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Liver transplantation in primary sclerosing cholangitis: timing, changing indications, results, and complications

ADADEMIC DISSERTATION

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1 Abstract

Background. Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease. Patients with PSC are at high risk of developing cholangiocarcinoma (CCA). The only curative treatment for PSC is liver transplantation (LTx), however, CCA is considered a contraindication. In 2001, our center started liver transplantations for patients with dysplasia in endoscopic retrograde cholangiography (ERC) brush cytology samples. These patients were considered to be at increased risk of developing CCA. This thesis compares LTx results in two groups of PSC patients with different indications.

Patients and Methods. This thesis includes all 199 consecutive PSC patients transplanted in the Helsinki University Hospital between 1984 and 2020. They were divided into two LTx indication groups, either symptomatic end-stage liver disease (n=151, classical indication) or suspicious findings in ERC brush samples (n=48, premalignant indication). Brush sample cytology and cytometry were compared with final histopathological findings of the explanted liver (I). Health-related quality of life (HRQoL) between the two indications were compared before and after transplantation (II). The 15D questionnaire was used to measure HRQoL. Histological findings in protocol graft biopsies of PSC were compared with another autoimmune disease, primary biliary cholangitis (PBC) (III). Complications after LTx were studied between the two PSC patient indications (IV). Comprehensive complication index (CCI®) was calculated and

analyzed between the two indications. Data for the studies were collected from electronic patients records and the Finnish Liver Transplantation Registry.

Results. Brush sample cytology and cytometry were compared with the histology of explanted liver in 101 patients: 66 patients with classical indication and 35 with premalignant indication. Cytology without flow cytometry was suspicious in 9 patients (14%) with classical indication and in 17 patients (49%) from the premalignant group. When the cytology findings were combined with flow cytometry, they were found to have 68% sensitivity and 86% specificity for malignant explanted liver histology. Ten-year survival was 91% in the premalignant group.

HRQoL results were from 48 PSC patients both pre-LTx and post-LTx (II). The premalignant group included 16 and the classical group 32 patients. HRQoL remained high after LTx in the premalignant group and was almost at the level of the age- and gender-standardized general population.

Protocol biopsies presented frequent histopathological findings in the grafts despite normal biochemistry (III). More than one abnormal histopathological finding was in 43% of PSC patients and in 62% of PBC patients. However, PBC patients had a longer follow-up. Immunosuppression was reduced based on protocol biopsy in 10% of patients and increased in 6% of patients. Findings leading to increase immunosuppression included significantly more portal, endothelial, interphase, and lobular inflammation.

All consecutive PSC patients (n=199) transplanted by the end of 2020 were included in the study to analyze one-year post-transplant and overall complications (IV). No significant differences emerged between the two PSC groups in one-year CCI® or overall CCI®. Long-term overall survival was similar in both groups. The only factor with statistical significance for survival was one-

year CCI® over 42, which predicted lower overall survival. Five- and 10-year survivals were 90% and 82% for premalignant indication and 88% and 86% for classical indication, respectively.

Conclusions. Dysplasia surveillance with brush cytology may help to find patients at risk of developing CCA and to optimize the timing of liver transplantation. However, it is possible that some transplanted patient's dysplasia would never have progressed to malignancy. Protocol biopsies are useful to safely reduce immunosuppression. LTx results are similar for premalignant and classical indication and complication rates are low after LTx. Long-term survival after LTx is excellent, however, whether overall survival improves in the premalignant group is unknown.

2 Abstrakti (finnish abstract)

Tausta. Primaarinen sklerosoiva kolangiitti (PSC) on sappiteiden krooninen kolestaattinen sairaus. PSC-potilailla on huomattava riski sairastua sappitiesyöpään (kolangiokarsinooma). Ainoa parantava hoitomuoto on maksansiirto, mutta jos sappitiesyöpä ehtii kehittyä, sitä on pidetty vasta-aiheena maksansiirrolle. Helsingissä aloitettiin vuonna 2001 maksansiirrot potilaille, joilla todetaan ERC-seurannassa harjasoluissa toistuva premaligni solulöydös (syövän esiaste). Näiden potilaiden arvioidaan olevan suurentuneessa riskissä sairastua sappitiesyöpään. Tämä väitöskirja vertaa maksansiirron tuloksia PSC-taudin kahdessa eri indikaatiossa.

Potilaat ja menetelmät. Tutkimuksessa ovat mukana peräkkäiset 199 PSC-diagnoosilla Helsingin yliopistollisen sairaalan elinsiirtoyksikössä maksansiirron saaneet potilaat vuosina 1984-2020.

Potilaat jaettiin kahteen ryhmään sen perusteella, oliko maksansiirron indikaatio loppuvaiheen maksasairaus tai hoitoresistentti sappitietulehdus/-kutina (n=151, klassinen indikaatio) vai sytologiset löydökset (n=48, premaligni indikaatio) ERC-seurannassa.

Sytologisia löydöksiä verrattiin lopullisiin histologisiin löydöksiin poistetusta maksasta (I). Elämänlaatua tutkittiin 15D-menetelmällä ennen ja jälkeen maksansiirron sekä verrattiin kahdessa PSC-indikaatioryhmässä (II). Protokollabiopsia löydöksiä verrattiin PSC-potilaiden ja toisen

autoimmuunisairauden, primaarin biliaarisen kolangiitin (PBC), välillä (III). Viimeisessä osatyössä (IV) tutkittiin siirron jälkeisiä komplikaatioita PSC-potilailla ja verrattiin klassisilla indikaatioilla ja premalignilla indikaatiolla siirteen saaneita potilaita toisiinsa. Komplikaatioiden mittarina käytettiin CCI®-indeksiä (Comprehensive Complication Index), joka on kehitetty leikkauspotilaille. Tiedot tutkimuksia varten on kerätty sähköisistä potilasrekistereistä ja Helsingin maksansiirtorekisteristä.

Tulokset. Harjasolunäytteitä verrattiin poistetun maksan histologiaan. Siirtoindikaatio oli 66 potilaalla klassinen ja 35 potilaalla premaligni. Sytologia ilman virtaussytometriaa oli epäilyttävä yhdeksällä (14 %) klassisen indikaation ryhmän potilaalla ja 17:llä (49 %) premalignin ryhmän potilaalla. Virtaussytometrian kanssa yhdistettynä epäilyttävällä sytologialla havaittiin olevan 68 % herkkyys ja 86 % spesifisyys histologisesti varmennettuun maligniteettiin.

Elämänlaatu tutkittiin yhteensä 48 PSC-potilaalta, joista 16 kuului premaligniin ryhmään ja 32 klassisen indikaation ryhmään. Elämänlaatu 15D-mittarilla tutkittiin ennen ja jälkeen maksansiirron ja ryhmiä verrattiin toisiinsa. Elämänlaatu pysyi korkeana maksansiirron jälkeen premalignissa ryhmässä ja oli lähes samalla tasolla kuin ikä- ja sukupuolivakioidulla muulla väestöllä.

Useampi kuin yksi yksittäinen histopatologinen muutos protokollabiopsioissa oli löydöksenä 43 %:lla PSC- ja 62 %:lla PBC-potilaista. Löydösten suhteen on huomioitava, että PBC-potilailla oli merkittävästi pidempi seuranta-aika. Hyljinnänestolääkitystä vähennettiin protokollabiopsian perusteella 10 %:lla potilaista ja lisättiin 6 %:lla. Biopsioissa, jotka aiheuttivat lääkitykseen lisäämisen, oli merkitsevästi enemmän inflammaatiota portaali-, endoteliaali-, interfaasi- ja lobulaarialueilla.

Yhteensä 199 PSC-potilasta oli saanut maksansiirron vuoden 2020 loppuun mennessä. Komplikaatioiden yhden vuoden indeksiä ja kokonaiskuormitusta maksansiirron jälkeen arvioitiin molemmissa ryhmissä käyttäen CCI®-indeksiä. Ryhmien välillä ei ollut tilastollisia eroja yhden vuoden CCI®:ssä tai pitkäaikais-CCI®:ssä. Pitkäaikainen kokonaiseloonjääminen oli samanlainen molemmissa ryhmissä. Premalignilla indikaatiolla viiden vuoden ja 10 vuoden eloonjääminen oli 90 % ja 82 % ja klassisella indikaatiolla vastaavasti 88 % and 86 %. Ainoa tekijä, jolla oli tilastollista merkitystä eloonjäämisen kannalta, oli yhden vuoden CCI® yli 42, mikä ennusti alhaisempaa kokonaiseloonjäämistä.

Johtopäätökset. Seuranta harjanäytteillä voi auttaa tunnistamaan potilaat, joilla on riski sairastua sappitiesyöpään ja samalla auttaa maksansiirron ajoitukseen suhteen. On kuitenkin mahdollista, että kaikkien potilaiden solulöydökset eivät välttämättä etenisi syöväksi.

Maksansiirto epäilyttävän sytologisen löydöksen vuoksi on perusteltua, tulokset ovat yhtäläisiä sekä klassisella indikaatiolla että premalignilla indikaatiolla tehdyissä siirroissa, elämänlaatu on hyvä ja komplikaatioiden osuus sekä niiden laatu ovat hyvin samanlaiset molemmissa indikaatioryhmissä. Pitkäaikaiseloonjääminen on korkea, mutta sitä, parannammeko premalignin ryhmän kokonaiselinaikaa maksansiirrolla, emme vielä tiedä.

3 Original Publications

I. Vannas MJ*, Boyd S*, Färkkilä MA, Arola J, Isoniemi H. Value of brush cytology for optimal timing of liver transplantation in primary sclerosing cholangitis. *Liver Int 2017.May;37(5):735-742*.

II. Vannas M, Färkkilä M, Sintonen H, Åberg F, Isoniemi H. Health-related quality of life before and after liver transplantation in patients with primary sclerosing cholangitis. *Scand J Gastroenterol 2020. Mar;55(3):347-353*.

III. Vannas M, Arola J, Nordin A, Isoniemi H. Value of posttransplant protocol biopsies in 2 biliary autoimmune liver diseases: A step toward personalized immunosuppressive treatment. *Medicine (Baltimore) 2022. Jan 14;101(2)*.

IV. Vannas M, Åberg F, Nordin A, Tukiainen E, Savikko J, Isoniemi H. Comprehensive complication index (CCI®) after liver transplantation for primary sclerosing cholangitis. *Annals of Surgery* 2023. Feb 24. doi: 10.1097/SLA.0000000000005831. Online ahead of print.

The publications are referred in the text by their Roman numerals. Articles are reproduced with the kind permission of their copyright holders. Additionally, some unpublished data are presented.

* equal contribution

4 Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACR	Acute cellular rejection
AIH	Autoimmune hepatitis
AKI	Acute kidney insufficiency
ALP	Alkaline phosphatase
AMR	Antibody-mediated rejection
CCA	Cholangiocarcinoma
CCI®	Comprehensive complication index
CKD	Chronic kidney dysfunction
CNI	Calcineurin inhibitor
CRC	Colorectal cancer
EASL	European Association for the Study of the Liver
ERC	Endoscopic retrograde cholangiography
FISH	Fluorescence in-situ hybridization
GAS	Global assessment scale
HCC	Hepatocellular carcinoma
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
IBD	Inflammatory bowel disease
MELD	Mayo model for end-stage liver disease
MRC	Magnetic resonance cholangiography
MRI	Magnetic resonance imaging
NGS	Next-generation sequencing
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
PTLD	Post-transplantation lymphoproliferative disorder
SIR	Standardized incidence rate
SMR	Standardized mortality rate
UDCA	Ursodeoxycholic acid

5 Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of the bile ducts leading to end-stage liver disease. Inflammation of the biliary tree is associated with inflammatory bowel disease (IBD) in 62-83% of patients.[1] The prevalence of PSC is especially high in Scandinavian countries, up to 16 adult cases per 100 000 population with increasing annual incidence.[2, 3] Likely underlying the etiology of PSC are both environmental and genetic factors.[4] The pathogenesis is still unclear and various pathways are presented.[5]
The diagnosis of PSC is based on magnetic resonance imaging (MRI) of the bile ducts or endoscopic retrograde cholangiography (ERC) together with increased cholestatic liver enzymes. [6, 7] The course of PSC disease is known to be progressive, leading to death or transplantation after 9.7-20.6 years from diagnosis, [8, 9] and no medical treatment options exist for slowing the disease.[4] The only known curative option is liver transplantation (LTx). The most feared complication of PSC is cholangiocarcinoma (CCA). The life-time risk is 20% and the annual risk is 2% in the first year, diminishing later.[9] In the past (1980s to 1990s), LTx was performed in CCA, but recurrence of the cancer was frequent and survival was poor. Due to the unfavorable results, CCA was considered a contraindication for LTx for many years. In the last two decades, however, a LTx program was started in selected perihilar CCA.[10] This program includes heavy neoadjuvant chemoradiation therapy. The success of this protocol is difficult to assess due to missing histological verification of malignancy,

especially in PSC patients.[11] Currently, CCA remains a contraindication for LTx for most patients.

No verified biomarkers are available to predict which patients are at risk of developing CCA. Helsinki University Hospital started a systematic follow-up of PSC patients with ERC and brush cytological specimens to detect early neoplasia.[12] If the surveillance indicates recurrent biliary dysplasia, LTx is considered by a multidisciplinary team before the development of CCA. This program was launched in 2001. The aim of this thesis was to examine critically the justification of this liver transplant program for premalignant findings in PSC without liver failure. The results are compared with those of PSC patients transplanted with classical indications.

6 Review of the Literature

6.1 Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by inflammation and scarring of the bile ducts, which can lead to liver damage, bile duct blockage, and ultimately, liver failure. Probably due to the lack of diagnostic tools, PSC was only noted in some case reports before 1960. As endoscopic retrograde cholangiography (ERC) became more common in the 1970s, larger studies of this disease have emerged.[13]

6.1.1 Etiology and Pathogenesis

The clinical definition of the disease was firmly established in the 1980s in three landmark studies. [14–16] PSC comprised increased liver enzymes, especially alkaline phosphatase, in patients with ulcerative colitis. Further, cholangiography showing intra- or extrahepatic strictures was associated with the disease. PSC is a rare disease, with both genetic and environmental factors speculated to be contributing causes. The pathogenesis remains uncertain, and various mechanisms have been proposed. [4, 5]

There is currently no definitive knowledge of the PSC pathogenesis, and various pathways have been presented as the underlying cause [4, 5]. An overview of the current understanding is presented below (Fig. 1).

