

Cardiac abnormalities in cirrhosis

- impact on outcome of liver transplantation and quality of life

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“A man ceases to be a beginner in any given science and becomes a master in that science when he has learned that... he is going to be a beginner all his life”

— R. G. Collingwood



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ABSTRACT

Background & Aims: Cirrhotics are frequently affected by cardiac dysfunction, both coronary artery disease and cirrhotic cardiomyopathy. However the prevalence and predictors of heart failure and cardiac events following liver transplantation is inadequately investigated. It is also not known if cardiac dysfunction affects quality of life in cirrhotics. We aimed to identify predictors and prevalence of post-transplant adverse cardiac events. We also aimed to assess the impact of cardiac dysfunction on quality of life in cirrhotics.

Methods: We conducted two retrospective cohorts studies of cirrhotics (n=234 and n=88), one that underwent liver transplantation and one at pre-transplant evaluation. In the first cohort we registered pre-transplant data of liver disease, medications, clinical evaluation, and cardiac workup. We then followed the patients (mean 4 years) and attempted to identify factors associated with cardiac outcome. In cohort two we registered the same data in addition to Quality of life questionnaires.

Results: Heart failure was found in approximately a quarter of patients following transplantation and transplanted patients were 14 times more likely to have a cardiac event compared to the general Swedish population (n=70). Risk factors included age, renal dysfunction, diastolic dysfunction, and ECG abnormalities. Quality of life does not seem to be affected to cardiac dysfunction in cirrhotics.

Conclusions: Cardiac complications are common in cirrhosis at liver transplantation and are associated with adverse outcome but not a lower quality of life.

Keywords: Cirrhosis, Heart failure, Cardiac events, Renal failure, Quality of life
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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Skrumplever är slutstadiet av leversjukdom där enda definitiva boten idag är levertransplantation. Man har tidigare sett att patienter med skrumplever i hög grad drabbas av hjärtsjukdom, både av kranskärlssjukdom och något som kallas "cirrhotisk kardiomyopati" som är en sorts latent hjärtsvikt. Man vet dock inte hur många patienter som drabbas av hjärtsvikt och andra hjärtkärl-komplikationer efter transplantation och vilka riskfaktorer som predisponerar patienter för att drabbas. Dessutom vet man inte heller om livskvaliteten hos patienter med skrumplever påverkas av hjärtsjukdom.

Metod: Vi gjorde studier på två grupper av patienter, i den ena genomgick alla patienter levertransplantation (234 st) och i den andra så utreddes alla inför eventuell levertransplantation (88 st). Vi registrerade tillgängliga variabler hos patienterna avseende leversjukdom, kroppsundersökningsfynd, mediciner, tidigare sjukhistora, och data från utredning avseende hjärtkärlsjukdom. Gruppen som utreddes inför levertransplantation fick också svara på 2 frågeformulär avseende livskvalitet. Datan vi samlade använde vi för att statistiskt länka faktorer före transplantation till hjärtkärl-komplikationer under uppföljningstiden (i medel följdes patienterna i 4 år i den första gruppen patienter) efter transplantation. Detsamma gjordes med datan från enkäterna om livskvalitet.

Resultat: Ungefär en fjärdedel av alla patienter drabbades av hjärtsvikt efter transplantation och 70 patienter av 234 fick någon annan hjärtkärl-komplikation efter transplantation. Vi identifierade flera riskfaktorer för att drabbas av hjärtkärl-komplikationer såsom njursvikt, hög ålder, EKG förändringar, och avslappningsstörning i hjärtmuskeln före transplantation. Vi fann också att patienter som har transplanterats löper ca 14 gånger högre risk att drabbas av hjärtkärlsjukdom än resten av den svenska befolkningen. Det höga insjuknandet i hjärtkärlsjukdom kvarstod även flera år efter transplantation. Vi kunde dock inte finna något samband mellan livskvalitet hos patienter med skrumplever och hjärtkärlsjukdom.

Slutsatser: Patienter med skrumplever löper hög risk att drabbas av hjärtkärlsjukdom efter transplantation, vi har identifierat flera riskfaktorer som kan hjälpa till i utredningsprocessen av patienter inför levertransplantation. Livskvaliteten förefaller inte påverkas nämnvärt av hjärtkärlsjukdom hos patienter med skrumplever.



LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Impact of peri-transplant heart failure & left-ventricular diastolic dysfunction on outcomes following liver transplantation

Josefsson A, Fu M, Allayhari P, Björnsson E, Castedal M, Olausson M, Kalaitzakis E.

Liver International 2012 32 (8) 1262-1269

II. Pre-transplant renal impairment predicts posttransplant cardiac events in patients with liver cirrhosis

Josefsson A, Fu M, Björnsson E, Castedal M, Kalaitzakis E.

Transplantation. 2014 98 (1) 107-114

III. Prevalence of pre-transplant electrocardiographic abnormalities and post-transplant cardiac events in patients with liver cirrhosis

Josefsson A, Fu M, Björnsson E, Kalaitzakis E.

BMC Gastroenterol. 2014 5;14:65

IV. Impact of cardiac dysfunction on health-related quality of life in cirrhotic liver transplant candidates

Josefsson A, Fu M, Björnsson E, Castedal M, Kalaitzakis E

Manuscript

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ABBREVIATIONS

ECG	Electrocardiogram
ALD	Alcoholic liver disease
CAD	Coronary artery disease
QoL	Health-related quality of life
MELD	Model of end stage liver disease
GFR	Glomerular filtration rate
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting
ICU	Intensive care unit
BMI	Body mass index
NTproBNP	N-terminal pro brain natriuretic peptide
SD	Standard deviation
SIR	Standardized incidence ratio
OR	Odds ratio
CI	Confidence interval
ACS	Acute coronary syndrome
SF-36	Short form 36
PCS	Physical component summary
MCS	Mental component summary
FIS	Fatigue impact scale
LVDD	Left ventricular diastolic dysfunction

DEFINITIONS IN SHORT

Peri-transplant events	An event occurring during the time period from liver transplantation to discharge at the immediate in-hospital period.
Late events	Events occurring after the “peri-transplant” period to last follow up
Total events	Peri-transplant events and late events together
Diastolic dysfunction	An E/A ratio equal to or below 1
Graft mortality	Patient death or retransplantation
Cardiac event	An arrhythmia (such as atrial flutter/fibrillation, severe brady arrhythmias or ventricular arrhythmias), acute coronary syndrome or sudden cardiac death
QTc prolongation	A rate corrected QT time above 440 ms
Features of heart failure with normal ejection fraction	Patients with normal ejection fraction, normal left ventricular diastolic diameter, normal left ventricular systolic diameter and left ventricular wall thickness above reference or left atrial diameter above reference



1 INTRODUCTION

1.1 Overview

Cirrhosis is the end stage of liver disease. It is associated with several alterations in the patient's circulatory system. There are complications that are intrinsic to the heart and those that involve other organ systems.

Architectural distortion in the liver by fibrosis leads to obstruction of blood flow, as well as by hepatic stellate cells contracting sinusoidal vessels.¹ Following the development of cirrhosis, intrahepatic portal hypertension arises.² In addition, formation of new blood vessels, also contributes to the development of portal hypertension in the liver and the splanchnic circulation. This results in production of vasoactive substances and causes blood flow redistribution throughout the body.³ Common clinical manifestations of this process are esophageal and rectal varices,⁴ reduced systemic resistance, splanchnic dilatation, portopulmonary hypertension, and hepatopulmonary syndrome.⁵⁻⁷

Intrinsic cardiac complications include coronary artery disease and cirrhotic cardiomyopathy. These intrinsic cardiac abnormalities are the focus of this thesis and are presented in greater detail below.

1.2 Cirrhotic cardiomyopathy

The entity called cirrhotic cardiomyopathy was first investigated in 1953 by Kowalski and Abelman,⁸ who found an increased cardiac output at rest and a prolonged QT-interval in patients with cirrhosis.

