumulative incidence at 5 years following LT of 18% and at 10 years, of above 25%. A single-center study from Ireland,[224] on the other hand, reported a 10-year cumulative incidence of severe renal dysfunction (GFR <30 ml/min) of 7%, whereas single-center reports from the USA have found 5-year cumulative incidences of CKD from 8%[137] up to 22%.[225] Because the latter study was performed in the era after implementation of MELD-based organ allocation, more prevalent pretransplant renal impairment emerges as one potential explanation for their higher posttransplant CKD incidence. The variation in reported cumulative incidences may also be explained by differing population characteristics; in the Finnish LT population viral hepatitis and

alcoholic cirrhosis – both associated with renal dysfunction – are less frequent than at most centers. Furthermore, our patient population included proportionally more ALF patients (23%) than in most nations, where about 10% are acute patients. Finally, the present study included only first transplants; inclusion of retransplants would likely result in somewhat higher CKD incidence.

ESRD, cumulatively affecting 2% of our patients by 5 years and 3% by 9 years, exhibited a slightly lower incidence rate than reported in other studies; Gonwa and colleagues[140] reported a cumulative incidence of 3% by 5 years and Cohen and colleagues[226] 10% by 10 years.

Cancer. The present study – estimating that one in six patients will develop some form of malignancy by 20 years after transplantation – confirms that for LT, cancer is a considerable long-term complication. The cumulative incidence rate of 13% at 10 years and 16% at 20 years is, however, markedly lower than that reported by others (Table 5). Due to exceptionally precise cancer data in Finland, bias due to failure to notice some neoplasias does not explain this lower cancer rate. The difference might, however, be attributed to diverse patient population characteristics and to ethnic differences in various general populations. The infrequent utilization of antibody induction at our institution may also explain the lower cancer risk. Additional differences between studies are discussed in detail later.

As in other reports (Table 5), nonmelanoma skin cancer and non-Hodgkin lymphoma predominated; accounting for 26% and 21% of all malignancies observed. Nonmelanoma skin cancer occurred mostly in older patients, and its risk did not vary between genders or by time after LT. This highlights the importance of regular skin exams at all posttransplant time-points, especially among the older recipients.

Conversely, non-Hodgkin lymphoma more frequently affected males and patients transplanted at younger age, and more commonly developed early after LT.

Cardiovascular risk factors. The present series leads to the estimate that among any 10 ALF patients having undergone LT, within 5 years, 1 has diabetes, 5 are overweight or obese, 6 have an abnormal lipid profile, and 7 are on antihypertensive medication. Whereas prevalence rates for hypertension and dyslipidemia are at the higher end of those reported in the literature, rates of obesity and diabetes are at the lower end.[12,167,186,189-192] The incidence of new-onset diabetes, new-onset obesity, and new-onset need for of lipid-lowering medication, furthermore, emerged as somewhat more infrequent than in other reports.[12,64,167,186,189-192] Whereas all the other series have examined CLD patients, the present study by intention included only ALF patients, because the health status of ALF patients shortly before transplantation is more closely comparable with that of the general population. Any deviation from population norms occurring after transplantation in the ALF group regarding the cardiovascular risk profile should thus be more attributable to transplant-related factors alone.

CLD patients generally differ from our ALF patients in usually being older, in being more likely infected with HCV, and in displaying more co-mordibity and pre-existing CV risk factors, and perhaps in having hepatogenous diabetes.

Cancer. According to the present study, LT patients have a 2.6-fold higher cancer incidence than does the Finnish general population. Despite these cumulative incidence rates being markedly lower than in other studies, the SIR was similar to others' (Table 6). Besides lymphoma and skin cancer, we did not observe other cancer types with significantly elevated SIRs, although some others have observed elevated SIRs for colorectal, pulmonary, and oropharyngeal cancers, as well as Kaposi sarcoma (Table 6).