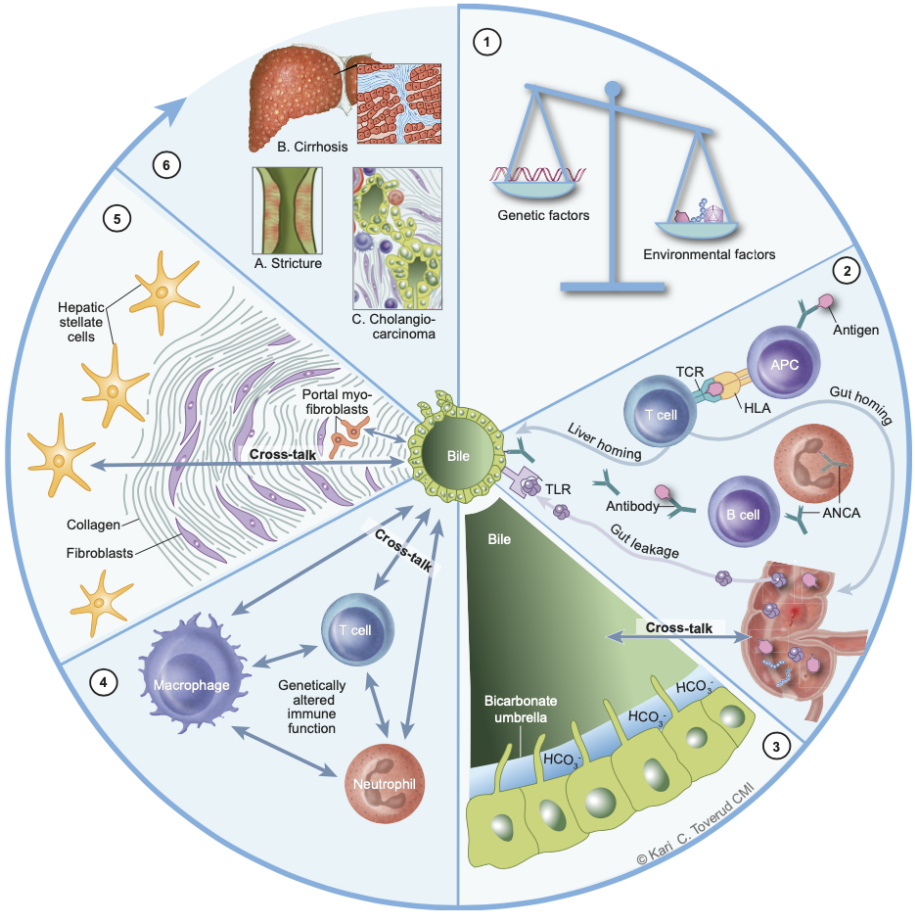


Figure 1. Current understanding of various pathways of pathogenesis in PSC. Initiating factors (1) include both genetic and environmental factors. Involvement of the gut (2) in the pathogenesis has been presented, both via the gut leakage of lipopolysaccharides that activate the innate immune response and by activation of B and T cells that target liver endothelial cells. Bile duct endothelium is protected from bile toxicity by a bicarbonate layer (3), the disturbance of which may contribute to the pathogenesis of the disease. Genetic findings may affect immune response cells in the proximity of the bile ducts (4). The aforementioned factors result in hepatic stellate cells and portal myofibroblasts, with cross-talk from cholangiocytes generating “onion skin” fibrosis (5). This finally leads to the known complications of PSC: biliary strictures, cirrhosis, and CCA (6). However, many details of the pathogenesis remain unknown. Printed with permission from Kari C. Toverud, originally printed in the Journal of Hepatology 2017, vol. 67.

Genetics has been shown to have an impact on the risk of PSC. At least 23 regions of the genome have been identified in a genome-wide association study to have a correlation with PSC, [17] with four loci being only associated with PSC risk. The strongest risk loci are focused on the human leukocyte antigen (HLA) complex. Also, the lower risk factor genes outside the HLA complex are related to immune-mediated or autoimmune conditions. In fact, while PSC is most often associated with IBD, it only shares 10 gene loci with it. Some of the other loci are shared with also other autoimmune diseases such as type 1 diabetes and multiple sclerosis.[4] Since PSC-related genes are associated with immune functions and autoimmune diseases, this supports the view that it is an autoimmune disease. While there are some loci involved in bile acid homeostasis, no Mendelian cholestasis syndrome-inducing genes have been identified in PSC.

Although genetics has an impact on the risk of PSC, its estimated liability is under 10%.[4] Therefore, environmental triggers are expected to have a larger impact. Smoking, diet, exposure to farm animals, and usage of contraceptive hormones have been suggested to affect PSC risk, but the pathways are unknown.[5]

Clinical features of PSC patients support these genetic findings. Patients are very likely to have IBD, either ulcerative colitis or Crohn's disease.[4] The percentage of PSC patients with IBD comorbidity is difficult to measure precisely, as sometimes patients have PSC diagnoses preceding any IBD. Reported rates of concurrent IBD range from one-third to two-thirds of all PSC patients.[4]

The strong association with IBD has resulted in the "microbiota hypothesis" of PSC pathogenesis. This hypothesis is also partly supported by the previously mentioned associations with dietary environmental triggers. This theory centers around the dysfunction of the intestinal microbiota, which leads to an

aberrant cholangiocyte response and changes in bile microbiota. The theory is somewhat supported by observations in vitro and in animal models. [5]
However, it has been unclear whether this change in microbiota occurs before or after changes in bile. Recently, it has been suggested that in addition of having an impact on pathogenesis of PSC, the bile microbiota itself may have affect initiation of CCA.[18]

6.1.2 Epidemiology

Global incidence of PSC was recently estimated in a meta-analysis to be from 0.04 to 1.58 per 100 000 person-years.[19] In the same article, the prevalence could not be meta-analyzed, but raw prevalence from the studies included was between 0 and 31.7 per 100 000 persons.
Regional differences were notable, with the lowest prevalence in Asia and the highest in Scandinavia. While some of the variability may be explained by the low number of studies in the areas with a lower prevalence, there are clearly some notable regional differences suggestive of a genetic influence in the etiology of the disease. Notably, in Europe there are multiple studies showing a clear difference in the prevalence and incidence between Scandinavian countries and southern Europe. The incidence of PSC in Finland, the Netherlands, Norway, and Sweden ranges from 0.5 to 1.3 per 100 000 person-years and the prevalence from 5.6 to 31.7 per 100 000 persons. [19]
In Finland, a recent population-based study reported an incidence ratio of 1.58 per 100 000 person-years and a prevalence of 31.7 per 100 000 persons.[2] The incidence is comparable to other studies, but the prevalence is significantly higher. In the Finnish study, the authors reported an increase in the incidence ratio after 2006, when a more standardized approach to diagnosis was established. Another issue suspected to increase the incidence was that

ursodeoxycholic acid (UDCA) became reimbursable for patients with PSC diagnosis, which may have increased assignation of this diagnosis temporarily. [2]

There is evidence of an increase in the incidence of PSC over time in Europe and North America [19, 20]. Various hypotheses exist to explain this, e.g. decreasing exposure to protective factors or increasing exposure to triggering factor or application of magnetic resonance cholangiography (MRC) instead of more invasive ERC in diagnosis.

6.1.3 Diagnosis and Symptoms

The diagnosis of PSC is based on clinical and radiological findings, biochemical markers, and histology. Especially in the early phase of the disease, patients are commonly asymptomatic and have none or very few radiological findings. [21] Elevated liver enzymes often offer the initial clue of chronic liver disease, spurring further investigations.[22] Recent articles report that half of the patients are asymptomatic at diagnosis.[21–23] However, both biochemical markers and clinical symptoms may fluctuate, and even patients with entirely asymptomatic disease frequently develop symptoms over time. [4]

6.1.3.1 Symptoms

Symptoms comprise those usually associated with cholestatic diseases such as pruritus, fatigue, and upper right quadrant abdominal pain. Symptoms fluctuate within the normal course of the disease, but suddenly worsening symptoms warrant evaluation of patients, as they can be a sign of biliary obstruction or acute bacterial cholangitis and eventually malignancy. [22] When the disease progresses to cirrhosis, portal hypertension with varices, ascites, and encephalopathy is seen.

6.1.3.2 Laboratory tests

Alkaline phosphatase. Alkaline phosphatase (ALP) is the most investigated single blood test for PSC. PSC patients are known to often have elevated ALP. Normalization or decline in ALP values has been shown to be related to better survival. However, there is variability in ALP cut-off values, limiting their use in clinical practice. [24]

Other liver enzymes. Alkaline phosphatase is the most common laboratory test value that increases with PSC. Increase in transaminases (alanine and aspartate transaminase) may suggest overlap with autoimmune hepatitis (AIH). Increase in bilirubin suggests more advanced disease.

Autoantibodies. There is no specific serum autoantibody test for PSC. However, atypical perinuclear antineutrophil cytoplasmic antibodies are commonly elevated. IgG4-related disease, AIH, and overlapping syndromes should be considered in patients with positive antinuclear antibodies, smooth muscle antibodies, or elevated concentrations of total immunoglobulins and immunoglobulin subsets. [25] Elevated IgG4 concentrations are also seen in PSC, therefore not being specific to IgG4-related disease.

6.1.3.3 Imaging

Magnetic resonance imaging. Current clinical experiences suggest that MRC with magnetic resonance imaging (MRI) is the standard modality for diagnosis when PSC is suspected. [1, 4, 26] Typical findings include multifocal strictures and/or areas of dilatation, ectasia, and ductal wall thickening. These findings can be observed in intra- or extrahepatic bile ducts, or both. By definition, if findings are made in MRI, the disease is categorized as large-duct PSC, as opposed to small-duct PSC, which requires histology for diagnosis. However, none of these findings can be used to distinguish between PSC and secondary

sclerosis such as that caused by choledocholithiasis or recurrent bacterial cholangitis (Table 1). Some parenchymal changes are also occasionally observed in PSC, but the value of these findings remains unclear. [27]

Table 1 Causes of secondary sclerosing cholangitis

Etiology	Disease
Chronic	Choledocholithiasis, malignancies, biliopathy, surgical trauma, chronic pancreatitis
Immune-mediated	IgG4-disease, sarcoidosis, eosinophilic cholangitis, mast cell cholangiopathy
Infectious	Pyogenic cholangitis, histiocytosis X, cryptosporidiosis, cytomegalovirus, AIDS
Ischemic	Liver transplantation, thrombosis, transarterial chemotherapy or embolization, vasculitis
Hereditary	Cystic fibrosis, ABCB4 deficiency
Toxic	Ketamine

Endoscopic retrograde cholangiography (ERC). Historically, ERC was the diagnostic method used to confirm PSC diagnosis. However, as MRI/MRC quality improved, it has become the standard modality over ERC.[28, 29] If the diagnosis of PSC is ambiguous in initial MRI/MRC, further diagnosis may be made by ERC. [30]

It has been suggested that the additional imaging value of ERC comes from the ability to apply pressure to the bile ducts, as the early changes in the bile ducts may not be visualized in MRI/MRC. A further advantage of ERC is the ability to

obtain cytological samples during the procedure. The ability to distinguish severity of strictures by using ERC in PSC diagnosis has resulted in standard scoring methods. [12, 31] Modified scoring has been shown to be useful in evaluating disease severity and especially with cytological samples to also have a clinical impact on patient care. [12]

Due to its invasive nature, ERC is not without complications and is now seldom used as a diagnostic method. The most common complications reported in recent meta-analyses were cholangitis (4.3%), post-ERC pancreatitis (4.2%), bleeding (0.3%), and perforation (0.7%). [32] The risk of complications can usually be managed. Prophylactic antibiotics may reduce the risk of cholangitis, [33] and careful technique can diminish the risk of post-ERC pancreatitis. [34]

The current EASL recommendation is that if MRI/MRC, followed by a liver biopsy, is not diagnostic, but there is a strong clinical suspicion of PSC, ERC may be performed. The routine use of ERC for diagnosis of PSC is no longer recommended due to its invasive nature. [30]

Other non-invasive imaging technologies, such as ultrasound (US) and computer tomography (CT), are not usually diagnostic for PSC, but they are extensively used for screening of complications, surveillance, and excluding secondary reasons for sclerosing cholangitis. [26] Quite often, patients have been previously evaluated with US and/or CT before proceeding to diagnosis of PSC with alternative imaging. [35]

6.1.3.4 Histology

Liver biopsy is normally not required to diagnose of PSC. If a patient is suspected to have PSC but MRC shows no cholangiopathy [1], a liver biopsy may be used to diagnose small-duct PSC, which may later progress to large-duct PSC. Histology is useful also to distinguish between IgG4 secondary

cholangiopathy and PSC overlap syndromes. Typical findings in liver histology are concentric “onion skin” fibrosis, bile duct proliferation, inflammatory changes, cholangiectasis, ductopenia, and fibrosis/cirrhosis. Histological changes, especially in early PSC, are usually mild, and biopsies are subject to missing histological changes due to the random distribution of affected bile ducts. [36] The most common findings are bile duct scarring and “onion skin” fibrosis. [37]

6.1.3.5 PSC diagnosis guidelines and differential diagnosis

None of the previously mentioned methods are definitive for PSC. The AASLD and EASL guidelines (Table 2) are very similar. The EASL guidelines include US before MRC, but this is used mostly to rule out alternative, more common reasons for cholestasis. Before a final diagnosis is made, secondary causes for sclerosing cholangitis must be excluded.

Table 2 PSC diagnosis guidelines by AASLD and EASL

AASLD guidelines	EASL guidelines
Serum liver tests, physical examination, and patient history	ALP and GGT and/or bilirubin, physical examination, patient history
MRI/MRC	MRC
Liver biopsy only if no typical cholangiography findings	Liver biopsy ultrasound
Rule out secondary sclerosing cholangitis	AMA + ANA (rule out PBC)
Repeat MRI/MRC at one year if equivocal result	
ERC should be avoided	

Various chronic and acute diseases can cause secondary cholangitis (Table 1), [7] especially those that also exhibit overlapping syndrome, such as AIH and IgG4-related cholangitis, as they have an impact on treatment and prognosis of the disease. [4]

Differential diagnosis for secondary cholangitis is done by using various modalities. Magnetic resonance imaging, US, and CT are used to exclude various hereditary, ischemic, and obstructive causes for cholangitis. Infectious and immune-mediated secondary causes can be diagnosed via a variety of biochemical tests. Patient and disease histories are also important. [4, 7, 21]

6.1.4 Complications

Cirrhosis. Eventually, PSC leads to cirrhosis, but currently there is no way to predict the speed of progression. Nor is there any proven medical therapy to

delay or prevent this eventuality. Chronic cholestasis before cirrhosis may result in metabolic bone disease, i.e. osteopenia, and eventually osteoporosis.