It has since been reported that patients with cirrhotic cardiomyopathy have several cardiac alterations. No accepted diagnostic criteria for cirrhotic cardiomyopathy are available currently, but the following has been suggested in a consensus meeting in 2005: diagnostic features – systolic and diastolic dysfunction, supportive criteria – electrophysiological abnormalities, cardiac structural abnormalities, and elevated cardiac biomarkers.⁹

1.2.1 Functional abnormalities

1.2.1.1 Systolic dysfunction

Patients with cirrhotic cardiomyopathy usually have an increased cardiac output at rest, however, systolic dysfunction becomes evident when the patient is subjected to stress, of a physiological and/or pharmacological nature.^{10, 11} As the systemic vascular resistance is low the cardiac output can remain high even if the systolic function is impaired.⁶ The hyperdynamic circulation resulting from liver cirrhosis may normalize following transplantation but studies are not unanimous.¹²⁻¹⁶

When subjected to exercise, cirrhotic patients had or were shown to have chronotropic incompetence,¹⁷ as well as a reduced increase of left ventricular ejection fraction, cardiac index and stroke volume compared to control subjects.^{15, 18-21} Patients with cirrhosis also seem to have decreased aerobic capacity.¹⁷ Exercise also leads to greater noradrenaline, adrenalin, and dopamine increase in cirrhotics than in controls,^{18, 22} but a lower response in heart rate, diastolic arterial pressure, and isometric contraction time in cirrhotics.¹⁸

Similar reactions can be seen with volume expansion in a cirrhotic patient. Again it does not result in an increase of left ventricular systolic function as compared to normal subjects.¹¹ However the cardiovascular reaction is not seen in all cirrhotics.²³

Pharmacological studies in patients with cirrhosis have also revealed comparable abnormalities. Infusion with Angiotensin II showed blunted stroke work index and pulmonary wedge pressure,²⁴ Isoprenaline infusion did not induce the same tachycardic response in cirrhotics as in controls (suggesting an altered beta-adrenergic receptor responsiveness).²⁵ Dobutamine did not change stroke volume in cirrhotics as expected.²⁶ The hemodynamic reaction on Dobutamine in cirrhotics has been suggested to be used as diagnostic criterium for cirrhotic cardiomyopathy.²⁷ Terlipressin has also shown a similar response in cirrhotics, an increase in mean arterial pressure and a lowered ejection fraction and cardiac output in addition to lowered wall motion in the anterior and posterior left myocardial wall.²⁸

1.2.1.2 Diastolic dysfunction

Diastolic dysfunction signifies relaxation abnormalities in the cardiac muscle. It is the abnormality in heart failure with normal (or preserved) ejection fraction.²⁹ Elevated filling pressures are the main physiologic consequence of diastolic dysfunction. Filling pressures are considered elevated when the mean pulmonary capillary wedge pressure is >12 mm Hg or when the left ventricular end diastolic pressure is >16 mm Hg.³⁰

The diagnosis may, in some cases be difficult to establish and several methods are available for diagnosing diastolic dysfunction, both invasive and noninvasive.³⁰ According to a consensus document from the European society of cardiology, it was recommended to use symptoms and signs of heart failure in combination with: normal (or mildly reduced) ejection fraction, normal left ventricular end diastolic volume index with either; invasive measurements abnormalities (see pressures above), natriuretic peptides and echocardiographic measurements (high left atrial volume, low E/A ratio and increased deceleration time, high left ventricular mass, or atrial fibrillation), or tissue Doppler imaging.³¹

Diastolic dysfunction in patients with cirrhosis has been assessed in several studies, most have used conventional Doppler echocardiography and most use the definition $E/A \text{ ratio} \leq 1$ and a prolonged deceleration time.³²⁻³⁴ Finucci et al noticed that a significant proportion of the cirrhotics had a pathological E/A ratio.³³ Other studies have confirmed this and up to 80% have been shown to have diastolic dysfunction.³⁵⁻³⁷ The highest number was observed in a study using tissue Doppler imaging.³⁵

A low E/A ratio implies decreased ventricular compliance and increased contribution of the atrium to the filling of the left ventricle.^{31, 38} The E/A ratio can be affected by the preload of the heart.³⁰ In the setting of abnormal left ventricular relaxation and elevated left atrial pressure, pseudo-normalization of the mitral inflow may occur, thus increasing the E/A ratio.³⁹ Age, hypertension, body mass index, left ventricular mass, anemia, and heart rate may also affect E/A ratio.^{30, 40-42} Heart rate has also been reported to affect the E/A ratio, with higher heart rate decreasing the E/A ratio (every 10 beats decreasing the ratio 0.059).⁴³

The pathogenesis of diastolic dysfunction in cirrhotics has not been fully elucidated and different studies have suggested varying mechanisms. An early autopsy study showed myocardial thickening, histological examination revealed cardiomyocyte hypertrophy, altered pigmentation, nuclear vacuolization, edema, and fibrosis.⁴⁴ The E/A ratio has been reported to ameliorate following paracentesis which may implicate that edema plays a part in live patients as well.³⁶ The E/A ratio may also ameliorate following transplantation.¹²

1.2.2 Structural abnormalities

Comparing cirrhotic hearts with controls using echocardiography have shown enlargement of the left atrium and left ventricular systolic diameter in patients with ascites.^{15, 37} Left and right atrium have been reported to be larger in cirrhotics compared to controls even in patients without ascites.^{35-37, 45} Left ventricular wall thickness may also be increased^{36, 37} along with intraventricular septal thickness.³⁷

Right ventricular diameter has also been found to be enlarged compared to controls.³⁵ A study has also evaluated these alterations prior and following transplantation has shown them to be reversible.¹⁵ A further study also evaluated cirrhotics with cardiac magnetic resonance imaging with late gadolinium contrast enhancement in cirrhotics have shown diffuse uptake in the ventricles resembling myocarditis, controls had no uptake at all.⁴⁶

1.2.3 Electrophysiological abnormalities

The most important and frequent ECG abnormality in cirrhosis is a prolonged rate corrected QT time (QTc). This prolonged rate corrected QTc has been reported in up to 56 % of patients with cirrhosis.^{47, 48} Studies have shown that most, but not all patients reverse the QTc time following liver transplantation.^{47, 49-53} Beta blockers have been shown to decrease the QTc time in patients with cirrhosis.⁵⁴⁻⁵⁶ Patients with more severely impaired liver function seem to have a longer QTc time^{48, 57, 58} but results are not unanimous.⁵⁰ QTc prolongation may also be more frequent in alcoholic liver disease, but results from different studies are conflicting.^{47, 52}

QT dispersion, the difference in QT time in different leads on the ECG, has also been shown to be increased in cirrhotics.^{53, 55, 57} Differences in electrical and mechanical systole has also been demonstrated in cirrhotics, named dyssynchronous electromechanical systole.⁵⁹

Autonomic dysfunction has also been investigated in patients with cirrhotics where cardiac reflexes were abnormal in almost half the patients and parasympathic dysfunction abnormal in 77% of patients.^{52, 58} Heart rate variability has also been shown to be decreased in cirrhotics which has been considered a marker of autonomic dysfunction.^{54, 60}

Patients with a prolonged QTc time seem to have a shorter survival than cirrhotics without QTc prolongation.^{47, 57, 58} However only one study found it to be associated with increased cardiac related mortality⁶¹. However, only patients with alcoholic liver diseases (ALD) were included and not all had cirrhosis.⁶¹

1.3 Coronary artery disease

Studies regarding the prevalence of coronary artery disease (CAD) in liver cirrhosis have been conflicting. Early studies using autopsy results showed a low incidence of myocardial infarction and stroke,⁶²⁻⁶⁶ although there were methodological limitations in these studies. Atherosclerosis generally has also been described to be less frequent in cirrhotics⁶⁷ especially in patients with cholestatic disease (even if most studies were done on non-cirrhotic individuals).⁶⁸⁻⁷⁰ However this has also been questioned

in other *post mortem* studies.⁷¹ A reason for the negative association found in the early autopsy studies might be due to the early mortality in patients with liver cirrhosis *per se* rather than a low frequency of myocardial infarction.⁷² Vanecek showed a higher prevalence of calcified lesions in the left anterior descending coronary artery than age standardized controls (patients included were all above the age of 40 years). Calcified lesions were as high as 52 % for men and 25 % for women with cirrhosis but the prevalence of fresh myocardial scarring in cirrhotic was low.⁷³

More recent studies in patients undergoing pre-transplant evaluation have found higher prevalence in patients with end stage liver disease. Numbers range from 2-26 %⁷⁴⁻⁷⁹ with the lower number representing patients with alcoholic cirrhosis in one study. According to a recent review the mean prevalence was 13.3 %⁸⁰. The pathogenesis of CAD in cirrhotics is not known but the incidence of diabetes mellitus has been shown to be increased in cirrhotics. However it is not clear if this might explain the increased CAD in this population.^{74, 81} Chae et al evaluated the value of pre-operative CT-coronary arteriography in patients with negative findings on routine preoperative cardiac workup (ECG, Echocardiography and thallium SPECT) still approximately 10 % had findings of CAD, however, no healthy controls were included.