Table 18 assembles noteworthy differences between these studies that may explain some of the variation in their SIRs. Some series have not included children, whose relative cancer risk is the highest. The LT population of most institutions is, on average, also somewhat older than that in Finland. Elevated SIRs for colon cancer are mostly from locales where PSC is common, and increased SIRs for oropharyngeal neoplasias and lung cancer where alcoholic cirrhosis is common (Table 18).[12,171] HCV is, furthermore, linked to higher rates of PTLD,[176] and in our population the number of patients with HCV is extremely low. Furthermore, lengths of follow-up differ, and relative cancer risk decreases along with longer follow-up times.

Variation in risk for Kaposi sarcoma is likely explained by the strong regional variation in seroprevalence of human herpes virus 8: low in Finland and high, for instance, in Italy.[168]

Risk for cancer relative to that of nontransplant controls of the same age and gender was higher for male LT patients than for their female counterparts. A likely reason is that PSC and alcoholic cirrhosis are more common among male patients.

Cardiovascular risk. Among the ALF patients, hypertension exhibited a 2.7-fold higher prevalence than for the controls, whereas dyslipidemia and IFG were significantly less prevalent among the patients. Based on this, the pharmacotherapy used in LT patients clearly had caused hypertension, but it is possible that the often-reported increased risk for diabetes in particular is related more to other factors.

Our findings regarding diabetes and IFG imply that LT-related immunosuppressive treatment may elicit diabetes in susceptible patients – patients who in the absence of transplantation and immunosuppressive treatment might suffer only IFG. This finding therefore emphasizes the essence of assessing established risk factors for diabetes in clinical practice. It is also possible that transplant patients, as compared with controls, adopt a healthier life-style after LT, and this could explain, for instance, their lower prevalence of dyslipidemia and obesity.

Only Sheiner and colleagues[167] assessed CV risk factors by a similar SPR method, hence allowing a comparison of theirs with our data (Table 19). Increased risk for hypertension in their and our study is similar, possibly reflecting the use of cyclosporine as opposed to tacrolimus as the main CNI agent at both institutions (Table 19). The Sheiner group report also includes actual blood pressure measurements, and their inclusion likely elevates prevalence figures for hypertension relative to control figures. The reason may be that hypertension in the closely followed LT population will more likely be treated with drug therapy.

Table 18. Differences between cancer findings in studies reporting standardized incidence ratios (SIRs).

Author, year, country	Sheiner et al,[167] 2000, USA	Haagsma et al,[159] 2001, The Netherlands	Oo et al,[107] 2005, UK	Jiang et al,[163] 2008, Canada	Baccarani et al,[168] 2009, Italy	Finkenstedt et al,[162] 2009, Austria	**Åberg et al 2008 (Study II), Finland**
Number of patients	121	174	1778	2034	417	779	540
Age at transplantation, years	Median 48	Median 43	Median 50	N.A.	Median 52	Mean 53	Mean 43
Follow-up, months	Median 65 (53-86)	Median 61 (18-225)	Median 65 (33-77)	N.A.	Median 83	Median 49 (0-288)	Mean 76 (0-288)
Exclusions	<5-year survivors	<1-year survivors	None	<1-month survivors, previous cancer	<1-month survivors, previous cancer	None	None
Proportion of children	<5%	0%	0%	>13%	0%	0%	14%
Proportion of alcoholic cirrhosis	N.A.	6%	10%	N.A.	N.A.	24%	10%
Proportion of viral hepatitis	37%	N.A.	21%	N.A.	N.A.	35%	3%
Proportion of PSC	9%	17%	N.A. (autoimmune-related, 46%)	10%	N.A.	<8%	14%
Overall SIR	3.9	4.3	2.1	2.5	2.6	1.9	2.6
Nonmelanoma skin cancer excluded from overall SIR	Yes	No	No	Yes	Yes	Yes	No
SIR: Colon cancer	N.S.	Increased	Increased	Increased	N.S.	N.S.	N.S.
SIR: Oropharyngeal cancer	N.S.	None observed	N.S.	N.S.	Increased [a]	Increased	N.S.
SIR: Lung cancer	N.S.	N.S.	Increased	N.S.	N.S.	Increased	N.S.
SIR: Kaposi sarcoma	N.S.	N.S.	None observed	N.A.	Increased	N.S.	N.A.