Biliary strictures. Almost half of PSC patients eventually develop dominant strictures. Dominant strictures are usually defined with stenosis in imaging of the biliary tract, either in common bile duct or in hepatic duct near main hepatic confluence, which causes biliary dilatation, clinical symptoms, or increased liver enzymes. [1] Appearance of dominant strictures is typically a sign of disease progression, but they may be present even without any symptoms. It has been shown that patients with dominant strictures have reduced survival and high risk of CCA. In a single-center 25-year follow-up, all patients developing CCA had dominant strictures, and 26% of those with dominant strictures developed CCA. [38]

Recurrent cholangitis. Primary sclerosing cholangitis patients frequently have variable symptoms and occasionally refractory cholangitis. While it has not been shown to affect overall transplantation-free survival or waitlist mortality, refractory cholangitis can result in hospitalization and a significant decrease in quality of life (QoL). [39] Therefore, it has been accepted as an indication for LTx in some countries, i.e. Norway and Finland.[4]

Pruritus. Pruritus is a common complication of PSC. It can also be present without clear biliary obstruction. [6] When endoscopically treatable biliary obstruction is present, its treatment may reduce symptoms. Numerous pharmacological treatments are available to treat pruritus, from antihistamines to bile acid sequestrants. Untreatable pruritus has a significant effect on QoL and induces depression.[40] Occasionally, the symptoms are so debilitating that LTx is required.

Cholangiocarcinoma. Cholangiocarcinoma is a well-established risk factor for PSC patients. Studies report the annual risk to be 400- to 600-fold that of the normal population. [9] The risk is highest during the first year after PSC diagnosis,

thereafter gradually diminishing. Lifetime risk of CCA has been reported to be as high as 20%. [9] Surgical treatment is possible only in very specific and early detected cases, and even then the 1-, 3-, and 5-year survivals have been only 77.5%, 48.4%, and 39.7%, respectively.[41] Liver transplantation for patients with CCA was previously not accepted due to abysmal prognosis and high recurrence rates. The last 15 years have shown some improvements, with slightly better results for perihilar CCA (Klatskin tumors) when combined with preoperative neoadjuvant radiochemotherapy. [10, 42]

Gallbladder carcinoma. The risk of gallbladder carcinoma is also increased in PSC patients, [7] and thus, regular follow-ups by US are recommended. Growing or large polyps or any other suspicious signs warrant cholecystectomy. [7]

Hepatocellular carcinoma. PSC eventually causes cirrhosis, and cirrhotic livers are subject to increased risk of hepatocellular carcinoma (HCC). Although the risk of HCC is lower than that of CCA, and, according to some studies[6], lower than other cirrhotic diseases, PSC patients with cirrhosis should be followed with care. [6] PSC patients with cirrhosis and emerging HCC should be referred to liver surgery and treated according to accepted HCC guidelines. [7, 43]

6.1.5 Prognosis and Surveillance

The current understanding is that PSC leads to either premature death or liver transplantation (LTx). The average age of patients at disease diagnosis is reported to be around 37-42 years [19] but with a large bimodal (peaks at 12-17 years and 37-42 years) spread.

6.1.5.1 Prognosis and prognostic markers

Progress of the disease is poorly understood, and the timing and speed of progression are not easy to predict [4]. Recently reported median survival from

diagnosis to disease-related death or LTx in a large multicenter study with 590 patients was 21.2 years [9]. In another study with 7121 patients, the average median transplant-free survival was 14.5 (13.6-15.2) years, and during the observation period 20% (at 5 years), 37% (at 10 years), 52% (at 15 years), and 64% (at 20 years) of patients underwent LTx or died [44].

Asymptomatic patients at diagnosis have better prognosis, but disease course is so variable that even this is difficult to estimate. Small-duct PSC similarly has better prognosis [9], but also can progress at variable speed to more classical PSC [4]. IgG4-associated PSC has been reported to be a risk factor for cancer [45].

Various scores incorporating different aspects and factors of the disease have been tested. Having a clear understanding of the different stages of the disease is important to facilitate effective (both cost- and health-wise) surveillance. ALP is known to have a naturally oscillating value in PSC patients, further limiting its usability. [4] However, some conclusions can be made from these studies. Patients with slight or no symptoms [4] and normal or near-normal ALP have better outcomes [46, 47]. Other novel biomarkers have also been evaluated, but none have currently shown any clinically meaningful correlations surpassing the existing prognostic markers. [24]

The most widely known risk score for liver patients is the Mayo Model for End-stage Liver Disease (MELD). While it is useful in patients with advanced liver cirrhosis, it does not help in estimating prognosis of PSC. The PSC-specific revised Mayo risk score (rMRS) currently used in many centers has been shown to be slightly better but still relies on factors only found in advanced disease. [4, 48] The UK-PSC risk score is established to be useful in individual risk assessment and in stratifying recruitment for clinical trials. It can be used to categorize high-risk and low-risk patients. [49] More recently, machine learning was used to develop Primary Sclerosing Cholangitis Risk Estimate Tool (PREsTo), which has

been shown to be better in predicting 5-year probability of decompensation than other models. [50]

Invasive tests include liver biopsy, bile and intrahepatic brush samples, and endoscopic retrograde cholangiography. Due to their invasive nature and risk of complications, they are mostly not used as general prognostic tools. [4, 7]

6.1.5.2 Surveillance

While all of these prognostic models and variables give some estimations of LTx-free or overall survival, none of them can accurately predict timing of the onset of CCA. All of the models described here predict progress of the disease towards cirrhosis, but tumors, especially CCA, also appear in non-cirrhotic livers. Rapid progression of disease and symptoms may signal the presence of a tumor[51] but usually too late to enable any intervention by LTx or liver surgery. In an epidemiologic study with 590 PSC patients and 44 CCA patients, 80% of the latter died within a median of one (range 0-7) year. [9]

Both AASLD (Fig. 2a) and EASL (Fig. 2b) surveillance guidelines suggest using primarily non-invasive methods, more specifically MRI/MRC or US.[6, 7] The main differences in the surveillance strategy guidelines are in the frequency of imaging and the need for repeat ERC in case of suspected malignancy. EASL guidelines recommend patient referral for further investigations in case of a single suspicious ERC brush finding.

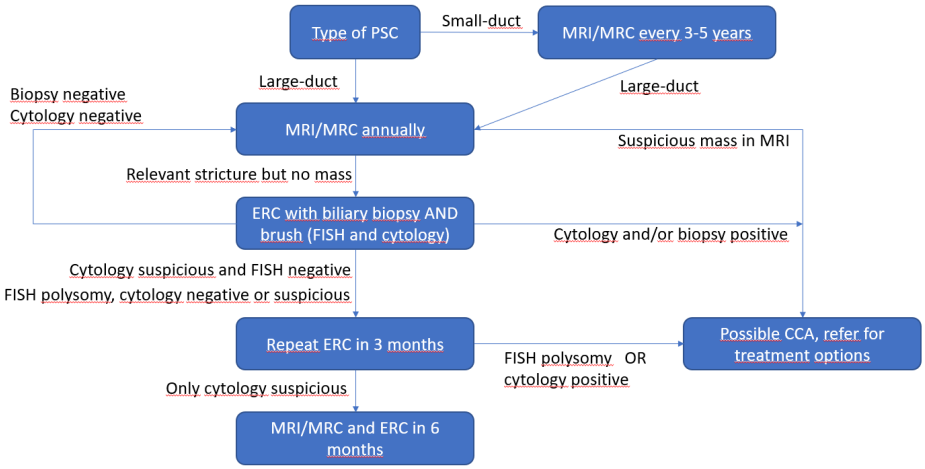
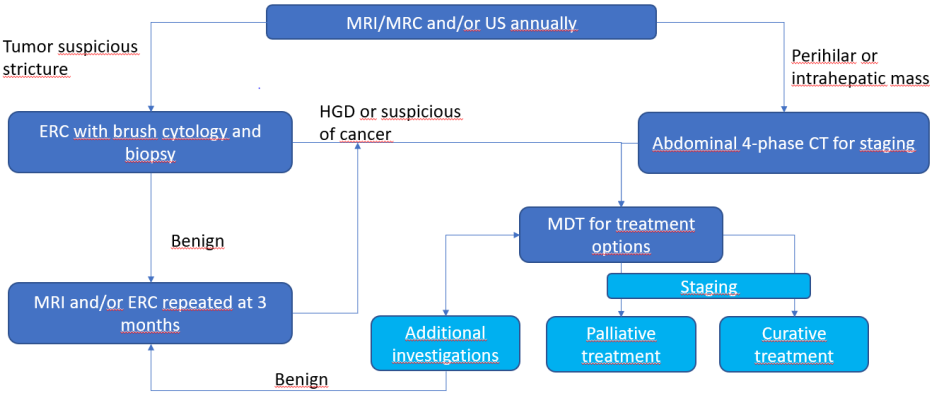


Figure 2a. Primary sclerosing cholangitis surveillance guidelines according to the American Association for the Study of Liver Diseases.



HGD, high-grade dysplasia; MDT, multidisciplinary meeting; US, ultrasound; ERC, endoscopic retrograde cholangiography; MRI, magnetic resonance imaging; CT, computed tomography

Figure 2b. Primary sclerosing cholangitis surveillance guidelines according to the European Association for the Study of the Liver.

Studies comparing surveillance with non-surveillance report clear differences between mortality rates and risk ratios. A European retrospective study with 2975 patients reported a mortality rate of 23.1 (18.1-28.1) (per 1000 person-

years) for non-surveillance, 12.5 (10.6-14.5) in the MRI and/or US group, and 8.4 (6.3-10.5) in surveillance that included ERC.[52] They reported an adjusted (sex, age, and start year of follow-up) hazard ratio of 0.61 (0.47-0.80) for risk of dying in PSC patients undergoing any type of surveillance. An earlier study (n=79) provided similar findings, with multivariable regression for surveillance status having a hazard ratio of 0.36 (0.14-0.75) for patient mortality. [53] Surveillance is clearly justified, and screening with MRC and monitoring of CA19-9 are recommended by the American College of Gastroenterology; [26] this practice is recommended by most experts. Both European[7] and British guidelines[1, 30] recommend inclusion of "on-demand" ERC with brush cytology. More controversial is the surveillance with ERC and brush samples. [12, 54] Specificity is high, but sensitivity is rather poor.[55] Fluorescence in-situ hybridization (FISH) and similar techniques were investigated to improve the sensitivity earlier [56], however, due to lack of availability these methods were not widely used in PSC surveillance and the increase in sensitivity was modest at best. Furthermore, some studies suggest that with sequential brush cytology similar results could be achieved for sensitivity.[57] More recently, there have been studies using DNA methylation markers in bile[58] and Next-Generation Sequencing (NGS) [59], which show promising accuracy with high specificity and sensitivity.

6.1.6 Treatment

6.1.6.1 Medical treatment

Ursodeoxycholic acid. Ursodeoxycholic acid (UDCA) has been used in cholestatic diseases extensively. It is known to protect cholangiocytes from the

toxic effect of bile, most likely due to stimulation of bicarbonate output.[60] It has been shown to reduce ALP and bilirubin levels of PSC patients, but in multiple meta-analyses this did not result in any improvements in HrQoL or have an impact on disease progression.[61–63] These studies have, however, been criticized for poor definition of end-points and relatively short follow-up times. Recently, studies have shown that UDCA may after all have a positive effect on LTx-free survival of PSC patients. [64]

UDCA is also genotoxic[60], and studies have linked it to an increase in colorectal cancer (CRC) and even HCC, especially in large doses.[60, 65] On the other hand, there are also studies linking it to a lower incidence of CRC when used in low or medium doses.[66]

Due to these multiple controversial results, the EASL current suggestion is that UDCA may be used to treat PSC patients but only at a smaller dose (5-15 mg/kg). [7] The 2010 AASLD recommended against using UDCA, however, the 2022 recommendation is more in line with the EASL recommendation; it may be used if tolerated and there is a meaningful decrease in ALP within 12 months. [6]

Glucocorticosteroids. Glucocorticosteroids are successfully used to treat other chronic inflammatory diseases, and prednisolone has been reported to have a favorable effect on pruritus, ALP, and IgG in PSC patients. [67] However, the 2010 Cochrane meta-analysis stated that glucocorticosteroids had no effect on PSC patients' symptoms or biochemical variables.[68] Furthermore, long-term use of glucocorticosteroids results in aggravated bone loss and calcium loss.

Antibiotics. Ursodeoxycholic acid combined with metronidazole has shown an added improvement in ALP. [63] However, this has not resulted in any clinical difference in disease progression or in decrease of symptoms. Similarly, peroral vancomycin has been studied in small trials, but the evidence is still too scarce to support its use. [6]

Immunosuppressive drugs. As the nature of the PSC is partially thought to be autoimmune, many trials have investigated immunosuppressive medication to treat PSC patients. However, none of these trials have demonstrated improvement or slowing down the progress of the disease. [1, 69]

Experimental drugs are being evaluated for treatment of PSC. These include new bile acid modulators (such as Cilofexor), fibrates, NOX 1-4 inhibitors, and microbiota manipulation (non-absorbable antibiotics). Slow progress of the disease and poorly understood pathophysiology hinder the testing of new drugs. [70]

6.1.6.2 Endoscopic treatment

Patients with symptoms may benefit from endoscopic treatment of strictures, either by dilatation or stenting via ERC. [71] Especially in the presence of dominant strictures, endoscopic treatment combined with brush samples is recommended. [6, 7]

Balloon dilatation. Patients with dominant strictures have been shown to benefit from balloon dilation. [72, 73] Dilation decreases ALP and improves symptoms.

Stenting. Bile flow can be further ensured by stenting if balloon dilatation proves inadequate. However, the results of previous studies on balloon dilation combined with stenting compared with balloon dilation alone were conflicting. [74] Recently, a randomized study was published that showed no superiority of short-term stenting and the stenting group had significantly more serious adverse events. [75] Recommended stenting time for dominant strictures is 1-2 weeks.[30] The current recommendation is to use balloon dilation as the first-line treatment for dominant strictures.

6.1.6.3 Surgery

Biliary strictures. For non-cirrhotic PSC patients with persisting biliary strictures, operative management may also be possible. Biliary bypass or biliary enteric anastomosis are potential treatments in case of extrahepatic strictures. While moderate success has been reported, some studies have shown that patients later undergoing LTx had increased risk of morbidity and mortality. [76] Most centers prefer endoscopic treatment due to the lower risk of complications.