The role of coronary revascularization is not yet fully established in the cirrhotic population as patients with cirrhosis may die of other causes and may have an increased risk of complications, however, it may be beneficial prior to liver transplantation.⁸²⁻⁸⁵

1.4 Renal failure and cirrhotic cardiomyopathy

The cardiorenal syndrome is a condition where, an acute or chronic disorder in one organ (heart or kidney) may induce dysfunction in the other.⁸⁶ In liver cirrhosis, there is a relative underfilling of the vessels which results in a reduction in vascular resistance due to portal hypertension.⁸⁷ Spontaneous bacterial peritonitis, a common precipitator of hepatorenal syndrome in cirrhosis,⁸⁸ has been associated with a reduction in cardiac output and mean arterial pressure in patients that developed renal failure in comparison with patients who did not.⁸⁹

A relationship with cardiac index and renal function in cirrhotics has been reported showing patients with lower cardiac index to have a lower renal function.⁹⁰ Ruiz-del-Arbol et al also showed that cirrhotics that did not develop hepatorenal syndrome compared to cirrhotics who did, had a higher cardiac output, a higher mean arterial

pressure but a lower hepatic venous pressure gradient, plasma renin activity, and norepinephrine concentration⁹¹. Only cardiac output and plasma renin activity were independent predictors of hepatorenal syndrome.⁹¹

1.5 Clinical implications and liver transplantation

Adverse cardiac events following transplantation and their impact on transplant outcome has previously been assessed. Studies are generally not limited to patients with cirrhosis but cirrhotics constitute a large part of the transplant population. Dec et al showed that 70 % of liver transplant recipients had a cardiac complication of which 23 % were labeled as a major cardiac complication following transplantation (definitions not clear), including arrhythmias and myocardial infarctions.⁹² Fouad et al showed that 42 % of patients suffered one or more cardiac complications during the first 6 months following transplantation of which pulmonary edema (no specified definition) was the most common one.⁹³ Overall 7 % of patients with cirrhosis had a myocardial infarction during the first 30 days following transplantation and preoperative coronary artery disease was associated with cardiac events (odds ratio 3.96).⁹⁴ A study by Johnston showed a Framingham risk score of 7.5 % for 10 years ischemic events with an increased relative risk for ischemic events at approximately 3 compared to an age matched cohort.⁹⁵ Patients with non alcoholic steatohepatitis may have an increased risk of cardiovascular events compared to those with alcoholic cirrhosis. One study showed a difference in incidence of cardiac complications of 26 % vs 8 % following transplantation.⁹⁶

Heart failure following transplantation has to our knowledge not been investigated in a systematic manner prior to the commencement of this thesis. However studies have indicated the magnitude of the problem: Snowden et al showed a 47 % incidence of postoperative pulmonary edema (radiological on chest X-ray) following transplantation.⁹⁷ Others showed an incidence of 9 % pulmonary edema, and 31 %, respectively (and an incidence of 3.5 % “overt heart failure”).^{92, 93} In another study 56 % of patients required diuretic for pulmonary edema.⁷⁷ About 25 % of the patients in one study had an abnormal cardiac response (decreased stroke work despite increased preload) during reperfusion at liver transplantation.⁹⁸ In another retrospective study the incidence of heart failure was only 7 % (confirmed by chest X-ray and echocardiography) but the authors speculated that the incidence may be higher as only a fraction of patients underwent postoperative echocardiography.⁹⁹ Patients who experienced early cardiac depression also seem to have a worse outcome.¹⁰⁰

An increased preoperative troponin T value has also been evaluated as an independent predictor of graft failure and mortality, even in patients without previous known cardiac disease.¹⁰¹ It has also been shown to be a marker of increased risk for post-transplant cardiac mortality.¹⁰²

More recent studies have also confirmed the high rate of postoperative cardiac complications. One study identified cardiovascular complications as the leading cause of mortality.¹⁰³

1.5.1 Causes of death after liver transplantation

Cirrhosis is the most frequent indication for liver transplantation in Europe (52 %). Survival rates in Europe regardless of indication is at one month - 94%, at three months 91% and at 6 months 88%.¹⁰⁴ Almost half the deaths occur during the first six months following transplantation (within a five-year follow up). The main causes of death are in descending order: 1 - General causes such as multiple organ failure, including cerebrovascular and cardiovascular complications (29%). 2 - Recurrence of primary disease (20%). 3 - Sepsis (18%). 4 - Technical complications (5%) 5 - Rejection (4%). 6 - Intra-operative deaths and primary non-function (3%). Cardiovascular complications alone following liver transplantations, regardless of indication at total follow up time (< 5 years) was reported to be 8 %.¹⁰⁴ Concerning liver cirrhosis alone and causes of death following transplantation a few studies have been undertaken. Patients with cardiac events following transplantation had a lower 5 year survival rate.⁹² In the study by Fouad et al, cardiac mortality accounted for 24 % of all mortality.⁹³

1.5.2 Post-transplant complications

The spectrum of complications following liver transplantation differs in frequency immediately following transplantation and later on. Common complications include acute or chronic rejection, complications of immunosuppression including hypertension, renal insufficiency, infection, malignancy, a variety of dermatologic conditions, and metabolic diseases (such as diabetes mellitus, obesity, hyperlipidemia, and bone disease). Other common complications include biliary complications and recurrence of the primary liver disease.^{105, 106}

In the early phase, bacterial infections are the most common.¹⁰⁷ Later, opportunistic infections as a result of increased immunosuppression.¹⁰⁸

In the early phase after transplantation allograft rejections occur in approximately half of patients,¹⁰⁹ and in the late phase in about a quarter.¹¹⁰ About a fifth of patients who experienced a rejection episode will suffer another.¹⁰⁸

Renal failure in patients with cirrhosis after liver transplantation is usually of multifactorial origin and includes diabetes, immunosuppression, pre-existing renal disease, acute tubular necrosis and hypertension.^{87, 111} Patients on calcineurin inhibitors have a higher risk of developing renal failure,¹¹² with 30% loss or more of renal function occurs in about a third of the patients.¹¹³

Malignant disease is also common among transplant recipients, about a fifth of patients will develop a *de novo* malignancy after transplantation, with the majority being skin related. Malignancies usually develop later on.^{114, 115}

1.6 Quality of life

Impaired health-related quality of life (QoL) is of concern in liver cirrhosis.¹¹⁶ As patients with compensated cirrhosis have a median survival time of more than 12 years¹¹⁷ patients will endure a long period of time with disease.