[a] 83% transplanted for alcoholic cirrhosis

Abbreviations: N.A., not available; N.S., not significant, PSC, primary sclerosing cholangitis

Sheiner and colleagues [167] noted a higher SPR for diabetes, despite their using a slightly higher glucose level in defining diabetes (Table 19). This difference may be attributed to their patients' more frequent pre-existing diabetes, to their greater proportion of HCV infection, and to their more frequent long-term use of corticosteroids; such steroid use may in part also underlie their slightly higher SPR for both dyslipidemia and excessive weight. Interestingly, the rather high prevalence of pre-existing overweight/obesity among our ALF patients – as compared with their populations' – decreased following LT, with posttransplant prevalence tending to be lower than expected. This contrasts with the weight gain typically seen among CLD patients after LT.[167,194]

Table 19. Comparison between present findings for cardiovascular risk factor prevalence and findings of Sheiner and colleagues.[167]

Characteristics	Sheiner et al,[167] 2000, USA	Åberg et al 2009 (Study IV), Finland
Population assessed	5-year survivors	Acute liver failure patients
Time-point of assessment	≥5 years (range 4.4-7.2)	5 years
Time-period of transplantation	Prior to 1991	1987-2004
Number of patients	96	77
Age at transplantation, years	Median 48	Mean 46
Characteristics of patients	>90% chronic liver disease patients; 33% hepatitis C virus	All acute liver failure patients
Main calcineurin inhibitor used	Cyclosporine (80%)	Cyclosporine (86%)
Proportion on long-term steroid therapy (dose)	98% (median prednisone 0.04 mg/kg/day)	42% (mean methylprednisolone 2.9 mg)
Cardiovascular risk factors		
Hypertension, SPR (95% CI)	3.1 (2.4-3.9)	2.7 (2.1-3.6)
Pre-existing, %	6%	12%
Definition	BP >140/90 mmHg consecutively or >160/100 mmHg once	Antihypertensive medication
Diabetes, SPR (95% CI)	6.0 (4.2-8.4)	1.9 (0.8-3.7)
Pre-existing, %	18%	4%
Definition	fP-glucose >7.8 mmol/L twice	fP-glucose >7.0 mmol/L or antidiabetic medication
Overweight or obesity, SPR (95% CI)	1.2 (0.9-1.6)	0.75
Pre-existing, %	17%	58%
Definition	Men: BMI ≥27.8 kg/m², Women: BMI ≥27.3 kg/m²	BMI ≥25 kg/m²
Dyslipidemia, SPR (95% CI)	0.9 (0.6-1.4)	0.7 (0.5-0.9)
Pre-existing, %	Not reported	4% (presence of medication)
Definition	Serum cholesterol ≥6.22 mmol/L	Fasting cholesterol ≥5.0 mmol/L, LDL ≥3.0 mmol/L, HDL ≤1.0 mmol/L, triglycerides ≥2.0 mmol/L, or lipid-lowering medication

Abbreviations: BMI, body mass index; BP, blood pressure; fP-glucose, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

PRE- AND EARLY POSTTRANSPLANT RENAL FUNCTION TO DETERMINE COURSE OF LONG-TERM RENAL FUNCTION

In LT recipients, a variety of potential factors may contribute to long-term renal dysfunction, factors tha may originate from the pre-, peri-, or posttransplant periods. In agreement with others' findings,[137,142,226,227] the most striking fall in renal function occurred between pretransplant and 1-year levels. This finding, together with the strong correlation between renal function at 1 year with function at up to 10 years, suggests that pre- and perioperative factors to a large extent determine long-term renal function. In particular, the better renal-function predictive value of GFR at 1 year than pretransplant (a finding largely supported by others[138,140,141,144,224,226,227]) emphasizes the contribution of perioperative acute kidney injury to later renal dysfunction and to CKD. Several perioperative events, including clamping of the caval vein, hemodynamic instability, blood loss, infection, high-dose CNI, and other drug nephrotoxicity, may cause reversible or irreversible kidney damage. By the end of the first posttransplant year, the course for later renal function will have become apparent. For example, Ojo and colleagues[139] noted a 2-fold higher CKD risk among patients who had experienced postoperative acute renal failure.