Malignancies. Surgical resections are the preferred treatment for solitary intrahepatic CCAs. Perihilar CCA is more complex to resect, but in the early stage with normal liver function, it can be considered. Surgical resection for PSC-related perihilar CCA is seldom achievable, and transplantation is a choice in only very selected cases.[6]

6.2 Liver Transplantation in PSC

Any solid organ transplantation is a life-changing operation, and liver transplantation is no exception. Recovery from the procedure usually takes at least 1-2 weeks in hospital, and patients are unable to return to work until several months later. [77] After the operation, patients require life-long immunosuppression, which has an impact on survival and morbidity. [78] Technically, liver transplantation for PSC patients is like any other indication for LTx. Vascular anastomoses are done based on surgeon and center preferences. Bile duct anastomosis, however, requires more attention, as PSC can affect also extrahepatic bile ducts. Historically, PSC patients were thought to benefit from Roux-en-Y, and it was the preferred method of anastomosis. [79] However in the last ten years, this has been debatable. [80, 81] Currently, the selection is based on clinical features of bile ducts in most centers. If extrahepatic bile

ducts are macroscopically normal in both imaging and during the operation and there is no suspicion of extrahepatic dysplasia, a duct-to-duct anastomosis is preferred. If dysplasia has previously been suspected, a frozen section of the bile duct should be examined by a pathologist before the type of anastomosis is decided.

6.2.1 Indications

Primary sclerosing cholangitis is currently the 5th most common indication for LTx (after HCC, hepatitis C-virus, acute liver failure, and alcohol liver cirrhosis), accounting for approximately 5% of all liver transplantations in Europe.[82] In Scandinavian countries, it is more common; in 2015, it was the most common indication (15.3%) [83] and in 2021 the 2nd most common indication (15.2%) for liver transplantations.[84]

Classical indications. Patients with end-stage cirrhosis, recurrent cholangitis, and/or intolerable pruritus are referred for liver transplantation (Table 3). [85] According to EASL clinical practice guidelines, the specific indications for LTx in PSC patients are long-standing severe jaundice, repeated episodes of cholangitis not controlled by antibiotics, secondary biliary cirrhosis with complication of portal hypertension or decompensation, and liver failure [78]. The AASLD 2022 recommendations are similar, while the MELD score is used to prioritize patients on the waiting list, including MELD exceptions based on hospital admittance and documented bloodstream infection or sepsis. [6]

Premalignant changes. More recently, the EASL clinical practice guidelines for PSC list high-grade dysplasia or suspicion of cancer in brush cytology as a reason to refer patients for multidisciplinary team meetings to consider LTx (Table 3). [7] The guidelines do not, however, clearly indicate whether LTx is an option for these patients. In some countries, such as Finland, patients with a

strong suspicion of premalignant changes are also referred to LTx. [54] The AASLD recommendations also include early-stage hepatobiliary cancers as an indication for LTx. Patients with malignant-appearing stricture, CA19-9 over 100 (without cholangitis), aneuploidy, or a hilar mass under 3 cm can qualify for MELD exception points. [6]

Table 3 AASLD and EASL recommendations for LTx indications in PSC. [6, 7]

AASLD	EASL
• LT should be considered in all patients with PSC and complications of end-stage liver disease, recurrent cholangitis, intractable pruritus, or early-stage hepatobiliary cancers • LT following neoadjuvant therapy should be considered for patients with perihilar CCA (≤3 cm in radial diameter) that is unresectable or arising in the setting of PSC • In patients with perihilar CCA being evaluated for LT, EUS-FNA of regional LNs should be performed to exclude patients with metastases before neoadjuvant therapy is initiated Operative staging after completion of neoadjuvant therapy and before LT to assess regional hepatic LN involvement and peritoneal metastases is required.	• Liver transplantation should be considered for people with PSC with recurrent bacterial cholangitis and/or severe pruritus or jaundice despite endoscopic and pharmacological therapy • Liver transplantation should be considered for people with PSC with recurrent bacterial cholangitis and/or severe pruritus or jaundice despite endoscopic and pharmacological therapy • Liver transplantation can be considered in people with PSC and high-grade biliary dysplasia confirmed by cytology or ductal histology • Liver transplantation for early-stage CCA in PSC can be performed within the context of clinical trials

6.2.1.1 Liver transplantation using neoadjuvant chemoradiation therapy for CCA

Liver transplantation for patients with CCA was not previously accepted due to abysmal prognosis and high recurrence rates. Some centers, however, consider

perihilar CCA within specified limits and responses to oncological treatment as an indication for LTx. [10]

Perihilar CCA. Patients accepted must have either a biliary biopsy- or cytology-confirmed malignancy or malignant-appearing stricture with CA19-9 over 100 or malignant-appearing stricture with suspicious cytology/FISH polysomy or perihilar mass in imaging with features of CCA. [10] Patient then receive neoadjuvant chemoradiation and a staging laparoscopy prior to LTx. Any metastasis or positive lymph nodes result in exclusion from LTx. Within these guidelines, 5-year overall survival as high as 82% was reported.[86, 87] This was further confirmed in a multicenter study with 12 centers in the United States, with results showing 65% overall survival and 78% recurrence-free survival in a 5-yearfollow-up. [88] However, these results have been criticized because of the high drop-out rate during and after chemoradiation and no tumors being detected in almost half of the explanted livers. [11]

Intrahepatic CCA. Recently, there have been studies reporting LTx with some success for non-PSC patients with unresectable intrahepatic CCA. In Spain, patients with LTx had incidental intrahepatic CCA and no recurrence of intrahepatic CCA if under 2 cm. This study reported an acceptable 5-year survival of 65% with 48 patients.[89] Another study treated unresectable (due to advanced tumors) intrahepatic CCA with preoperative chemotherapy and then proceeded to LTx with 9 patients. They reported a 5-year overall survival of 83%. [90, 91] Currently, this is only an experimental indication according to the AASLD guidelines, to be considered only under research protocols. [6]

6.2.1.2 Contraindications

Before being accepted to a transplantation list, patients usually undergo vigorous investigations to ensure eligibility for LTx. Absolute contraindications

are becoming increasingly rare, [92] excluding untreatable or recently treated extrahepatic cancers. Old age has been a relative limiting factor (75 or 80 years, depending on the center), but the cut-off point has become more and more vague.[78] Most contraindications are relative and with effective management can be handled so that LTx is an option. [78]

6.2.2 Outcome

The overall short-term outcome of LTx has improved in the last three decades. Most of the graft losses within one year of the LTx were caused by rejections; these losses have been markedly diminished with better immunosuppression protocols combining different immunosuppressive medications.[93] Other advancements are better selection and optimization of transplant candidates, better donor selection, and improved perioperative care. [94]

While the short-term outcome has improved, the long-term outcome has not. In Europe, the one-year overall survival for all LTx indications was 75% in 1990-1994 vs. 85% in 2005-2009, showing an improvement of 10%. However, the corresponding 10-year survival was 56% and 60%, respectively, having improved only by 4%. [82]

The Nordic Liver Transplantation Group reported a one-year PSC LTx patient survival of 89% in 1994-2004 and 96% in 2005-2013 and a 5-year survival of 81% and 87%, respectively. [83] The Nordic Liver Transplantation Registry 2021 annual report noted one-year survival of 98% and 5-year survival of 90% for PSC patients transplanted in 2012-2021. [84] Higher long-term percentages are mostly due to clear improvement in the short-term survival of the patients (Fig. 3).

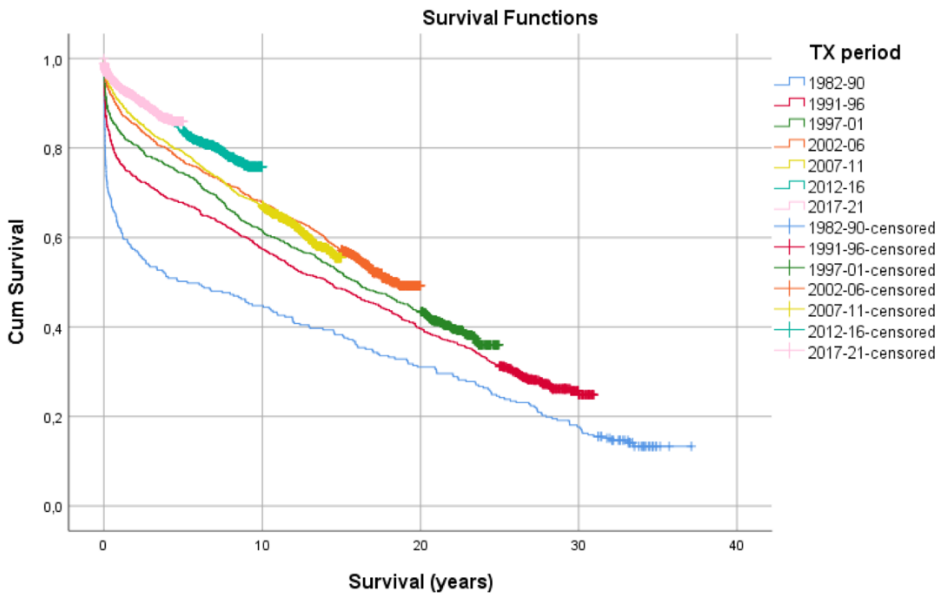


Figure 3. Nordic Liver Transplantation Report 2021: survival curve for all transplantations divided by transplantation periods (calculated using Kaplan-Meier). Printed with permission of the Nordic Liver Transplant Steering Group.

6.2.3 Follow-up

Follow-up of LTx patients is important to ensure that long-term benefits of transplantation are achieved and to reduce the adverse effects of immunosuppression medication. Because life-long immunosuppression increases the risk of multiple systemic diseases, a systematic and thorough evaluation of the recipient during scheduled follow-up visits is important. Involvement of multiple layers of the healthcare system provides the best results. [95]

6.2.4 Immunosuppression

The introduction of cyclosporine in 1981 is considered a turning point in the history of transplantations. While the improvement of overall survival of

transplant patients derives from a combination of several factors, improved immunosuppression is arguably one of the most important. [96]

Calcineurin inhibitors. The cornerstone of modern immunosuppression of LTx patients comprises calcineurin inhibitors (CNIs), namely cyclosporine and tacrolimus. Up to 97% of patients discharged after LTx have CNI-based immunosuppression. [78] CNIs function by preventing *IL2* gene transcription, which results in inhibition of T cell activation. [97] Two large meta-analyses of LTx patients found that tacrolimus compared with cyclosporine better reduced mortality, graft loss, and rejections at one year post-transplantation. [98, 99] This resulted in tacrolimus being the favored CNI in many centers. However, some studies suggest that cyclosporine might be better for PSC patients, showing less recurrent PSC and biliary strictures. [100, 101]

Antimetabolites. Two of the most widely used antimetabolites are mycophenolate mofetil and azathioprine. Both work by inhibiting iosine monophosphate dehydrogenase, which affects T and B cell proliferation. They are commonly used with CNIs to allow lower dosages. [78, 96]

Glucocorticosteroids. Glucocorticosteroids have multiple pathways of immunosuppression and were extensively used before CNIs. As such they are still widely used, especially as a first-line therapy in case of acute rejection and in induction of immunosuppression. If initially used, due to their long-term negative side-effects, they are usually weaned within the first year after LTx, except in some autoimmune diseases. [96]

Rapamycin inhibitors. The mammalian target of rapamycin inhibitors (mTOR inhibitors) are somewhat similar in their function as CNIs, binding on the same target. However, they do not inhibit calcineurin, but instead work by blocking transduction signals from IL-2 receptors, thus reducing T cell activity. Two mTOR inhibitors are currently generally available, sirolimus and everolimus. Everolimus also reduces angiogenesis. [96] Initially, sirolimus was associated with

an increase in hepatic artery thrombosis, and thus, was not recommended for LTx patients. However, further studies have shown that such an increase does not exist, and sirolimus has subsequently also been used in LTx patients. [78] The mTOR inhibitors have the added benefit of being antineoplastic [102], which has resulted in increased use in patients with pre-LTx HCC or otherwise considered at high risk of neoplasia. [96] Recently, a prospective multicenter trial has, however, found that patients transplanted for HCC did not benefit in disease-free survival or overall survival from sirolimus.[103] The antineoplastic benefit of mTor inhibitors is still being debated. Due to adverse effects on wound healing, mTOR inhibitors are not commonly used in induction of immunosuppression but are later added to or used in place of CNIs. [102]

Antibodies. Monoclonal antibodies, usually basiliximab, are normally only used either as induction agents or in rejection treatment. Basiliximab is an IL-2 receptor antibody, resulting in activated T cell-mediated immunosuppression. Anti-thymocyte globulin is a polyclonal antibody. It functions by depleting the immune system of lymphocytes, thus resulting in lymphopenia. [96]

Modern immunosuppression for PSC patients is usually induction with corticosteroids and basiliximab, followed by mycophenolate mofetil and delayed introduction of CNI.

6.2.4.1 Adverse effects

Immunosuppressive medication has numerous side-effects. Due to their function, they all predispose the patients to opportunistic infections and malignancy. While the profiles of the side-effects are similar, there is large variation in the seriousness of the side-effects. Side-effects are dose-dependent. Both CNI and mTor inhibitors need regular concentration follow-ups.

Table 4 lists the predominant adverse effects of common immunosuppressive drugs.

Table 4 Common adverse effects of immunosuppressive medication.

	Cyclosporine	Tacrolimus	Corticosteroids	Sirolimus	Everolimus	MMF
CKI	Frequent	Frequent	No	Rare	Rare	No
Hyperlipidemia	Common	Rare	Frequent	Rare	Rare	No
Diabetes	Rare	Common	Frequent	(Rare)	(Rare)	No
Hypertension	Frequent	Common	Frequent	No	No	No
Osteoporosis	Rare	Rare	Frequent	No	No	No
Skin/Mucosal lesions	No	Rare (rash)	Common	Common	Common	Rare
Wound healing Impaired	No	No	Rare	Common	Common	No
Bone marrow impairment	Rare	Rare	No	Common	Common	Rare
Pneumonitis	No	No	No	Rare	Rare	No
Hirsutism	Rare	No	No	No	No	No
Gingival overgrowth	Frequent	Rare	No	No	No	No
Hypomagnesemia	Common	Common	No	No	No	No
Other	Headaches, paresthesia, hyperkalemia, tremors	Neurotoxicity	Skin atrophy, cognitive functions	diarrhea, proteinuria	diarrhea, proteinuria	Nausea, diarrhea, headaches

CKI, chronic kidney insufficiency; MMF, mycophenolate mofetil

The combinations of medications for immunosuppression are usually tolerated by most patients, but in some cases, tailoring is required to find a sufficiently tolerated combination that is still effective.