QoL is known to be impaired in non-cirrhotic patients with heart failure who frequently also experience fatigue.^{118, 119}

Although several factors and complications as well as specific symptoms, have been reported to affect QoL in these patients,^{120, 121} the pathogenesis of its impairment is complex and remains incompletely understood. Liver disease severity¹²²⁻¹²⁵ and hepatic encephalopathy^{123, 126} are known to have a negative impact on QoL. Liver disease etiology has also been assessed in several studies but results are conflicting whether it has any impact in QoL or not^{124, 126-128}. Decompensation in liver cirrhosis is also associated with poorer QoL.¹²⁹ Ascites or previous ascites has also been linked to lower QoL, mostly through physical impairment.^{123, 125, 130} Other factors have also been associated with lower QoL such as hyponatremia,¹³⁰ increased number of comorbidities, unattached marital status,¹³¹ and development of hepatocellular carcinoma.¹³²

There are several different ways of assessing QoL in patients with liver cirrhosis of which the patient derived scale “Short form – 36” is the most used one¹³³. It consists of 36 questions, divided into eight domains with two summary scores, physical summary score and mental summary score.¹³⁴

Only one study has assessed cardiac impact on QoL in cirrhotics, it did not show any significant relationship with cirrhotic cardiomyopathy and QoL.¹³⁵

2 AIMS

Paper I

To systematically evaluate the prevalence and predictors of peri-transplant heart failure in a cohort of patients with liver cirrhosis and to study the potential relation of heart failure with morbidity and mortality post-transplant.

A secondary aim was to study the potential impact of left ventricular diastolic dysfunction on post-transplant morbidity and mortality.

Paper II

To investigate the potential role of pre-transplant renal function impairment in cardiac events following liver transplantation and to create a risk model for prediction of post-transplant cardiac events.

Paper III

The primary aim was to study the prevalence and predictors of pre-transplant ECG abnormalities in patients with cirrhosis.

The secondary aims were to define the risk for cardiac events in liver transplant recipients in relation to the general population and the potential relation of pre-transplant ECG abnormalities to post-transplant cardiac morbidity and mortality.

Paper IV

The primary aim was to investigate the potential relation of cardiac abnormalities, in particular diastolic dysfunction, with QoL impairment in cirrhotic liver transplant candidates.

A secondary aim was to assess the role of serum adiponectin on cardiac abnormalities in these patients

3 PATIENTS AND METHODS

3.1.1 Paper I

We did a retrospective cohort study where all patients with liver cirrhosis undergoing first-time liver transplantation between 1999 and 2007 in our institution were included. Patients were identified through the Swedish Liver Transplant Registry. Exclusion criteria were age < 18yr, acute liver failure, multi-visceral transplantation or liver transplantation for indications other than cirrhosis or its complications. The study protocol was approved by the regional ethical committee of Region Västra Götaland.

Patient data were collected from medical records, including etiology and complications of liver cirrhosis as well as comorbid illness and medication. Previous diagnosis of heart disease and risk factors for coronary artery disease were also collected from medical records. These included data regarding diabetes mellitus, history of arterial hypertension, smoking habits, and hereditary predisposition for CAD (any first degree relative with coronary artery disease, 55 years or younger for male and 60 years or younger for female relatives). The results of any pre-transplant test for CAD were also registered. In our transplant program pre-transplant testing for CAD is conducted in all patients who had several risk factors for CAD (such as age > 50 years, smoking, arterial hypertension, diabetes mellitus, family history of CAD) and/or when clinical suspicion of CAD was present (e.g. suspicion of angina pectoris, history of atherosclerotic disease such as stroke, etc). Patients were tested primarily by means of myocardial scintigraphy (or, more rarely, stress echocardiography or treadmill/bicycle exercise test depending on availability and if considered fit for one), followed by coronary angiography in the event of positive findings. A patient was classified as having CAD if they had previously been diagnosed with myocardial infarction, heart failure due to ischemia, unstable angina pectoris or if they had ever had any positive test for CAD, such as coronary angiography, exercise test, myocardial scintigraphy, or stress echocardiography. Liver disease severity along with basic blood chemistry was recorded. At pre-transplant evaluation, all patients were evaluated for ascites, varices, and encephalopathy.

Table 1. Baseline characteristics of all patients included in the study (n=234)

Age (years)	52 (range 19-72 SD 10.5)
Sex (female)	72 (31 %)
Etiology of liver disease	
ALD or mixed ¹	85 (36 %)
Viral hepatitis ²	55 (23.5 %)
Cholestatic disease ³	42 (18 %)
Cryptogenic cirrhosis	20 (8.5 %)
Autoimmune hepatitis	14 (6 %)
Other ⁴	18 (8 %)
Child Pugh class A/B/C	28 (12 %) / 104 (44 %) / 102 (44 %)
Child Pugh score	9 (range 5-14, SD 2.2)
MELD score	16.5 (range 6.4-40, SD 6.8)
Varices	167 (71 %)
Previous variceal bleeding	59 (25 %)
Ascites	167 (71 %)
Hepatic encephalopathy	53 (23 %)
Hepatorenal syndrome	43 (18 %)
Hepatocellular carcinoma	26 (11 %)
GFR (ml/kg/1.73m²)	82.6 (range 0-156 SD 29.5)
Cardiac parameters	
Heart rate (bpm)	72 (range 50-120 SD 11)
Blood pressure (map)	85.5 (range 55-123 SD 12)
Prolonged QTc on ECG ⁵	58/186 (32 %)
Cardiovascular Diseases	
Coronary artery disease	18 (8 %)
Previous PCI/CABG	3 (1.5 %)
Heart failure	5 (2 %)
Atrial fibrillation	8 (3 %)
Stroke	5 (2 %)
Cardiovascular risk factors	
Diabetes mellitus	48 (20 %)
History of arterial hypertension	28 (12 %)
Family history of coronary artery disease ⁶	16 (7 %)
Current or ex-smoker	118 (50 %)
Cardiovascular medications	
Beta blockers	112 (48 %)
Diuretics	152 (65 %)

Data are presented as mean (range, SD) or n(%) as appropriate
MELD, model for end-stage liver disease; ALD, alcoholic liver disease; CABG, Coronary artery bypass grafting; PCI, Percutaneous coronary intervention; bpm, beats per minute; map, mean arterial pressure

¹ ALD and viral hepatitis 15 %

² Hepatitis C 14 %, hepatitis B 10 %, hepatitis C and hepatitis B 0.5 %

³ Primary biliary cirrhosis 7 %, primary sclerosing cholangitis 11 %

⁴ Other etiologies include cholestatic and autoimmune, Wilson disease, Alpha-1 Antitrypsin deficiency, drug induced liver disease, cystic fibrosis, secondary sclerosing cholangitis

⁵ ECG was only available for retrospective review in 186 patients

⁶ Any first degree relative with coronary artery disease, 55 years or younger if male and 60 years or younger if female

Outcome and events

Peri-transplant heart failure was assessed using the Boston classification for heart failure,¹³⁶ as no perioperative echocardiography was available during the immediate inpatient period following transplantation. Scoring according to the Boston classification is based on three different domains. The first domain uses clinical symptoms suggestive of heart failure. The second domain uses physical data including heart rate, jugular venous pressure, and auscultatory findings of the lungs. The third domain consists of any chest radiographic findings suggestive of heart failure. A maximum of 4 points can be given from each domain, thus yielding a maximum score of 12. A score of 8 or more was classified as “highly possible” and 7 or below as “unlikely”.

Mortality and cardiac events were analyzed during the immediate post-transplant inpatient period until discharge, labeled “peri-transplant events” and post-hospital discharge until last follow-up, labeled “late events”. A cardiac event was defined as arrhythmias (such as atrial flutter/fibrillation, severe brady arrhythmias or ventricular arrhythmias), acute coronary syndrome (diagnosed by an attending cardiologist in the immediate inpatient period post-transplant and/or as ICD-10 codes in the post-discharge period) and sudden cardiac death. The period of time spent in the intensive care unit (ICU), and that spent hospitalized post-transplant as well as rejection episodes and other adverse events (such as re-transplantation and infections) were also analyzed. Cut-offs of ischemia duration > 12 hours and donor age > 55 years were used to dichotomize the cohort.

Cardiac evaluation

The Q-T interval was registered manually and was rate corrected according to the Bazett formula ($QT \text{ time} / \sqrt{RR \text{ interval}}$)¹³⁷. All available baseline resting echocardiograms (performed routinely at pre-transplant evaluation) were reviewed by a trained technician. Standard echo dimensions, wall sizes, and dynamic data were registered. HFNEF was defined as normal ejection fraction, normal left ventricular diastolic diameter, normal left ventricular systolic diameter and left ventricular wall thickness above reference or left atrial diameter above reference³¹. Diastolic dysfunction was defined as an E/A ratio ≤ 1 ³².