Although less marked, a steady gradual decline in renal function continued during the following 10 years. Years 1 to 10 also demonstrated a gradual shift from stage 1 and 2 renal dysfunction to increased proportions of stage 3 and 4.

In light of this, minimizing or avoiding long-term use of nephrotoxic drugs such as CNIs for patients with noticeable renal impairment at 1 year may prevent progression to CKD or ESRD. Less clear, however, is the need for such CNI-avoidance in the subset of patients with well-preserved renal function at 1 year. This neglected issue deserves further investigation.

Pretransplant renal impairment. Regarding pre-existing renal dysfunction, our findings suggest an indication-dependent pattern of reversibility in the sense that, following successful LT, even severe renal impairment in ALF patients often resolves, whereas moderate to severe impairment in CLD patients is most likely irreversible. With the same pattern, pretransplant GFR showed a moderate correlation with long-term renal function in the CLD group.

This difference between CLD and ALF groups may be due to dissimilar etiologies underlying pretransplant renal dysfunction, or due to differences in the duration of such impairment. The etiology of pre-existing renal dysfunction was not investigated here, because few kidney biopsies were performed prior to LT. It can be speculated, however, that among CLD patients, such liver disease-independent kidney diseases as diabetic nephropathy or hypertensive kidney disease – both often irreversible – are more prevalent. Another explanation may be that a greater proportion of CLD patients are affected by type II hepatorenal syndrome, whereas type I is likely to predominate to complicate the course of ALF. The more slowly developing type II hepatorenal syndrome may prove less reversible – either through its longer duration or by its nature. We found that CLD patients required 3-fold longer dialysis prior to LT, but the actual duration of pretransplant renal impairment remained unassessed.

CANCER AND CARDIOVASCULAR RISK IN RELATION TO IMMUNOSUPPRESSION REGIMEN AND REJECTION EPISODES

Antibody induction therapy. Antibody therapy in the induction phase was associated with a 4-fold overall cancer risk, in particular, with a 6-fold risk for skin tumors. On the other hand, no increased cancer risk was evident when antibodies served as treatment for steroid-resistant rejection. During the period of our study, ATG (for induction) and OKT3 (for rejection) have been the main agents employed at our institution. Although it is well established that both of these preparations cause a risk for lymphoma,[85,173] to our knowledge, no relationship has been reported with skin cancers. In addition, even if the development of nonmelanoma skin tumors strongly correlates with immunosuppression per se, the link is considered stronger for chronic maintenance immunosuppression than for short periods of intense immunosuppression, as with the use of antibodies.[85,179] Any association between antibody induction therapy and skin cancer does therefore deserve future scrutiny. The nature of the association between antibody use and development of new-onset hypertension and diabetes also remains unclear.

Maintenance immunosuppression. In addition to cyclosporine's being the predominating CNI agent used at our institution, some patients have received both cyclosporine and tacrolimus sequentially, and in a retrospective study the reason for conversion is difficult to ascertain. For these reasons, a proper comparison between cyclosporine and tacrolimus is difficult to carry out. No obvious differences between these two were, however, observed.

Although steroid withdrawal definitely conveys beneficial metabolic and CV effects,[12,96] when comparing patients on steroids at 5 years to patients not using steroids at the same time point in Study IV, no such benefit was evident. This finding may, however, have at least two causes. First, all patients received steroids in the induction phase, and this may already elicit most of the CV derangements that, in general, steroids elicit. Second, the steroid doses received at the 5-year time-point were low: on average a daily 2.9 mg methylprednisolone. It is possible that such small steroid doses may cause no additional CV risk.