6.2.4.2 Rejections

Three different types of rejection are usually recognized: acute cellular rejection (ACR), antibody-mediated rejection (AMR), and chronic rejection.

Acute cellular rejection. By far the most common type of rejection is acute cellular rejection (ACR) or T cell-mediated rejection. It is suspected in patients with elevated or increasing liver enzymes and usually confirmed by graft biopsy. Approximately 15-30% of LTx patients have one or more ACR during the first year after LTx. [78] Earlier studies [104, 105] have reported much higher percentages, but current immunosuppression regimens and management of patients have significantly reduced the incidence of ACR.[105] If ACR is treated promptly and effectively, it has no apparent effect on LTx patient or graft survival.[104]

Acute cellular rejection is usually treated with a high dose of corticosteroids for 3-5 days. Rejections that persist after this are called steroid-resistant rejections. Steroid-resistant rejections are treated with anti-thymocyte globulin.[96, 106] Successful treatment is defined by normalization of liver enzymes.

Antibody-mediated rejection. Historically, AMR has been of little consequence in LTx, as it has been shown to affect less than 1% of patients. [104] There has been some speculation that patients transplanted for autoimmune diseases are more susceptible to AMR, but evidence supporting this is scarce.[107] Unlike AMR in kidney transplant patients, there is no standard treatment for AMR for LTx patients.

Chronic rejection. Chronic rejection is a slow degradation of the liver tissue and bile ducts due to immune-mediated factors. [104] While historically more common, with new immunosuppression medication it has become rarer (2-5%) in the adult liver transplant population in a 5-year follow-up.[108] Chronic rejection is especially difficult for PSC patients, as recurrent PSC is partly similar

histologically. Differential diagnosis is not solely based on histological findings, also requiring imaging, laboratory values, and clinical examination. [105] Quite often, chronic rejection is preceded by either steroid-resistant rejections or inadequate treatment of ACR. Clinically, patients commonly have non-adherence or inadequate levels of immunosuppression. [108]

6.2.5 Complications after liver transplantation

Most deaths occur within the first postoperative year, the most common causes being infections and surgical complications. [78] In European data, 46% of deaths and 67% of re-transplantations occur within the first year of LTx.[82] After the first year, mortality from technical complications and infections decreases markedly.

After the first year, deaths are caused more often by cardiovascular diseases, malignancies, and recurrence of original diseases.[109]

6.2.5.1 Short-term complications

Acute kidney injury. Short-term acute kidney injury (AKI) is common after LTx, occurring in up to half of LTx patients. [110, 111] More variance appears in how many patients actually require renal replacement therapy (hemodialysis): 11-52% of AKI patients. [110, 111] Acute kidney insufficiency and chronic renal dysfunction are associated with increased mortality and morbidity. [112]

Biliary complications. There are multiple complications involving the biliary system after LTx, the most common being leakages and biliary strictures with choledocholithiasis. Complications requiring endoscopic, percutaneous, or surgical interventions have been reported to have an incidence of 12.9%, 17.2%, and 20.0% after 1, 3, and 5 years, respectively. [113] Conflicting results have been reported on whether biliary complications have an impact on

patient or graft survival. Recently, a retrospective study of 1041 patients reported a biliary complication rate of 23%, and patients with biliary complications had worse 1-, 3-, and 5-year overall patient and graft survival. [114] Another study reported no difference in graft or patient survival. [113]

Vascular problems resulting in ischemic cholangiopathy as well as anastomosis type have been presented as causes of biliary strictures. [100, 113] This is particularly important as Roux-en-Y anastomosis has been more common in PSC patients. One study of PSC patients reported significantly less strictures in Roux-en-Y patients. [100] However, another study categorizing strictures between non-anastomotic and anastomotic groups found that there were actually more non-anastomotic strictures in patients with Roux-en-Y.[81] Recurrence of PSC can also result in biliary strictures, however, this is a more common cause in the long term. [100]

Early allograft dysfunctions. Early allograft dysfunction (EAD) has a significant effect on patient and graft survival. While there is some variation in the definition, it usually consists of one or more of the following: bilirubin, INR, and/or ALT or AST being elevated on postoperative day 7. [115] Patient with EAD have shown worse short-term survival, longer hospital stay, and poorer 3- and 5-year overall survival. [116]

Infections. Extensive surgery and maximum immunosuppression in the months following LTx are speculated to be reasons for increased mortality and morbidity due to infections. [78] Infection rates as low as 14.2% over 3 months and as high as 45% over 6 months have been reported. [117] During the initial months after transplantation the most common infections are surgical site infections, pneumonia, urinary tract infections, and bloodline-related infections. While surgical site infections were associated with worse survival, the latter three did not have a significant effect on survival. [117]

6.2.5.2 Long-term complications

Recurrence of original disease. Recurrence of PSC after LTx has been reported to be 15-25%.[105, 118–120] Higher recurrence rates have previously been reported, but there were differences in how recurrence was defined and the studies were single-center studies with small numbers of patients. [118] A report based on the European Liver Transplant Registry in 2021 with 1549 patients presented a prevalence of 16.7% and a median time to recurrence of 5.1 years. [120] Other reports have a median time of recurrence ranging from 2 to 5 years. [105, 121] A previously mentioned report based on ELTR data shows a significant negative effect on patient and graft survival of recurrent PSC. [120]

Chronic kidney dysfunction. Chronic kidney dysfunction (CKD) can develop in patients even after the first year. CNIs are nephrotoxic in high concentrations and may cause CKD. Reportedly, 24% of patients without CKD at one year may develop CKD at 10 years. [122] A Finnish study reported CKD prevalence of 16-28% at 10 years. [123]

Cardiovascular complications. Dyslipidemia, diabetes mellitus, and hypertension are common long-term complications after LTx. Arterial hypertension is the most common long-term complication after LTx. It has been reported to be present in 36-77% of patients at a 10-year follow-up. [122, 123] Other 10-year cardiovascular risk factors are dyslipidemia (27-66%) and diabetes mellitus (13-42%). [122, 123] A cardiovascular event was reported in 24% of patients; thus, it is more than three times more likely to occur than in the general population.[123]

Osteoporosis. Especially in cholestatic patients, osteoporosis is common before LTx. CNI [123] and glucocorticoids [124] are suspected to cause bone density loss after LTx. Thus, osteoporosis does not necessarily improve in cholestatic patients immediately after LTx. [123] Osteoporotic fractures cause severe morbidity in LTx patients. [124] The incidences of osteopenia, osteoporosis, and

fractures have been reported in a recent meta-analysis as 17-56%, 5-24%, and 13-30%, respectively. The mean follow-up time for all studies was not available and there was considerable variation in inclusion of LTx patients, which explains the large variation in incidence. The most common fractures were vertebral, with hip fractures being relatively rare. [124]

6.2.6 Malignancies After Transplantation

Immunosuppressive medication is known to increase the incidence of de novo malignancies. The incidence of malignancies in LTx patients is 2- to 3-fold that of the general population, with almost 20% of LTx patients eventually developing cancer.[124–126] After the first year of transplantation, it is the leading cause of mortality in LTx patients.[82, 95]

Skin cancer. Incidence of non-melanoma skin cancer (NMSC) in LTx patients is significantly higher than in the general population.[128] Standardized incidence ratio (SIR) has been reported to be 16.4 - 51.9. [126–128] Melanoma incidence is much lower, with the SIR being 1.2-2.4.[127–129] Basal cell carcinomas are a slow-growing and common skin cancer in the general population. Due to their rather benign nature, they are not always included in cancer databases, making their comparison difficult.[128] In a Finnish study, the SIR for basal cell carcinoma was 3.7.[127] Non-melanoma skin cancers do not affect patient survival after LTx.[129]

Post-transplantation lymphoproliferative disease. Incidence of post-transplantation lymphoproliferative disease (PTLD) is low, at 1-3%, [130, 131] and the SIR is 8.8-15[126, 127, 129], but it has significant effect on patient survival. Patients with PTLD have been reported to have an overall survival of 56-85% at one year and 38-69% at 5 years, which is significantly worse than survival without PTLD. [130, 132, 133]

Other cancers. Incidence of other individual cancers is much lower, with a reported combined incidence of 16%. [125] However, PSC patients are at higher risk of developing CRC. Cumulative incidence has been reported to be 7.4%, [134] and more recently dysplasia incidence at one year, 5 years, and 10 years has been reported to be as high as 5.5%, 22.8%, and 36.9%, respectively.
All LTx patients with cancer have higher mortality rates than non-LTx patients with similar cancers. [129] A Nordic study reported non-PSC LTx patient SIR for CRC at 1.03, while PSC LTx patient SIR was much higher at 4.04. [126]

6.2.7 Graft Biopsies

Liver biopsies after transplantation are in most cases taken based on indication. A common reason for indication biopsy is the suspicion of rejection. Indication graft biopsies are sometimes taken in less acute situations, usually to assess whether there are any long-term changes in the liver that could explain mild biochemistry changes or clinical symptoms.
Protocol biopsy. Protocol biopsies are taken according to a predefined schedule as opposed to being based on clinical factors. Previously, protocol biopsies were widely used. They were discontinued due to improved documentation of allograft dysfunction, alternative methods for diagnoses, and risk of serious complications (excluding hepatitis C patients). [135] However, in the last decade there has been increasing interest since advanced biopsy techniques cause less complications. [136] A long-term effect of medication on the graft can be minor and without symptoms or other clinical features.[137] Biopsies may be useful to detect these effects.
With normal biochemistry, liver biopsies can reveal steatosis, fibrosis, chronic rejection, hepatitis, or recurrent diseases.[138] Even biopsies that are classified

as normal can be useful, as the more subtle, non-specific changes can be used to modify treatment.[137,139]

Chronic rejection. Obliteration of arteries and progressive loss of bile ducts (vanishing bile duct syndrome) can be indicative of chronic rejection. Especially if detected at an early stage, it may be possible to reverse these changes by alteration of immunosuppression.[135]

Chronic hepatitis. Portal and lobular inflammatory cell infiltration without signs of acute hepatitis is considered chronic hepatitis. This may eventually lead to fibrosis and result in long-term loss of the graft. Early detection is important, and again modification of immunosuppression may be able to reverse the changes.[135]

Recurrence of original disease. Recurrence of PSC can be recognized from histological samples before it causes any changes in liver biochemistry. Recurrence rate of PSC after LTx has been reported to be 16.7% within a 5-year follow-up. [120] Unlike chronic hepatitis or rejection, there are currently no good options for medical treatment to prevent these changes[135], but intensifying patient follow-up is warranted.

Even protocol biopsy with no findings can be considered useful, as it can be used to justify a decrease in immunosuppression.[137]

6.2.7.1 Biopsy complications

Non-graft liver biopsy complications have been extensively studied. Large variation exists in reported complications, both minor and major. A recent meta-analysis reported the risk of any complication to be 0-7% in the adult population and the risk of a major complication to be less than 2%. [136] Mortality is considered low; historically, in a large series of 68 276 patients there were only six deaths (0.009%), none of which were from healthy livers.[140]

6.3 Quality of Life After Liver Transplantation

Quality of life, more specifically health-related quality of life (HRQoL), is considered to be critical in patients receiving LTx. [78] Improving patients' HRQoL is one of the most important outcomes of LTx. There have been many studies exploring the immediate effect (within one year), [78] and most recipients do indeed show improvement within the first year after LTx. However, longer studies have more variance in the results. This is undoubtedly due to the long-term effect of medication, especially immunosuppression. [141]

6.3.1 Measuring Health Related Quality of Life

Quality of life is usually measured from three separate aspects: physical, mental, and social. Each of the aspects is a combination of variables representing different functions (Fig. 4). [142] Considering how widely the different aspects are distributed, any tool has a considerable challenge in covering them all. Most tools can only evaluate some part of the dimensions, and there are vast differences in how patients feel the HRQoL questionnaires capture their difficulties. [141]

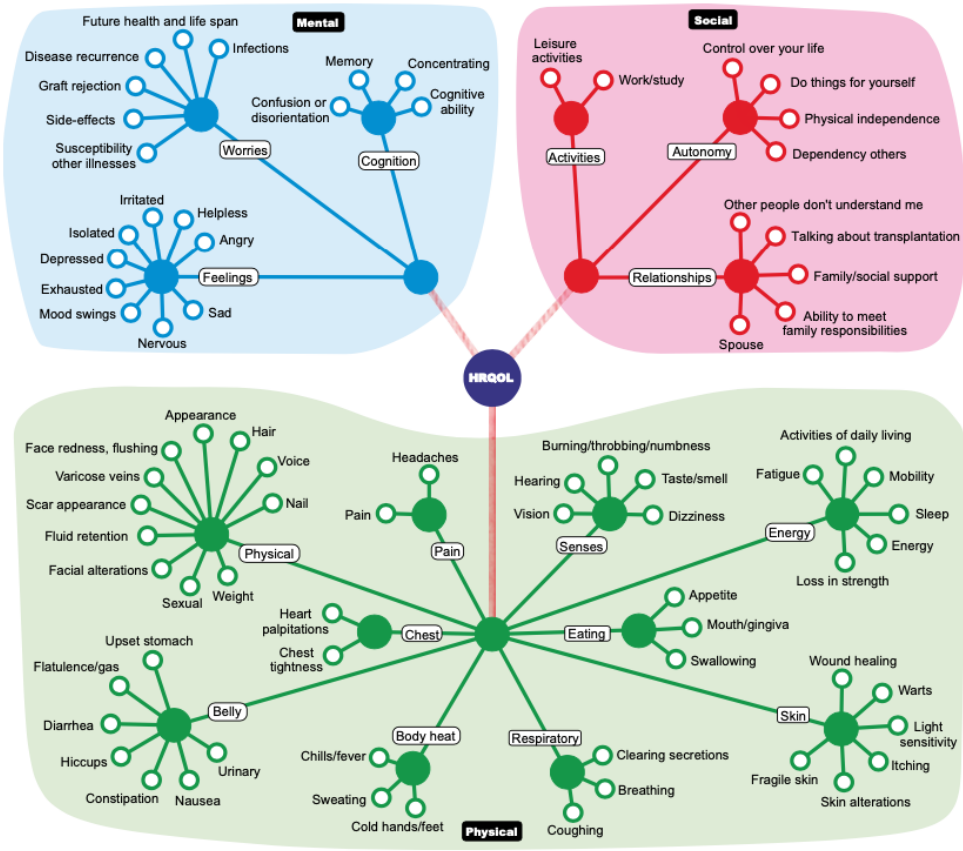


Figure 4. Dimensions of health-related quality of life and various factors affecting the dimensions. (Reprinted with permission from Parizi et al. A Scoping Review of Key Health Items in Self-Report Instruments Used Among Solid Organ Transplant Recipients. The Patient e Patient-Centered Outcomes Research 2019[142]).