Follow-up

Mortality and cardiac events were analyzed from the date of liver transplantation until last follow up and were labeled either as peri-transplant or as late events. Patients were followed from the date of liver transplantation to the date of death or last day of follow-up until December 31, 2009. Three strategies were used for follow-

up: 1.date and cause of death were obtained from the National Cause of Death Register (updated until December 31, 2009); 2. Information on any post-transplant cardiac events occurring in other institutions was obtained through the national in- and out-patient diagnosis register (updated until December 31, 2009); and 3. Information on all cardiac or other events prior to and during the peri-transplant period through follow-up to last in- or out- patient episode until December 31, 2009 was obtained from local hospital medical records.

3.1.2 Paper II

Patients and methods

The same cohort as in paper I was used for this study. However, as we aimed to study the impact of renal function on cardiac events we excluded all patients who did not have an available glomerular filtration rate (GFR), assessed by 51Cr-EDTA clearance (32 patients excluded, 202 included). The GFR was routinely assessed at pre-transplant evaluation and one year post-transplant by means of 51Cr-EDTA clearance measurement. Impaired renal function was defined as a GFR below 60 ml/min/1.73 sqm (i.e. \geq grade 3 renal impairment)¹³⁸.

QT interval and echocardiography were recorded and included as in paper I. QT interval according to the Bazett formula and considered prolonged if \geq 440 ms.⁵⁸ Left ventricular diastolic dysfunction was defined as an E/A ratio \leq 1.

Table 2 Renal parameters in patients of paper II (n=202)

Hepatorenal syndrome	35 (17.5 %)
Type 1	22 (11 %)
Type 2	13 (6 %)
Renal function	
GFR ml/min/1.73sqm	82.7 (SD 29.5 range 0-156)
GFR < 60 ml/min/1.73sqm	48/202 (24 %)
GFR < 30 ml/min/1.73sqm	7/202 (3.5 %)
Chronic renal disease	5/202 (2.5 %)
Hemodialysis	3/202 (1.5 %)

Outcome

Events were defined in the same way as in paper I. We added late and peri-transplant events to a new definition, “total events”, if a patient had either one, they were classified as having an event.

Risk model development

To develop a pre-transplant risk model prognostic of the occurrence of post-transplant cardiac events, we did a cox regression analysis to identify factors of importance to having post-transplant cardiac events. We then used the pre-transplant risk factors identified and divided into four categories according to number of risk factors they had (0-3): low risk (no risk factor), intermediate risk (1 risk factor), high risk (2 risk factors), and very high risk (3 risk factors). The c-statistic of the model was calculated for prediction of cardiac events at 3- months and 12 months post-transplant. We also did an internal validation of the model using a bootstrapping procedure. A new population of 202 individuals was randomly drawn with replacement from the original population of 202 individuals. Logistic regression was performed on the model (excluding the time variable) in order to validate the c statistic. This procedure was carried out a 1000 times. Odds ratios (OR) were assessed for each group with logistic regression analysis.

3.1.3 Paper III

Patients and methods

Again, the same cohort as in paper I and II was used. For the purposes of this paper, to study the relationship of ECG alterations and cardiac events, we excluded all patients who did not have an available ECG for retrospective review (total included=186). However, as a secondary aim was to assess the frequency of cardiac events in liver transplant patients compared to the general public, we also used the full cohort (n=234) for comparison with the general Swedish population.

Weight and height were measured at pre-transplant evaluation and body mass index (BMI) was calculated this data was added to the analysis. Patients with a BMI > 25 kg/m² were considered overweight and those with a BMI > 30 kg/m² were considered obese.¹³⁹

ECG analysis

All available baseline electrocardiograms, routinely obtained at pre-transplant evaluation (mean time on transplant list was 2 months, range 0-14), were reviewed by two investigators, without knowledge of the clinical characteristics of the patients. ECGs were analyzed according to the Minnesota code for resting electrocardiograms¹⁴⁰, consisting of nine domains: the presence of a Q wave, QRS axis deviation, high-amplitude R waves, ST segment depression, T wave abnormalities, A-V conduction defects, ventricular conduction defects, arrhythmias and a miscellaneous items domain (including low QRS amplitude, ST segment elevation, pathologic QRS transition zone and high P or T wave). The Q-T interval was also manually assessed. The ECG was considered to be positive for CAD if Q wave, ST segment depression and/or a pathologic T wave was present. All ECG features were analyzed only if the ECG was considered to be of sufficient quality to be interpreted.

A control group of individuals (n=92) with similar age and gender distribution to the group of patients with an available pre-transplant ECG was used for comparison of the prevalence of ECG abnormalities. Controls were enrolled mainly among hospital staff and relatives. None of the controls had a medical history and, in particular, all denied a diagnosis of CAD or liver disease. All the controls had normal liver tests.

Outcome

The same outcome measurements were analyzed as in paper II. Cardiac events were then compared to the Swedish general population, the method for this is presented in the statistics section below.

3.1.4 Paper IV

Patients and methods

Post hoc analysis of data from a cohort of cirrhotic liver transplant candidates included in a prospective study between May 2004 and April 2007 aiming to assess fatigue determinants before and after liver transplantation was undertaken.¹²⁰ In short, consecutive adult cirrhotic transplant candidates regardless of cirrhosis etiology were included (n=88 out of 108 patients in the original study). Data regarding cirrhosis etiology and complications, and comorbid illness, including cardiac disease, were collected from medical records. The E/A ratio, was also included. The study was approved by the regional ethics committee.

Questionnaires

All patients were asked to fill out questionnaires assessing health-related QoL: Short-form 36 for QoL,¹³⁴ Fatigue impact scale for fatigue¹⁴¹ and Hospital Anxiety and Depression Scale for assessing depression and anxiety.¹⁴² QT interval and echocardiography was assessed in a similar manner as in paper I-III.

Cardiac biomarkers were analyzed in a subset of patients (n=61/88, 69 %) from blood samples at pre-transplant evaluation and stored in a -80° C freezer and thawed for the purposes of this study: i. NTproBNP, which is highly sensitive for heart failure and associated with prognosis and quality of life in non-cirrhotic individuals with heart failure¹⁴³; ii. High-sensitive Troponin T, a marker of cardiac myocyte damage due to a number of clinical conditions, including heart failure; and iii. Adiponectin. Local cut-off values from our laboratory were used for NTproBNP (For patients ≤ 50 years old: NTproBNP <300 ng/L, normal; 300-400 ng/L, possible; and >400 ng/L, likely heart failure. For patients between 51-76 years old: NTproBNP <400 ng/L, normal; 400-900 ng/L, possible; >900 ng/L, likely heart failure) and Troponin T (≤ 14 ng/L, normal).

Table 3 Baseline patient characteristics (n=88)

Age (years)	53.5 (9.5)
Gender (F/M)	28/60 (32 % / 68 %)
Etiology of liver cirrhosis	
Alcoholic liver disease or mixed	33 (37.5 %)
Viral	22 (25 %)
Cholestatic	15 (17 %)
Cryptogenic/nonalcoholic steatohepatitis	7 (8 %)
Other	11 (12.5 %)
Complications of liver cirrhosis	
Ascites	30 (34 %)
Hepatic encephalopathy	17 (19.5%)
Previous variceal bleed	25 (28.5 %)
Hepatocellular carcinoma	18 (20.5 %)
Severity of liver cirrhosis	
Child–Pugh class A/B/C	12/45/31 (14% / 51% / 35%)
Child–Pugh score	9 (2.2)
MELD score	15 (5.8)
Cardiovascular parameters and risk factors	
Coronary artery disease	6 (7 %)
Previous stroke	1 (1 %)
Diabetes mellitus	27 (31%)
History of arterial hypertension	9 (10 %)
Serum Cholesterol > 4.5 mmol/L	22 (25 %)
Previous or current smoker	48 (54.5 %)
Treatment with beta blockers	41 (46.5 %)
Comorbid illness	63 (71.5 %)

Data are presented as mean (SD) or n (%) as appropriate.