Acute rejection. Interestingly, a history of acute rejection paralleled a 59% lower cancer incidence; one most strongly correlated with lymphomas. In this retrospective study setting, any explanation is difficult to provide. Patients who experience one or more rejection episodes may have been less immune suppressed, and, thus, at lower risk for cancer. The majority of rejection episodes, however, occur within 3 weeks, and differences in posttransplant immunosuppression levels during such a short period are perhaps unlikely to explain such differences in cancer risk.

QUALITY OF LIFE AND EMPLOYMENT OUTCOMES

Although renal dysfunction, cancer, and various CV risk factors become increasingly prevalent after LT and often require medication, the HRQoL of patients remains comparable with that of the general population. Patients' overall HRQoL differed in no clinically important ways from controls' HRQoL. In some physical dimensions – including moving, sleeping, elimination, usual activities, and sexual activity – however, LT patients displayed statistically significant deficits, but no corresponding level for a clinically important difference has been determined for the individual dimensions of the 15D instrument, as opposed to that for overall 15D score. LT patients, moreover, did not differ from controls in mental and psychological dimensions, and scored better on the dimension of discomfort and symptoms.

A recent meta-analysis[22] of 16 cross-sectional studies comparing HRQoL of LT patients with that of nontransplant control populations by means of the Short Form-36 instrument likewise concluded that LT recipients displayed inferior ratings mainly in physical dimensions. The largest effect sizes were in physical functioning, role physical, energy, and general health,[22] with pain and mental health demonstrating nonsignificant differences. These results would imply that novel posttransplant rehabilitation interventions should focus primarily on physical functioning.

Longitudinal studies for the most part display an improvement in HRQoL pre- to posttransplant, but follow-up is usually limited to 1 or 2 years.[22,108-111,113-116] We demonstrated in a cross-sectional fashion, with patients at different points of follow-up, that although long-term survivors exhibited somewhat worse HRQoL than did medium-term survivors, this difference was due to their age. Increasing follow-up, conversely, seemed to produce no additional fall in HRQoL scores.

Despite the improvement in HRQoL noted by others,[22,108-111,113-116] and the improvement in working capacity reported by the majority (87%) of our recipients, only 43% of LT patients returned to work. Among those under 40 at LT, however, approximately 70 to 80% returned to work. In more than half of those unemployed after LT, early retirement was the explanation. As in other reports of quite similar overall posttransplant unemployment rates,[22,117,119,122,123] we did not assess the medical conditions or complications underlying early retirement. Such assessment could facilitate prediction of posttransplant unemployment and enhance development of proper rehabilitation interventions. Nonetheless, considering the highly age-dependent trend toward returning to work and the frequency of early retirement, our findings would support a strategy of performing LT at an earlier disease stage; specifically, before the disease has progressed so far that the patient is incapable of gainful employment and receives a disability pension. Early retirement before transplantation may restrain enthusiasm for returning to work, especially among older recipients, even if LT restores working capacity.

FUTURE CONSIDERATIONS

Until induction of allograft tolerance in LT eventually makes immunosuppression unnecessary, achieving adequate immunosuppression and simultaneously avoiding chronic drug toxicity remains a major challenge. Deciding on the best

immunosuppression regimen for the induction phase and then for early and long-term maintenance therapy requires characterization of the patient's individual risk profile and tailoring of the immunosuppression regimen accordingly. The present work brings some new clarification to this subject, but at the same time raises some new questions.

Risks and benefits of managing specific long-term complications by adjustments in immunosuppression therapy versus use of other means merit attention. Regarding traditional CV risk factors such as hypertension, thresholds for initiating pharmacotherapy and target levels for treatment await specific data for the LT population. Given the critical influence of CV disease on long-term outcome in this population, prospective studies would be appropriate.

In the majority of cases, pre-existing renal impairment is, in CLD patients, unlikely to resolve. Studies investigating the etiology of such pre-existing dysfunction by kidney biopsy are, however, lacking. Awareness of the effects of etiology and duration of pretransplant renal dysfunction on its reversibility would, especially in CLD patients, aid in predicting post-LT renal function, and might assist in the difficult decision to proceed to combined liver-kidney transplantation.