Another problem is the large variety of tools available to measure HRQoL. [141] No standard tool exists to measure QoL, and results from different measurement tools are difficult to compare. Another issue with most HRQoL tools is that they measure summarized data without indication of the intensity and/or frequency of the measured variable. [141]

6.3.2 Impact of liver transplantation on patient HRQoL

Numerous studies have shown that HRQoL improves after LTx. [143] It has been suggested that the improvement would bring the HRQoL of LTx patients almost to the level of the general population. [144] This remains controversial, as some studies also show that HRQoL remains below that of the general population on all dimensions. [95, 143] The degree of improvement mostly depends on the patient's preoperative health; the poorer the health before transplantation, the greater the improvement. This is especially true in the short term, as in the long term the effect of immunosuppression and potential complications lowers the patient's HRQoL. [144]

Physical health-related dimensions benefit the most from LTx, while mental and social dimensions are less affected or may even diminish. [141, 145]

6.3.3 HRQoL of Primary Sclerosing Cholangitis patients

Studies using the more general SF-36 HRQoL tool have shown that PSC patients´ HRQoL is lower than that of the general population. [146] The results are consistently lower in all domains, excluding physical function and bodily pain. However, transplanted PSC patients did not have a significantly lower score in any domain except general health.

IBD is a reported predictor of lower HRQoL, but it seems to have less impact in PSC patients. [145, 147] Other symptoms associated with lower HRQoL are pruritus, ascites, and fatigue, which, unlike IBD, are usually relieved after LTx. [146]

6.4 Summary of liver transplantation in PSC in literature

Conventional indications for LTx in PSC disease are established practice. Dysplasia as an indication for LTx is controversial but is increasingly accepted. Timing of transplantation in dysplasia is difficult, and the long-term results with this indication are not known. Even though the risk of cholangiocarcinoma is high in PSC, there is a risk of futile transplantation because dysplasia does not always progress to malignancy.

Liver transplantation results are good, as measured by overall survival. However, not only survival is important but also the HRQoL after transplantation. There have been no studies of the HRQoL with premalignant indication. Short- and long-term complications after LTx are moderate, and many of these are caused by immunosuppression. The role of protocol biopsies in guiding immunosuppression is unclear.

Currently, no good treatment options exist for PSC patients who develop CCA. Different methods of examination for early detection of CCA have been investigated, with ERC with brush samples being the only one that is today actively used and accepted.

7 Aims of the study

The aim of this thesis was to investigate the timing and changing indications of liver transplantation as well as the post-transplantation results in PSC patients. Specific aims were to determine the following:

1. What is the value of brush cytology surveillance for optimal timing of liver transplantation (I)?
2. Comparison of brush cytological findings before LTx with final histology of explanted liver (I).
3. Does HRQoL differ in the PSC groups transplanted with classical indications compared with premalignant indication (II)?
4. What is the importance of protocol biopsies after LTx in PSC and PBC patients and can protocol biopsies be used to guide immunosuppression (III)?
5. Comparison of comprehensive complication index (CCI®) in PSC patients transplanted with classical indications and in PSC patients with premalignant indication (IV).
6. Defining risk factors for prognosis of LTx in PSC patients (IV).

8 Patients and Methods

The first liver transplantation for PSC in our center was performed in November 1984, and this patient was still alive at the latest follow-up in 2020. A total of 199 consecutive PSC patients were included in this study. They were transplanted between November 1984 and December 2020. Up to the year 2000, the indication for LTx of all PSC patients was either end-stage liver disease or highly symptomatic disease with recurring cholangitis or intolerable pruritus. From 1984 to 2000, only 17 patients were transplanted. In January 2001, the first patient was transplanted due to suspicion of incipient CCA based on ERC brush cytology. The number of yearly transplantations according to the indication is shown in Figure 6.

The transplantations were divided into two groups based on transplant indication, either classical indication or premalignant indication.

Classical indication. Primary sclerosing cholangitis patients with end-stage liver disease have symptoms and complications such as severe cholestasis, ascites, variceal bleeding, and/or hepatic encephalopathy. This group also includes patients without end-stage liver disease but with a difficult symptomatic disease such as recurrent cholangitis or refractory pruritus.

Premalignant indication. The liver function of these PSC patients is normal or close to normal. Clinical findings may include rapid radiological disease progression, often together with increasing carbohydrate antigen CA19-9 (CA 19-9) or repeatedly suspicious cytological and/or aneuploid DNA flow

cytometry findings. They are evaluated in a multidisciplinary team meeting, and if there is strong suspicion of progressing dysplasia in bile ducts, patients are accepted in the waiting list with this indication.

Study III includes also patients diagnosed with primary biliary cholangitis (PBC) as a control group. A total of 152 consecutive PBC patients transplanted in 1985-2014 are included in this study.

Table 5 Study design and demographics in Studies I-IV.

Study	I	II	III	IV
Study aim	Brush cytology compared with explanted liver histology	HRQoL after LTx in PSC groups	Protocol graft biopsies	Complications after LTx in PSC groups
Liver disease	PSC	PSC	PSC/PBC	PSC
LTx indication	Classical/Pre-malignant	Classical/Pre-malignant	PSC/PBC	Classical/Pre-malignant
LTx period	1984-2012	2007-2011	1987-2014	1984-2020
Last follow-up	Oct 2014	Oct 2017	May 2015	Jan 2022
Number of LTx*	91/35	32/16	100/83	
Number of patients*	91/35	32/16	92/77	148/51
Re-transplantations	No	No	Yes	Yes

* per indication LTx, liver transplantation; HRQoL, health-related quality of life

8.1 Histological samples

Histological samples were collected in Studies I and III. In Study I, explanted liver histology was examined. In Study III, protocol liver biopsies of the graft were examined. In the study III protocol, biopsies were taken at predetermined times, at one year and every 5th year after transplantation (also at 3 years if

the original liver disease was HCV). All samples were investigated by an experienced liver pathologist.

Explanted liver histopathology. All explanted livers were investigated carefully both macroscopically and histologically. Liver hilum including hilar fat tissue and lymph nodes, extrahepatic bile duct, and liver parenchyma were separately processed into tissue blocks and analyzed.

Frozen samples. If CCA was suspected before transplantation, frozen samples of hilar lymph nodes and samples from bile ducts were examined at the beginning of LTx. Our center has a pathologist on call when a transplantation is planned for a patient with suspicion premalignant or malignant findings before operation. If malignancy is confirmed, transplantation is not performed.

Liver graft biopsies. Biopsies were taken by an experienced radiologist under ultrasound guidance with Biopty™ device, using either 16- or 18-G needle. Results are reported in a structured format (Table 6) and also in a free-hand pathology report. Abnormal biopsies are usually presented by the pathologist in a multidisciplinary meeting. Liver biopsies are routinely stained in our laboratory, including H&E, Herovici, Periodic acid-Schiff-diastase, and cytokeratin 7.

Table 6 Structured parameters of liver biopsy report at Helsinki University Hospital. Inflammation was graded according to BANFF RAI scoring[148] and fibrosis according to Metavir.[149]

Parameter	Study Interpretation
Portal inflammation, cholangitis and endothelial inflammation	Absent (0), Mild (1), Moderate (2), and Severe (3)
Interphase Inflammation	Absent (0), Mild (1), Moderate (2), and Severe (3)
Parenchymal inflammation	Absent (0), Mild (1), Moderate (2), and Severe (3)
Fibrosis	Metavir classification
Arterial Obliteration	
None	*Normal portal arteries*
Mild	*1-9% of arteries have signs of sclerosis*
Moderate	*10-19% of arteries have signs of sclerosis*
Severe	*Over 20% of arteries have signs of sclerosis*
Other	*No normal arteries found*
Parenchymal Necrosis	None, 0-4%, 5-9%, 10-14%, or over 15% necrosis.
Cholestasis	Any signs of intracellular or canalicular cholestasis
Vacuolization	Percentage of liver cells with vacuolization; 0-4%, 5-30%, 31-60%, and over 60%.
Hemorrhage	Any sign of hemorrhage in biopsy
Congestion	Any sign of congestion in biopsy
Regeneration	
Degeneration	

8.2 ERC and Brush cytology

In Finland, PSC patients are regularly followed by the Gastroenterology Department of Helsinki University Hospital or by the local hospital with either ERC or MRI, but there have been some changes over time. More standardized surveillance in Helsinki was started in 2006, and its current form is presented

here in Figure 5. The follow-up protocol of biliary surveillance was planned and developed by Professor Martti Färkkilä of the University of Helsinki. It uses the modified Amsterdam score (mERC) [12] and biliary brush cytology combined with NGS analyses to evaluate the risk for biliary neoplasm.

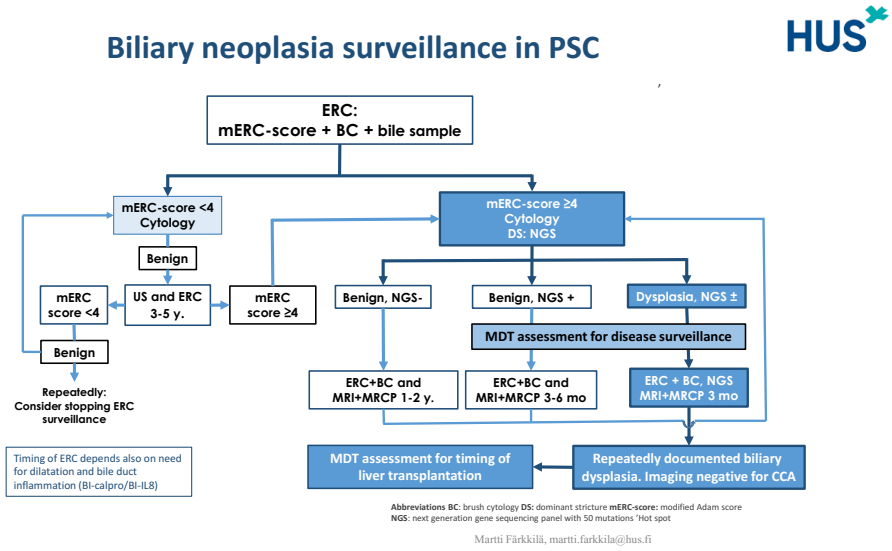


Figure 5. Biliary surveillance of PSC patients at the Gastroenterology Department of the University of Helsinki.

ERC brush cytology. All ERC brush samples since 2006 have been taken according to a standardized sampling technique. Samples are taken from intra- and extrahepatic bile ducts. To increase sample size, cells were flushed from brush shaft and the tip of brush was cut for cytological analysis. Quality and quantity of the samples since 2006 have been determined to be generally good. Evaluation of the cell block aims to distinguish between inflammatory changes and premalignant cells. Suspicion of pre-malignant cell is based on biphasic appearance. Some samples were also evaluated using DNA flow cytometry. A DNA index of 0.9-1.1 was considered diploid.[150]

8.3 Finnish liver Transplant registry

Finnish liver transplant patients are followed by the national transplant center at the Helsinki University Hospital Transplantation and Liver Surgery Clinic and by local hospitals with gastroenterological clinics. The transplantation coordinators collect complications from patient records at the transplantation center after the operation and submit these to the Finnish Liver Transplant Registry. They also later receive reports from the local hospitals. Furthermore, Finland has only one liver transplant center, and all transplanted patients attend regular visits at the transplant center according to the protocol. Follow-up by the national transplant center is done every three months in the first post-transplant year. Thereafter, the follow-up schedule by the national center is less frequent but continues with follow-up visits every 1-3 years, depending on the patient. Local hospitals follow the patients more frequently. The registry is mandated by law and is regularly audited for completeness and accuracy.

8.4 Complications

Patients' complications were collected from the Finnish Liver Transplant Registry. The registry includes separate sheets to list complications. These include graft complications, infections, reasons for immunosuppression changes, and other complications. Complications in detail are listed in Table 7. These complications were then graded according to Clavien-Dindo classification for Study IV. Patient medical records were also examined for accurate grading of complications.

Table 7 Complications listed in the Finnish Liver Transplant registry database.

	Complications	
Graft complications	Primary non-functioning	Hepatic artery thrombosis
	Acute rejection	Portal vein thrombosis
	Chronic rejection	Hepatic vein thrombosis
	Temporary dysfunction	Bile duct stricture
	Other severe dysfunction	Non-compliance
	Recurrence of original disease	
Infections	Abscess	Cytomegalovirus
	Cholangitis	Other viral
	Sepsis	Fungal
	Pneumonia	Parasite
	Other bacterial	
Other complications	PTDM	Myocardial infarction
	Fracture/osteoporosis	Coronary disease / ASO
	Cataract diagnosis	Lung emboli
	Cataract operation	Hypertension
	Kidney insufficiency	Dialysis treatment
	Psychiatric treatment	Transient ischemic attack
	Severe skin problems	Infarction
	Serious neurological complication	Hemorrhage
	Gastrointestinal bleeding	Cancer code ICD-10
	Gastrointestinal ulcer	

8.5 Health-related quality of life

Generic 15D questionnaire was used to measure HRQoL.[151] It can be used both as a profile with different domains and as a single-index measure.

Health-related quality of life (HRQoL) questionnaire was collected in three different ways. Helsinki University Gastroenterological Clinic routinely collects 15D HRQoL questionnaires of PSC patients during ERC follow-up. Additionally, some patients were prospectively asked to enroll in 2007-2011, during which they responded to 15D questionnaire once before LTx and at 6, 12, 18, and 24 months after LTx. For Study II, we identified all PSC patients who had responded to the questionnaire before LTx (either in a gastroenterology department follow-up or in the prospective study) and then asked these patients to respond to the questionnaire again. Comparison was also made with the general population, data being available from the Finnish national surveys in 2000 and 2011.[152, 153]

8.6 Statistical analysis

In all studies, we used either Pearson's chi-square or Fisher's exact test to analyze goodness of fit when comparing groups. For normally distributed data, means were calculated, and t-test was used for statistical analysis. When normality could not be determined, median values were used instead, and either Kruskal-Wallis or Wilcoxon non-parametric tests for significance were performed. Survival figures were created with Kaplan-Meier algorithm and log-rank analysis was performed for groupwise statistical differences. Differences were considered significant if P was <0.05.