3.2 Statistics

Paper I

Data were expressed as means and standard deviation (SD) or as n and percentages as appropriate. When comparing two groups, the chi square test was used for dichotomous variables. For comparison of continuous variables the student's t-test was used. In an attempt to identify independent predictors of left-ventricular diastolic dysfunction, peri-transplant heart failure and peri-transplant mortality, variables that achieved a p-value <0.1 in univariate analysis were included in multivariate analyses using a logistic regression procedure. For late mortality univariate analysis was performed using the method of Kaplan-Meier and groups were compared using the log-rank test. In order to identify independent predictors of late mortality during follow-up, variables that achieved a p-value <0.1 in univariate analysis were included in a multivariate analysis using a proportional hazards Cox regression procedure. All

tests were two-tailed and were conducted at a 5 % significance level. Statistics were calculated with SPSS v 17.0 (Chicago, Illinois) for the Microsoft Windows operating system.

Paper II

Similar statistics as in paper I were used. In addition, to identify variables independently related to cardiac events and cardiac event-free survival, variables with a p-value <0.1 in univariate analysis were included in multivariate analysis using a Cox regression procedure. We adopted a staged approach in regression analysis due to difference in data availability in subgroups (data for QTc and diastolic dysfunction 82 % and 55 % respectively). In the first stage we included all variables but prolonged QTc time and left ventricular diastolic dysfunction, these were added in stage two. Using the pre-transplant risk factors identified by regression analysis, we developed a risk model of the occurrence of post-transplant cardiac events. All tests were two-tailed and were conducted at a 5 % significance level. All authors had access to all data and reviewed and approved the final manuscript.

Paper III

Similar statistics as in paper I were used. In addition, to calculate the difference in incidence of cardiac events between our cohort and the general Swedish population, the expected number of cases used to calculate standardized incidence ratio (SIR) for post-transplant cardiac events was obtained by multiplying person-years in the cohort with the corresponding incidence in the entire Swedish population. Data from the Swedish population were collected from the national inpatient diagnosis registry maintained by the Swedish National Board of Health and Welfare (cardiac events defined as specified above). The national inpatient diagnosis registry covers virtually all inpatient episodes in Sweden since 1987, with only about 0.9-1.5 % per year of all ICD-10 code statistics being lost due to insufficient data submission. Exact confidence intervals of SIRs and p-values were calculated assuming Poisson-distributed number of observed cardiac event cases. All statistical tests were two-sided and were conducted at a 5% significance level.

Paper IV

Data were expressed as mean and SD or as n and percentages as appropriate. When comparing two groups, the chi square test was used for dichotomous variables. For comparison of a continuous variable and a dichotomous variable the student's t-test or the Mann-Whitney U test was used, as appropriate. For comparing two different continuous variables we used the Pearson product-moment correlation or the Spearman's rank correlation as appropriate. The correlations of cardiac parameters

with health-related QoL were adjusted for potential confounders by means of a linear regression model or binary logistic regression model as appropriate. All tests were two-tailed and were conducted at a 5% significance level.

4 RESULTS

4.1 Paper I – Post-transplant heart failure and outcome

Twenty-seven percent of patients experienced highly possible heart failure during the peri-transplant period as assessed by means of the Boston classification. Pre-transplant factors that were univariately associated with peri-transplant heart failure are listed in table 4 and factors in logistic regression analysis independently associated with highly possible heart failure in the peri-transplant period were prolonged QTc time (OR 9.10, 95 % CI 3.77-21.93) and lower baseline mean arterial pressure (OR 0.94, 95 % CI 0.91-0.98).

Table 4 Baseline characteristics of patients with and without heart failure according to the Boston classification in the peri-transplant period (n=234)

	Highly possible heart failure (n=63)	Unlikely heart failure (n=171)	p-value
Age (years)	55.5 (range 25-72, SD 8.8)	51.5 (range 19-72, SD 11)	0.009
Sex (female)	27 (43 %)	45 (26 %)	0.015
Previous or current smoker	32 (51 %)	86 (50 %)	0.789
Ascites	42 (66.5 %)	90 (53.5 %)	0.054
MELD score	18.7 (range 6.4-40, SD 7)	15.7 (range 6.4-40, SD 6.5)	0.003
Child-Pugh score	9.5 (range 5-14, SD 2.4)	8.9 (range 5-14, SD 2.2)	0.064
Coronary artery disease	4 (6.5 %)	14 (8 %)	0.064
Beta blocker	27 (43 %)	85 (49.5 %)	0.363
Prolonged QTc time	31 (16.5 %)	27 (14.5 %)	<0.001
Left-ventricular diastolic dysfunction	8 (21.5 %)	14 (16 %)	0.444
HFNEF	12 (37.5 %)	18 (27.5 %)	0.326
Blood pressure (map) (mmHg)	80.5 (range 55-120, SD 14)	87.2 (range 66-123, SD 10.8)	<0.001
GFR (ml/kg/1.73m ²)	74.2 (range 0-117, SD 27.2)	86.1 (range 0-156, SD 29.8)	0.009
Plasma sodium levels (mmol/l)	134 (range 119-142, SD 5)	135.5 (range 111-148, SD 5)	0.047

Data are presented as mean (range, SD) or n (%) as appropriate

MELD, model for end-stage liver disease; map, mean arterial pressure; GFR, glomerular filtration rate; HFNEF Heart failure with normal ejection fraction

Peri-transplant highly possible heart failure was associated with a longer stay in the intensive care unit (14.5 days (SD 16) vs. 4 days (SD 4.8), $p<0.001$), and longer duration of hospitalization immediately following transplantation (33 days (SD 24) vs. 21 days (SD 10), $p<0.001$). Patients with highly possible heart failure were also more likely to die or receive a re-transplantation in the peri-transplant period compared to the rest of the cohort (17.5 % vs. 0.5 %, $p<0.001$, and 24 % vs. 2 %, $p<0.001$, respectively). In the peri-transplant period, all patients who died (n=12) had

a Boston score ≥ 8 (highly possible heart failure) apart from one who had 7, and the relative risk of mortality with “highly possible heart failure” was 30. Peri-transplant heart failure was related to late graft mortality and patient mortality throughout the entire follow up period post-transplant (figures 1 and 2, below).

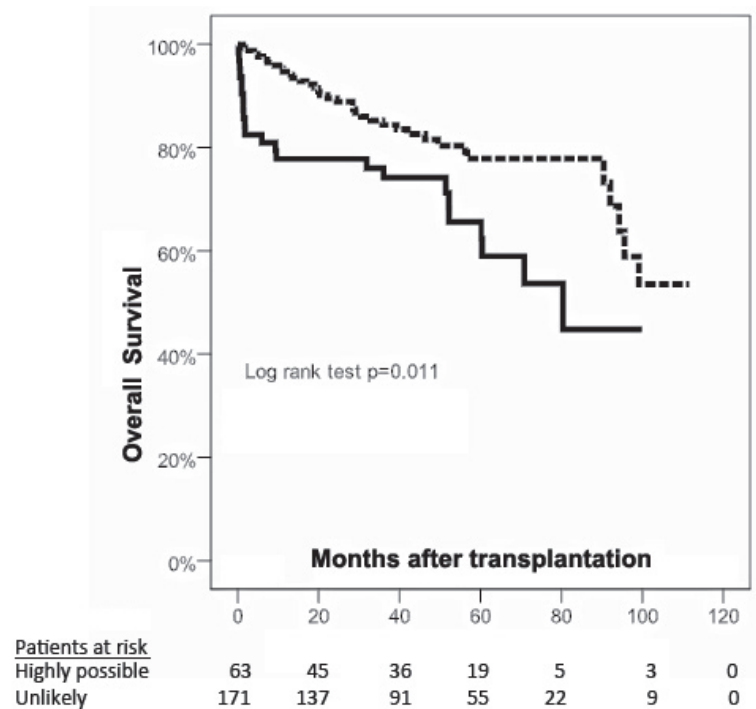


Figure 1: Patient survival and heart failure. Dotted line represents patients without heart failure and solid line patients with heart failure.