Especially in LT patients with marked renal impairment at 1 year, CNI-minimization seems appropriate. On the other hand, the progression of mild to moderate renal dysfunction to CKD or ESRD is probably affected by factors other than CNI, but these remain uncharacterized. Chronic CNI nephrotoxicity in patients who have preserved renal function at 1 year but who are on long-term CNI also remains unclear.

Regarding risk for malignancy, larger cohorts will better clarify which cancer types other than skin cancer and lymphoma may show an elevated incidence. Such studies should also further scrutinize the association shown here between acute rejection and cancer risk.

Whether more intense cancer surveillance would have detected our patients' malignancies at earlier stages remains unclear, as is whether survival would have been extended. Due to the small number of cancer cases in most such series, it is difficult to compare outcomes for specific neoplasias with outcomes in the nontransplant population. Limited data make it equally problematic to develop for the LT population any specific cancer-screening guidelines. With time, however, accumulating data from well-performed retrospective reports will elucidate these issues.

One fundamental goal of LT is to restore the patient's ability to return to work. A considerable proportion of patients, however, remained unemployed after LT. Current impressive outcomes in terms of survival and quality of life may justify transplanting patients at an earlier disease stage in order to support those remaining in the work force. Effective rehabilitation interventions encouraging a return to work should also be sought.

With a longer perspective, identification of patients exhibiting allograft tolerance who may be completely weaned off immunosuppression, as well as the induction of such tolerance, emerge as important targets for the future. In an even longer view, hepatocyte transplantation or tissue engineering may provide an alternative to, or altogether replace, whole-liver transplantation.

Conclusions

Liver transplantation is a life-saving intervention that may change life expectancy for the majority of patients from a year or even a day to more than two decades. Although chronic complications are quite common and accumulate in the long term, the quality of life of liver transplant recipients, even over decades, nonetheless remains comparable with that of the general population.

The following specific conclusions can be drawn:

1. After liver transplantation, renal function generally deteriorates. The cumulative incidence of chronic kidney disease is 10% at 5 years and 16% at 10 years. Chronic renal impairment often has a multifactorial etiology, and the degree of irreversibility of pre- and perioperative kidney insults usually become evident by the end of the first posttransplant year, determining the course of later renal function. Pretransplant renal dysfunction is more often irreversible in patients with chronic liver disease than in patients with acute liver failure.

2. Among patients transplanted for acute liver failure, 92% exhibited at least one cardiovascular risk factor at 5 years after transplantation: 71% received antihypertensive therapy, 61% had dyslipidemia, 10% had diabetes, 32% were overweight, and 13% obese. Compared with a matched Finnish general population, patients displayed a 2.7-fold hypertension prevalence, but significantly less frequently dyslipidemia or impaired fasting glucose.

3. The cumulative incidence of malignancy increased from 5% at 5 years to 13% at 10 years. Liver transplant patients were subject to a 2.6-fold cancer risk as compared with the general population's. This elevated risk was mostly attributable to nonmelanoma skin cancer and lymphoma. Antibody induction therapy was associated with a 4.3-fold cancer risk (especially skin cancers), whereas acute rejection not requiring antibodies was associated with a lower cancer risk.

4. Health-related quality of life was generally comparable among liver transplant patients and the Finnish general population. Patient quality of life scores decreased with age, but not with increasing time since transplantation. Although the majority of patients (87%) reported improved posttransplant working capacity, less than half (43%) of all patients had returned to working life – their most frequent reason being early retirement. Employment after transplantation exhibited an age-dependent trend, with the younger patients returning to work in 70% to 80% of cases. Being employed generally indicated better quality of life.

Liver transplantation and associated immunosuppression therapy aggravated risk for renal dysfunction, cancer, and hypertension, and seemed linked with diabetes in susceptible patients, but was associated with neither dyslipidemia nor weight gain.

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