The 15D instrument produces scores that can be classified into five global assessment scales (GAS) [154]. This scale can be used to assess the clinical importance of the change in QoL, in addition to statistical significance. The categories of the scale are major positive change, slight positive change, no change, slight negative change, and major negative change. Comparison with the general population was done by paired samples t-test.

In Study I, statistical analysis was performed using IBM SPSS, version 22. In Studies II and III, statistical analysis was done using IBM SPSS, version 25. Study IV statistical analysis was done entirely in R language using RStudio©, version 2021.09.0 Build 351.

8.7 Ethical considerations

Organ transplantation is regulated by law and requires research on its effectiveness. Follow-up of patients who have received an organ transplant and maintenance of the transplant register are therefore required.
Studies I, III, and IV are retrospective studies mainly based on Finnish liver register data and patient case records. Biopsies of the grafts and fine needle aspirations were taken according to follow-up protocols in the clinics and not for research purposes.
Ethical approval for Study II was obtained from the Ethics Committee of the Hospital District of Helsinki and Uusimaa (538/E0/02). All patients signed an informed consent before they completed the 15D questionnaires.

9 Results

9.1 Patient characteristics

In Studies I, II, and IV, only PSC patients were analyzed. Study III also included PBC patients as a control group. Study IV patients (n=199) include all PSC patients transplanted in Finland between 1984 and 2020; PSC patients in other studies are thus a subset of the patients in this study (Table 8). Patients transplanted for premalignant indication are younger than those transplanted for classical indication, 38 vs. 48 years ($p<0.0001$). They have shorter cold ischemia time, 279 vs. 309 minutes ($p=0.024$), and their MELD score is lower, 7 vs. 14 ($p<0.0001$) (Table 8).

Table 8 Patient characteristics in Studies I-IV.

A. Patients in study I

	Classical n=91	Premalignant n=35	Total n=126	P-value
Gender				**0.84**
Male	57 (63%)	21 (60%)	78 (62%)	
Female	34 (37%)	14 (40%)	48 (38%)	
Age at LTx	47 (39 - 56)	38 (33 - 50)	45 (37 - 55)	0.006
BMI at listing	23 (21 - 26)	23 (22 - 26)	23 (21 - 26)	0.084
MELD at listing	14 (8 - 18)	7 (6 - 8)	10 (7 - 16)	< 0.0001
MELD at LTx	12 (8 - 18)	8 (6 - 9)	9 (8 - 16)	< 0.0001
Waiting time (days)	42 (16 - 84)	89 (36 - 141)	49 (17 - 112)	0.021
Cold Ischemia (min)	321 (273 - 380)	274 (258 - 304)	303 (266 - 360)	0.002
Anhepatic time (min)	53 (47 - 60)	50 (48 - 56)	52 (47 - 58)	0.30
Follow-up time (years)	13 (8 - 18)	12 (8 - 16)	13 (8 - 17)	0.43
Retransplantations				**1.0**
No	91 (100%)	35 (100%)	126 (100%)	
Yes	0 (0%)	0 (0%)	0 (0%)	
Type of anastomosis				**0.034**
Duct to Duct	11 (12%)	0 (0%)	11 (9%)	
Roux-en-Y	80 (88%)	35 (100%)	115 (91%)	
Latest outcome				**0.18**
Alive	49 (64%)	25 (78%)	74 (69%)	
Dead	27 (36%)	7 (22%)	34 (31%)	

C. Patients in the study III

	PSC n=100	PBC n=83	Total n=183	P-value
Gender				**< 0.0001**
Male	62 (62%)	10 (12%)	72 (39%)	
Female	38 (38%)	73 (88%)	111 (61%)	
Age at LTx	43 (36 - 56)	52 (46 - 61)	48 (40 - 58)	< 0.0001
BMI at listing	23 (21 - 26)	23 (21 - 26)	23 (21 - 26)	0.84
MELD at listing	8 (6 - 15)	17 (14 - 20)	14 (8 - 18)	< 0.0001
MELD at LTx	9 (6 - 14)	18 (15 - 22)	13 (8 - 19)	< 0.0001
Waiting time (days)	52 (20 - 111)	24 (8 - 52)	40 (14 - 84)	< 0.0001
Cold Ischemia (min)	283 (263 - 344)	305 (260 - 361)	290 (261 - 351)	0.23
Anhepatic time (min)	52 (48 - 57)	52 (48 - 59)	52 (48 - 58)	0.69
Follow-up time (years)	14 (10 - 17)	19 (13 - 25)	15 (11 - 20)	< 0.0001
Retransplantations				**1.0**
No	92 (92%)	77 (93%)	169 (92%)	
Yes	8 (8%)	6 (7%)	14 (8%)	
Type of anastomosis				**< 0.0001**
Duct to Duct	7 (7%)	80 (98%)	87 (48%)	
Roux-en-Y	93 (93%)	2 (2%)	95 (52%)	
Latest outcome				**0.023**
Alive	77 (77%)	54 (65%)	131 (72%)	
Dead	14 (14%)	25 (30%)	39 (21%)	
Retransplanted	9 (9%)	4 (5%)	13 (7%)	

B. Patients in the study II

	Classical n=31	Premalignant n=17	Total n=48	P-value
Gender				**0.76**
Male	20 (65%)	12 (71%)	32 (67%)	
Female	11 (35%)	5 (29%)	16 (33%)	
Age at LTx	45 (36 - 54)	34 (30 - 48)	44 (34 - 52)	0.038
BMI at listing	23 (22 - 25)	22 (22 - 24)	23 (21 - 25)	0.48
MELD at listing	14 (8 - 16)	8 (6 - 8)	9 (6 - 15)	0.0003
MELD at LTx	12 (8 - 17)	6 (6 - 8)	9 (6 - 14)	0.001
Waiting time (days)	31 (14 - 130)	56 (38 - 100)	54 (16 - 126)	0.43
Cold Ischemia (min)	302 (269 - 336)	280 (266 - 313)	292 (268 - 324)	0.52
Anhepatic time (min)	53 (48 - 58)	52 (49 - 55)	52 (48 - 57)	0.55
Follow-up time (years)	7 (5 - 10)	8 (7 - 10)	7 (6 - 10)	0.34
Retransplantations				**1.0**
No	31 (100%)	17 (100%)	48 (100%)	
Yes	0 (0%)	0 (0%)	0 (0%)	
Type of anastomosis				**1.0**
Duct to Duct	1 (3%)	0 (0%)	1 (2%)	
Roux-en-Y	29 (97%)	17 (100%)	46 (98%)	
Latest outcome				**1.0**
Alive	26 (93%)	14 (93%)	40 (93%)	
Dead	2 (7%)	1 (7%)	3 (7%)	

D. Patients in the study IV

	Classical n=148	Premalignant n=51	Total n=199	P-value
Gender				**0.50**
Male	92 (62%)	35 (69%)	127 (64%)	
Female	56 (38%)	16 (31%)	72 (36%)	
Age at LTx	48 (39 - 56)	38 (32 - 51)	47 (36 - 56)	0.001
BMI at listing	23 (21 - 26)	23 (22 - 26)	23 (21 - 26)	0.64
MELD at listing	14 (9 - 17)	7 (6 - 8)	11 (7 - 16)	< 0.0001
MELD at LTx	13 (9 - 18)	8 (6 - 8)	11 (8 - 17)	< 0.0001
Waiting time (days)	44 (16 - 127)	78 (33 - 123)	52 (18 - 124)	0.079
Cold Ischemia (min)	310 (270 - 370)	279 (265 - 306)	302 (267 - 360)	0.021
Anhepatic time (min)	53 (48 - 60)	52 (48 - 58)	53 (48 - 60)	0.64
Follow-up time (years)	9 (3 - 16)	9 (6 - 15)	9 (4 - 16)	0.74
Retransplantations				**0.79**
No	132 (89%)	47 (92%)	179 (90%)	
Yes	16 (11%)	4 (8%)	20 (10%)	
Type of anastomosis				**0.14**
Duct to Duct	22 (15%)	3 (6%)	25 (13%)	
Roux-en-Y	125 (85%)	48 (94%)	173 (87%)	
Latest outcome				**0.70**
Alive	113 (77%)	41 (80%)	154 (78%)	
Dead	34 (23%)	10 (20%)	44 (22%)	

9.2 Brush Cytology and Explanted Liver Histology (I)

Brush samples. Brush cytology was available for 66 patients with classical indication and 35 patients with premalignant indication. Flow cytometry was available for 25 patients with classical indication and 24 patients with premalignant indication. Cytology was suspicious in 13.6% vs. 48.6% ($p<0.001$) and flow cytometry was aneuploid in 24.0% vs. 62.5% ($p=0.007$), respectively.
Histology. Biliary neoplasia was found in 16.6% of classical indication patients vs. 42.9% of premalignant indication patients (Study I, Table 3). Dysplasia was found in 7.3% of classical indication patients and in 34.3% of premalignant indication patients. Explanted liver histology showed CCA in three patients of the classical indication group and in two patients of the premalignant indication group. However, five patients in the classical indication group were diagnosed with CCA intraoperatively, and thus, were not transplanted. In total, CCA was present in 8.3% of patients in the classical indication group vs. 5.7% in the premalignant indication group.
Combining brush samples with explanted liver biliary neoplasia findings resulted in 57% sensitivity and 86% specificity with cytology and 80% sensitivity and 83% specificity with DNA flow cytometry. Brush samples having either cytology-suspicious or DNA aneuploidy had a sensitivity of 55% and a specificity of 90% (Study I, Table 5).

9.3 Complications After Liver Transplantation (IV)

The classical indication group had more Clavien-Dindo grade I complications than the premalignant indication group ($p=0.006$). This difference is mostly due

to the classical indication group having more than 3-fold the occurrence of osteoporotic fractures (p=0.010). No significant differences existed in the rates of other Clavien-Dindo stages. However, bile duct strictures were more common in the premalignant group than in the classical indication group (p=0.047). Clavien-Dindo grade II complications were the most numerous, with altogether 798 complications observed.

The median CCI® score within the first post-transplantation year for the classical indication group was 29.6 and for the premalignant indication group 26.2. During the entire follow-up period the CCI® score increased to 43.2 for the classical indication group and to 46.8 for the premalignant indication group. These differences were not statistically significant at either time-point. Higher MELD score and having been transplanted before the year 2000 had a significant effect on the CCI® score. Patients with MELD score over 20 had a first-year CCI® score of 36.2, those with MELD score under 10 had 29.6, and those with MELD score of 10-20 had 22.6 (p=0.012). The CCI® score for the entire follow-up period was 52.6, 46.6, and 37.7, respectively (p=0.005). Patients transplanted before the year 2001 had a first-year CCI® score of 37.2 and those transplanted later 25.2 (p=0.001). The score for the entire follow-up period was 62.4 and 41.8, respectively (p<0.001). Patients with a body mass index between 22 and 25 had the lowest CCI® score during both the first year and the entire follow-up period the difference for the entire follow-up being significant (p=0.023) (Table 4 from Study IV).

9.4 Protocol Biopsies (III)

Liver biopsies of PSC patients were more likely to be interpreted as normal than those of PBC patients at any time-point (p=0.002). Diagnoses of recurrence of original disease were more frequent in PBC patients (p=0.001).

No differences emerged in protocol biopsies between groups of patients having either reduced immunosuppression or unchanged immunosuppression. However, more portal inflammation (p=0.004), endothelial inflammation (p=0.008), interphase inflammation (p=0.021), and lobular inflammation (p<0.001) were seen in biopsies of patients with increased immunosuppression.

9.5 Survival After Liver Transplantation (I, IV)

For all PSC patients in Study I, the overall survival was 97% at one year, 87% at 5 years, and 84% at 10 years. For patients transplanted after January 2001, cumulative survival was 100% at one year and 91% at 10 years. No difference in survival emerged between classical indication and premalignant indication groups. There were five patients who were not transplanted due to intraoperatively diagnosed CCA from the frozen section taken at the beginning of the operation. Four of these five patients died within a median of 1.3 years after the LTx attempt. One was still alive at 2.3 years after the attempt.
Patients' overall survivals were calculated for different patient groups based on transplantation era, one-year CCI® score, MELD score, and indication (IV). Overall survival was significantly lower for patients with CCI® score over 42 (Study IV, Figure 1). There were no other differences in overall survival rates between patient groups.
Survival for all PSC patients transplanted between 1994 and 2020 (n=199) was re-calculated for this thesis. No difference emerged in overall survival between the premalignant and classical groups (Fig. 6, log rank p=0.8). The 5- and 10-year survivals for the premalignant indication group were 89.5% and 81.6%.

The corresponding figures for the classical indication group were 87.9% and 85.6% (Fig. 6).

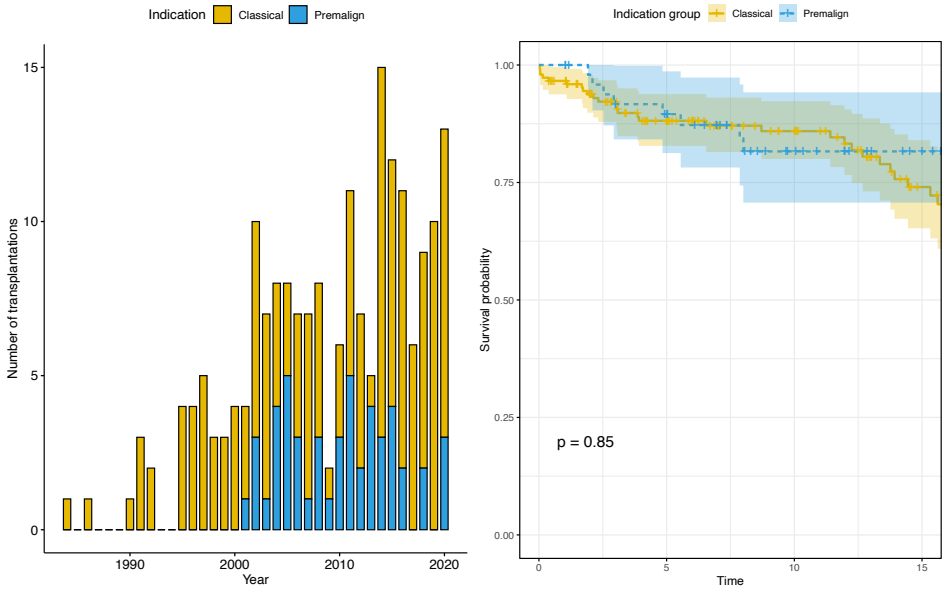


Figure 6. Annual primary sclerosing cholangitis liver transplantations during 1984-2020 and survival based on indication groups (M.V. et al., unpublished results).