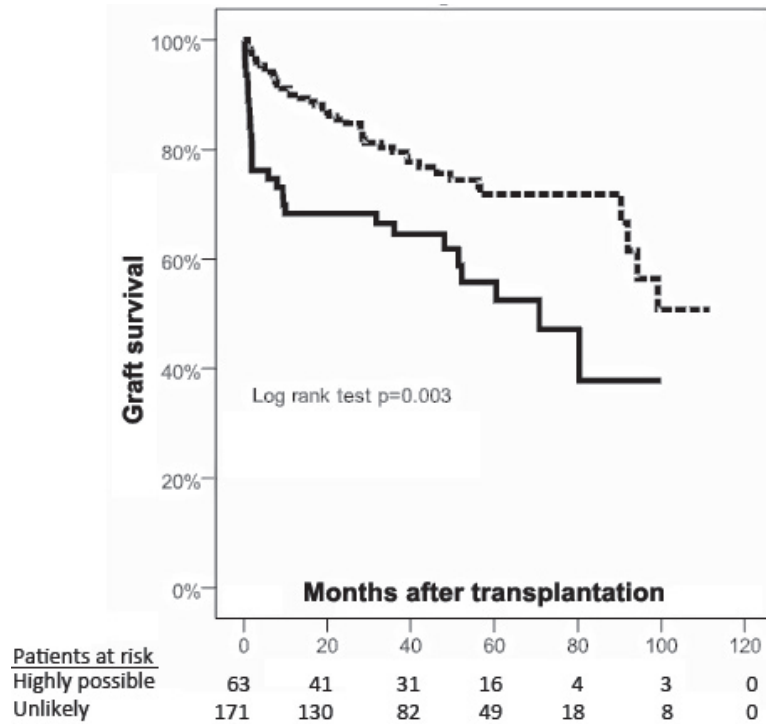


Figure 2: Graft survival and heart failure. Dotted line represents patients without heart failure and solid line patients with heart failure.

In multivariate analysis, peri-transplant mortality was independently related to highly possible heart failure (OR 15.11, 95 % CI 1.76-129.62) and the need of dialysis in the peri-transplant period (OR 14.18, 95 % CI 1.65-121.89) but not to any other cirrhosis, cardiac or transplant-related factors (data not shown).

In Cox regression analysis, factors independently related to late overall patient mortality were history of arterial hypertension (HR 6.58, 95 % CI 1.88-23.08), use of beta blockers preoperatively (HR 0.25, 95 % CI 0.08-0.75), history of hepatorenal syndrome (HR 6.47, 95 % CI 1.90-22.05), hepatocellular carcinoma (HR 8.61 95 % CI 1.87-39.68) and hospital admission in the first year post-transplant due to infection (HR 3.29, 95 % CI 1.14-9.53) but not any other cirrhosis, cardiac or transplant-related factors (data not shown).

In logistic regression analysis, factors independently related to mortality or retransplantation in the peri-transplant period were only need of dialysis (OR 7.54, 95 % CI 1.85-30.69), cardiac events other than heart failure (OR 5.74, 95 % CI 1.64-20.05) and significant infection (OR 9.90, 95 % CI 2.03-48.24).

Using Cox regression analysis, factors that were independently related to late graft mortality (after the immediate in-patient period), were only diastolic dysfunction at baseline (HR 4.82, 95 % CI 1.78-13.06), history of hepatorenal syndrome (HR 4.02, 95 % CI 1.53-10.60), hepatocellular carcinoma (HR 4.18, 95 % CI 1.446-12.106) and hospital admission within the first year post-transplant due to infection (HR 7.72, 95 % CI 2.97-20.03).

Diastolic dysfunction

Eighteen percent of patients had left ventricular diastolic dysfunction at baseline but it was not related to peri-transplant heart failure, mortality, or graft mortality. In logistic regression analysis, the only baseline factors that were found to be independently related with diastolic dysfunction were age ≥ 53 yrs (Odds ratio (OR) 6.72, 95 % confidence interval (CI) 1.85-24.38), hemoglobin level (OR 1.05, 95 % CI 1.01-1.10) and use of beta blockers (OR 0.26, 95 % CI 0.08-0.87). Neither etiology, severity or complications of cirrhosis nor history of CAD or cardiovascular risk factors were related to diastolic dysfunction (data not shown).

4.2 Paper II – Renal impairment and cardiac events

Patients with renal impairment, compared to the rest of the cohort, were older (58 yr (7) vs. 50 yr (11), $p=0.001$), had higher MELD score (19 (5.5) vs. 15 (6.2), $p=0.001$), more frequently ascites (75 % vs. 19 %, $p=0.001$) and hepatorenal syndrome (34 % vs. 13 %, $p=0.001$), but did not differ in gender or etiology of liver disease ($p>0.05$ for both), in history of CAD (8.5 % vs. 6 %), diabetes mellitus (27 % vs. 17.5 %), smoking (54 % vs. 51 %), or family history of CAD (8.5 % vs. 8 %). However, a history of stroke and arterial hypertension was more common in the former (8.5 % vs. 0.5 %, $p=0.003$; and 27 % vs. 8 %, $p=0.001$, respectively), and prolonged QTc

interval was more common in patients with renal impairment (47.5 % vs 27 %, $p=0.015$).

Occurrence of cardiac events and cardiac event-free survival following liver transplantation

A total of 56/202 (28 %) patients had one or more cardiac events following liver transplantation, with 35 (17 %) patients experiencing a peri-transplant cardiac event and 24 (12 %) patients a late cardiac event. Arrhythmias, notably atrial flutter/fibrillation, were more common than coronary events in the peri-transplant period, while in the late period arrhythmias and coronary events were almost equally common.

Peri-transplant mortality was attributed to cardiac causes in 30%, compared to 13% in the late, post-discharge period.

Factors related to cardiac events following liver transplantation

Baseline renal impairment, prolonged QTc time, and left-ventricular diastolic dysfunction were related to lower cardiac event-free survival post-transplant and increased frequency of cardiac events although left-ventricular diastolic dysfunction was not univariately related to cardiac events. Upon stratification of patients according to baseline renal function, cardiac events at 12 months post-transplant occurred in 29% of patients with pre-transplant GFR <30 ml/min/1.73, 42% of those with GFR between 30 - 60 ml/min/1.73, in 17% with GFR between 60 - 90 ml/min/1.73 and 14% in with GFR >90 ml/min/1.73 (log rank test $p=0.002$). In Kaplan-Meier analysis, after exclusion of patients with arrhythmias, acute coronary syndromes (ACS) occurred more frequently in patients with renal failure vs. those without (data not shown; log rank test $p=0.012$). Following transplantation, renal function improved in only 4/24 patients with pre-transplant renal impairment. There was no significant difference in the occurrence of post-transplant cardiac events between patients with renal impairment (GFR<60) one year following liver transplantation compared to the rest of the cohort (log rank test $p=0.65$).

In Cox regression analysis, pre-transplant renal impairment, age above 52 years, severe infection requiring hospitalization during the first year post-transplant, and prolonged QTc interval (QTc only in stage 2 of the model – see statistics section), but not left ventricular diastolic dysfunction, were independently related to post-transplant cardiac events.

4.2.1 Model for risk assessment

Using the main pre-transplant risk factors identified in the Cox regression model we attempted to develop a risk model for prediction of the risk of posttransplant cardiac events. Depending on the number of pre-transplant factors present, each patient received a score between 0-3, one for each risk factor (i.e. prolonged QTc time, renal impairment, age above 52). Patients were subsequently divided into 4 risk groups: low (score 0), intermediate (score 1), high (score 2) and very high (score 3). In Kaplan-Meier analysis the occurrence of cardiac events was shown to be significantly different among the groups (figure 3). All but one patients with myocardial infarction (n=15) had one or more risk factors (no factors = 1 patient, one factor = 2 patients, two factors = 9 patients, three factors = 3 patients).