9.6 Cancers (I, IV)

Study I. In explanted livers (Study I), there were five CCA, three in the symptomatic group and two in the premalignant group. Five patients were diagnosed with CCA in the symptomatic group intraoperatively and were not transplanted.

Study IV. During the follow-up in Study IV the most common cancer was post-transplant lymphoproliferative disorder (PTLD), affecting 16 patients (8%). Four new hepato-pancreatico-biliary cancers developed post-transplantation; three were pancreatic cancers and one was cancer in the papilla vater. Four patients

had CCA diagnosis from explanted liver. No differences emerged in occurrence of posttransplant cancers between the classical indication group and the premalignant indication group.

9.7 Quality Of Life (II)

Before liver transplantation, the classical indication group has a lower HRQoL than the general population. This difference was both clinically and statistically significant. The premalignant group had almost normal scores, which did not differ from those of the general population (Fig. 7).

After transplantation, the mean HRQoL measured with 15D was lower in primary sclerosing patients than in the general population, but this difference is not statistically significant. The premalignant indication group had a higher HRQoL than the classical indication group, but this difference was not statistically significant. However, compared with the general population, the classical indication group had a significantly lower HRQoL (mean score 0.889 vs. 0.937, p=0.024) (Study III, Fig. 3). The difference in HRQoL between the premalignant group and the general population was not statistically significant.

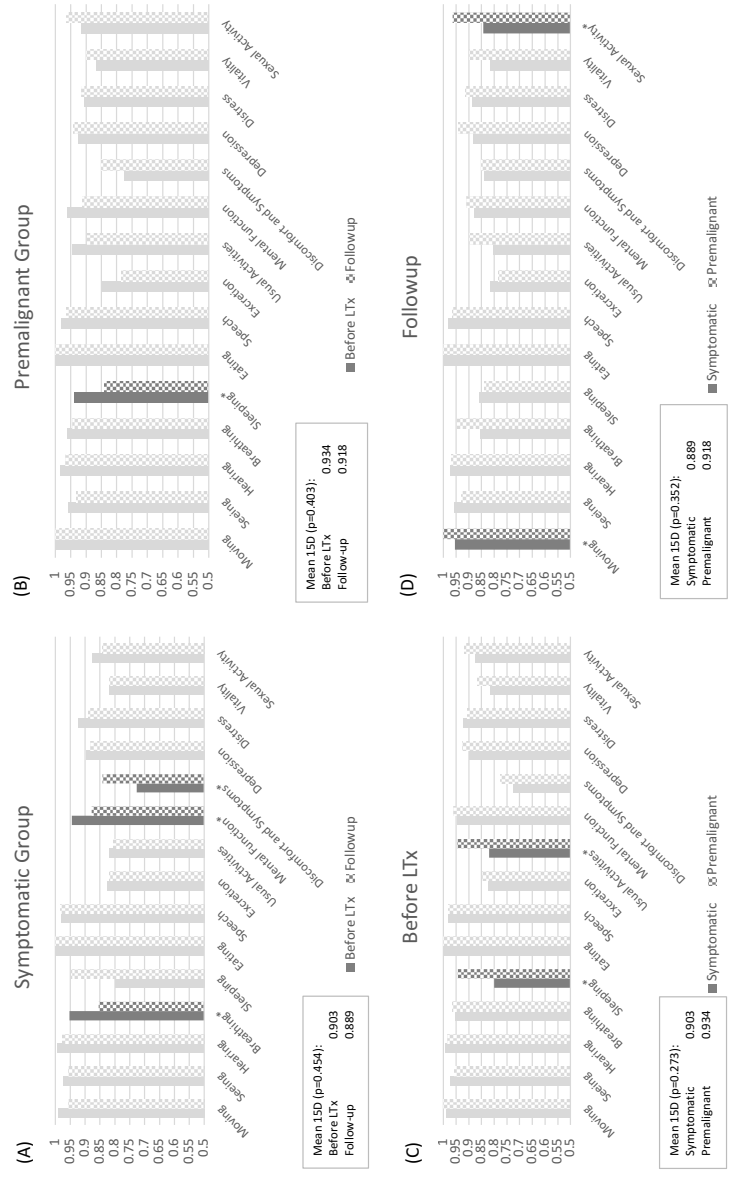


Figure 7. HRQoL and dimensions (Reprinted with permission from Scand J Gastroenterology).

The mean 15D score of the premalignant group was lower after LTx than before LTx (0.934 vs. 0.918, p=0.403), and the 15D score decreased similarly in the classical indication group (0.903 vs. 0.889, p=0.403).

10 Discussion

Our center has transplanted PSC patients based on premalignant findings since 2001. As these patients are generally healthier pre-LTx, it is important to show that their long-term morbidity and mortality are at least equal to those of classical indication patients.

10.1 Risk of malignancy and timing of transplantation (I, IV)

Cholangiocarcinoma is the most common cause of mortality in PSC patients, and if CCA develops it is usually a contraindication for LTx. We investigated whether ERC surveillance with brush cytology will improve the timing of liver transplantation, e.g. before malignancy develops. In Study I, there was clearly more dysplasia proportionally in liver histology of patients with suspicious brush samples. For dysplastic explanted liver histology, sensitivity was 58% with cytology only and 68% if either cytology or DNA flow cytometry was positive. Specificity was 86% with both methods. Boyd et al. studied PSC patients undergoing ERC and BC surveillance in Helsinki University Hospital with 2006 and 2011 brush samples, respectively, and found similar sensitivity and specificity, 65% and 94% with cytology only and 69% and 86% for either cytology or DNA flow cytometry[54].

There is evidence supporting the transition from hyperplasia and dysplasia to carcinoma of bile ducts in PSC. Lewis et al.[155] has shown in 100 explanted livers

that dysplasia was significantly more common in the livers with than without CCA. Furthermore, low-grade dysplasia predicted high-grade dysplasia, and high-grade dysplasia predicted CCA. Our findings support this dysplasia-neoplasia-carcinoma pathway.

A Nordic study on epidemiology, risk of malignancy, and survival of PSC patients reported 68 deaths in 580 patients, 38 (56%) of which were malignancy-related.[2] The most common malignancy was CCA (55%). Compared with the general population, this resulted in SIR of 3.4 and SMR of 5.9. Cholangiocarcinoma SMR was 244. Recently, Bergqvist et al. [52] reported that PSC patients with ERC surveillance have reduced mortality. They found the mortality rate for patients with MRI/MRC surveillance to be 12.5 and for those with surveillance that included ERC 8.4.

Another Nordic study on malignancy risk of PSC patients after liver transplantation reported SIR of 2.5 for any malignancy and SIR of 1.9 if non-melanoma skin cancers were excluded. [126] For comparison, transplanted PSC patients´ SIR was 2.5 and non-transplanted PSC patients´ SIR was 3.4. [2] We note that incidence of any cancer is lower in PSC patients than in LTx patients. In Study IV, 23% of patients were diagnosed with malignancies after transplantation, with PTLD being the most common. There were no differences in incidence of cancers between premalignant and classical indication patients. Our premalignant indication group had proportionally more dysplasia in the explanted liver (I), and thus, we can argue that this group would have been much more likely to have developed CCA without transplantation. On the other hand, some patients with dysplasia might not have developed malignancy, and their LTx would have been unnecessary or premature.

Scheduled ERC with brush samples is not considered standard surveillance in AASLD or EASL guidelines for PSC patients.[6, 7] In suspect situations with non-

invasive surveillance they suggest ERC and brush samples. Our center has since also slightly eased away from ERC surveillance, with ERC surveillance now only used in more advanced disease. When suspicious brush samples are found, LTx is then considered an option.

10.2 Complications (IV)

With long-term overall survival rates, patients' morbidity becomes more relevant. Morbidity also has a significant effect on a patient's quality of life. Postoperative complications have been traditionally measured with Clavien-Dindo classification,[156] but this classification only works in the short term and takes into account the worst complication. In our study, we used CCI®, which considers multiple complications and also creates an index based on both multitude and severity of the complications. Initially, CCI® was developed for 3-month postoperative complications, but it has since been extended to longer follow-up periods.[157] It has previously been shown that CCI® values over 42 in the one-year follow-up signify significantly lower overall survival.[158] Our findings agree with this assessment; survival was significantly lower in patients with CCI® higher than 42. There was no difference in either one-year or overall CCI® between our premalignant and classical indication groups.

While overall complications are as previously reported, the premalignant group has a slightly different complication profile. Cholangitis was more common in the premalignant group, not being explained by bile anastomosis since both groups had very few end-to-end anastomoses. Osteoporosis was more frequent for the classical indication, as expected due to pre-LTx cholestasis.

10.3 Importance of protocol biopsies (III)

Liver graft biopsies have usually been taken with clinical indication. Today, biopsies using an automated device with ultrasound guidance are rather safe.[140] Our pathologist investigated altogether 14 histopathological parameters of protocol biopsies from PSC and PBC patients. No abnormal histopathological findings were reported in only 12% of PBC patients and 26% of PSC patients. PBC patients had a longer follow-up, but when analyzed at the same points after LTx, PBC patients had more abnormalities with fairly normal biochemistry. Abnormalities were mostly mild, as 78% of PSC and 60% of PBC patients' biopsies were interpreted as normal in the final statement. Recurrence of original disease was more common in PBC patients than in PSC patients, at 15% and 3%, respectively. However, these numbers are based solely on histology in protocol biopsies. Diagnosis of PSC recurrence is usually based on radiological findings.

Of all patients, immunosuppression was reduced in 24 (10%). Protocol biopsies of these patients had very few abnormalities and almost no inflammation in any part of the histology. In other studies, a larger proportion (up to 25%) of patients with protocol biopsies has been identified as having reduced immunosuppression.[139] In 15 patients (6%), immunosuppression was increased based on the protocol biopsy. These biopsies had more abnormal parameters. This number is similar to that of other studies. [139]

All of our protocol biopsies are evaluated in MDT meetings. No clear cut-off values for reducing or increasing immunosuppression could be identified. However, our routine evaluation of biopsies and their presentation in a structured format in the MDT meeting facilitate decision-making.

Long-term side-effects of immunosuppression are common and become increasingly important with longer survival of LTx patients. Protocol biopsies

enable us to safely minimize immunosuppression, reducing morbidity and mortality.[93]

10.4 Health-related Quality of Life (II)

Overall, the main 15D score for our premalignant indication patients before LTx was almost as good as that for the age- and sex-matched general population. In contrast, the classical indication patients´ HRQoL was lower than age- and sex-matched general population before LTx. Premalignant indication group patients are usually in good physical condition. Changes in the dimensions from pre-LTx to follow-up reflect this, as changes in physical domains were slightly lower, while those for mental dimensions improved more. The overall 15D score of both premalignant and classical indication patients after LTx was slightly lower than the pre-LTx values, but the difference was not statistically significant.

Primary sclerosing cholangitis patients have lower HRQoL scores in mental dimensions. This is considered to reflect that fact that the disease is progressive and has increased risk of malignancy.[146] This is especially true for patients with good liver function, as they are still at considerable risk of CCA. Individual dimensions of 15D results seem to reflect this in the premalignant indication patients.

LTx has been reported to improve patient HRQoL in numerous studies[77, 144]. In our study, HRQoL of premalignant indication patients did not improve after LTx, but it remained close to the age- and sex-matched general population. Premalignant patients did not have liver insufficiency before LTx.

10.5 Strengths and limitations

In all studies, data were collected from the Finnish Liver Transplant Registry. This registry is regularly updated and maintained. It is also audited. Furthermore, all transplant patients in the studies were followed by our transplant center in Helsinki, which is the only transplant center in Finland.

To measure, HRQoL, we used the 15D instrument, which is commonly employed in Finland in national health survey studies. [152] This instrument provides us with good general population control group. A limitation of the instrument is that it reflects general HRQoL and is not disease-specific. There are also no other studies on PSC patients with 15D results available from other countries.

A strength of our biopsy study is the structured report of histopathological findings. A limitation is the large variation of time from LTx to the first protocol biopsy. Protocol biopsies were started in 2009, and for those transplanted earlier the first protocol biopsy was taken on the next planned control visit.

Studies analyzing patients' immunosuppressive medication (III, IV) have a bias from the era effect. Patients transplanted in different eras have had different immunosuppression regimens, making it difficult to distinguish era effect from the effect of different medications.

The retrospective nature of the studies is clearly a weakness. Prospective randomized studies of LTx indications are difficult, if not impossible. Primary sclerosing cholangitis is a globally accepted LTx indication when symptomatic. Our center's practice of transplanting PSC patients based on premalignant findings is controversial internationally. Studies I, III, and IV also include patients from different eras, which may affect the results. Patient numbers in some groups were rather small.

10.6 Future considerations

Patients transplanted in Finland for premalignant indication are at least comparable in post-LTx survival and HRQoL with patients transplanted for classical indication. In the future, a more accurate method of predicting the risk of CCA, such as the NGS panel, may expand the number of patients accepted with this criterion. The problem with ERC surveillance is the invasive nature of the surveillance, thus, a method for accurately detecting premalignant changes in the liver with a non-invasive method would likely lead to a wider acceptance of this indication. One especially interesting technique is cell-free DNA or more precisely circulating tumor DNA detection as a biomarker for early cancer detection. [159] Follow-up analyses should be made when sufficient numbers of patients have been transplanted since the initiation of the standard ERC surveillance protocol in 2006.

11 Conclusions

1. Surveillance with brush cytology of PSC patients may help the timing of liver transplantation before CCA develops. If CCA develops, the prognosis is poor, and thus, the aim is to transplant before neoplasia progresses to malignancy. However, it is possible that dysplasia will not progress to malignancy in some patients without transplantation.
2. Explanted livers often present with biliary dysplasia in the premalignant group with suspicious brush cytology. The sensitivity of brush cytology is acceptable.
3. After transplantation, HRQoL of patients with premalignant indication is generally better than that of patients transplanted for symptomatic disease, and HRQoL is close to the age- and sex-matched general population.
4. Histopathological findings were common in protocol biopsies of grafts with normal biochemistry. Protocol biopsies can guide safe changes in immunosuppressive treatment.
5. CCI® was similar between premalignant and classical indication patients at one year post-transplant and at the latest follow-up.
6. One-year CCI® can significantly predict survival after transplantation with a cut-off value of 42. MELD and LTx era did not have significant predictive value for overall survival in PSC patients. Patient survival was similar for premalignant and classical indications.

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