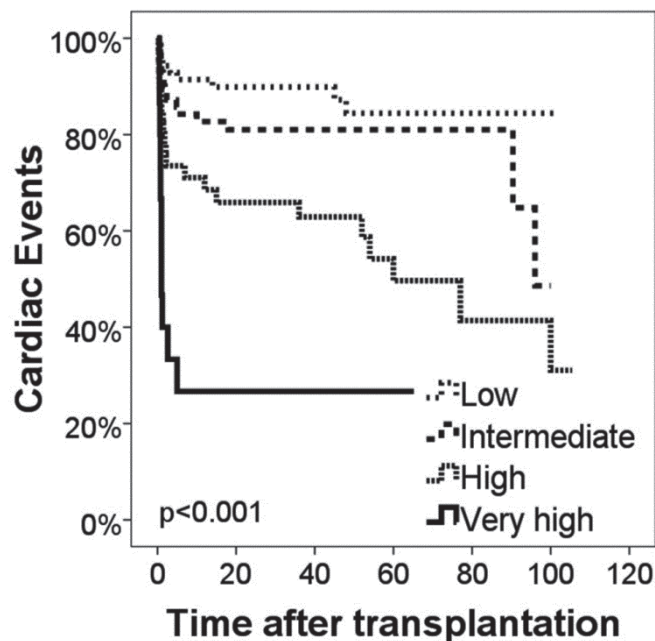


Figure 3. Cardiac events and pretransplant risk stratification.

The statistics for the riskmodel is shown in table 5. Our model was the most frequently selected one in the validation process (described above), as this occurred 469/1000 times (46.9 %) with the second most frequently selected model being

selected 164 times (16.4 %). The model performed similarly when using estimated glomerular filtration rate (eGFR) with modified diet in renal failure 4 (MDRD4) formula (table 5).

Table 5 Risk of cardiac events 3 months and 12 months post transplant.

Risk group	No (%)	Cardiac events at 3 months (95 % CI)	Cardiac events at 12 months (95 % CI)
Low	70 (34.5 %)	1	1
Intermediate	71 (35 %)	OR 2.40 (0.70-8.18)	OR 2.17 (0.77-6.15)
High	46 (23 %)	OR 5.82 (1.75-19.43)	OR 4.67 (1.64-13.29)
Very high	15 (7.5 %)	OR 33.00 (7.56-144.02)	OR 29.33 (7.11-121.08)
c-statistic		0.75 (0.66-0.84)	0.73 (0.64-0.82)
R ²		22.7 %	21.2 %
c-statistic with MDRD4 eGFR		0.75 (0.66-0.84)	0.73 (0.64-0.82)
c-statistic for ACS only*		0.77 (0.61-0.93)	0.81 (0.70-0.93)

OR, Odds Ratio; CI, Confidence Interval; R², R-square Nagelkerke; MDRD4, modified diet in renal failure 4;

eGFR, estimated GFR; ACS, Acute Coronary Syndrome

Each patient was classified according to how many riskfactors they had at pretransplant evaluation: impaired renal function, prolonged QTc interval and age > 52. Patients were classified into 3 different categories depending on their riskfactors.

*After exclusion of arrhythmic events

4.3 Paper III – ECG and outcome

Prevalence of ECG abnormalities at pre-transplant evaluation (n=186)

When compared with controls, patients with cirrhosis at pre-transplant evaluation had more frequently a prolonged QTc interval, a Q wave, abnormal QRS axis deviation, ST segment depression, a pathologic T wave and ECG features compatible with CAD (p<0.05 for all). BMI was not associated with ECG abnormalities.

ECG and outcome

The majority of patients suffering a post-transplant cardiac event had at least one of the ECG abnormalities mentioned above (37/54, 69%). Total cardiac events were associated with prolonged QTc time, the presence of a pathological Q wave and, the presence of any ECG feature compatible with CAD, but not with QRS axis deviation or ST-segment depression. The occurrence of post-transplant ACS and arrhythmias,

in particular atrial arrhythmias, was also associated with prolonged QTc interval (log rank test, $p=0.01$ and $p<0.001$, respectively), the presence of a Q wave (log rank test, $p=0.005$ and $p=0.008$, respectively), and any feature of CAD on ECG (log rank test, $p=0.029$ and $p=0.001$, respectively), but not QRS axis deviation nor ST segment depression ($p>0.05$ for both). Post-transplant mortality was increased in patients with prolonged QTc interval (log rank test, $p<0.001$) and the presence of a Q wave (log rank test, $p=0.044$) at pre-transplant evaluation, but not with any other ECG abnormality ($p>0.05$ for all).

Incidence of cardiac events following liver transplantation (n=234)

Transplanted patients were 14 times more likely to suffer a cardiac event following liver transplantation compared to the general Swedish population. Risks were increased both for ACS and arrhythmias, but reached statistical significance only in the former as regards to late events.

Table 6. Standardized incidence ratios for cardiac events in patients with cirrhosis (n=234) following liver transplantation

	Observed person years	Observed events ¹	Expected events ²	SIR	95% CI	p-value
Total cardiac events ³	728.9	70 ⁵	13.96	5.014	3.909 - 6.335	<0.001
Total ACS ³	728.9	16	4.336	3.69	2.109 - 5.992	<0.001
Total arrhythmic events ³	728.9	49	9.624	5.091	3.767 - 6.731	<0.001
Late cardiac events ⁴	846.0	31 ⁵	17.1	1.813	1.232 - 2.573	0.003
Late ACS ⁴	846.0	13	5.264	2.469	1.315 - 4.223	0.006
Late arrhythmic events ⁴	846.0	14	11.84	1.183	0.647 - 1.984	0.603

SIR, Standardized incidence ratio; CI, Confidence interval; ACS, acute coronary syndromes. For the calculation of SIRs, data on the occurrence of cardiac events in the general Swedish population were obtained from the national inpatient hospital registry

1. Observed events; the number of observed events in our cohort
2. Expected events; the number of events that occurred in the age and gender matched group of the general population
3. All events occurring after liver transplantation until death or end of follow-up
4. All events occurring after the immediate inpatient post-transplant period
5. The non-ACS and non-arrhythmic events were severe cardiac failure/sudden cardiac arrest of uncertain origin

4.4 Paper IV – Quality of life and cardiac abnormalities

In all, 88 patients with a digitally available resting echocardiogram performed at pre-transplant evaluation were included. 30.5% had LVDD and 25% had features of HFNEF. One fifth of the patients had increased serum high-sensitive troponin T and 14% had possible or likely heart failure, as assessed by means of the serum NTproBNP levels.

Echocardiographic abnormalities

The mean PCS (36.5, 95% confidence interval (CI) 34.0-39.1) and mean MCS (40.8, 95% CI 38.0-43.7) were lower compared to reference values from the general Swedish population (48.6, 95% CI 48.0-49.3 and 47.9, 95% CI 47.2-48.5, respectively). Fatigue scores were also increased compared to controls from the general population. Neither diastolic dysfunction nor features of HFNEF or any other echocardiographic parameter were related to the SF-36 PCS and MCS scores or to the FIS domain scores.

Prolonged QTc interval

Patients with a prolonged QTc interval had significantly lower SF-36 scores as well as increased fatigue scores compared to the rest of the cohort (figures 4 and 5). However, after adjustment for age, sex, cirrhosis severity (Child-Pugh score), ascites, encephalopathy, and comorbidity, as well as for depression and anxiety, assessed by the HAD, prolonged QTc interval remained significantly related only to MCS (Beta=-9.7, $p=0.009$) but not to any other SF-36 domain score or PCS ($p<0.05$ for all). After adjustment for factors known to predict FIS domain scores (i.e. depression and anxiety, assessed by the HAD, ascites, anemia, and GFR), prolonged QTc interval was still significantly related to the physical FIS domain score (beta=10.5, $p=0.004$), but not to the psychosocial, cognitive or total FIS scores ($p>0.05$ for all; data not shown).

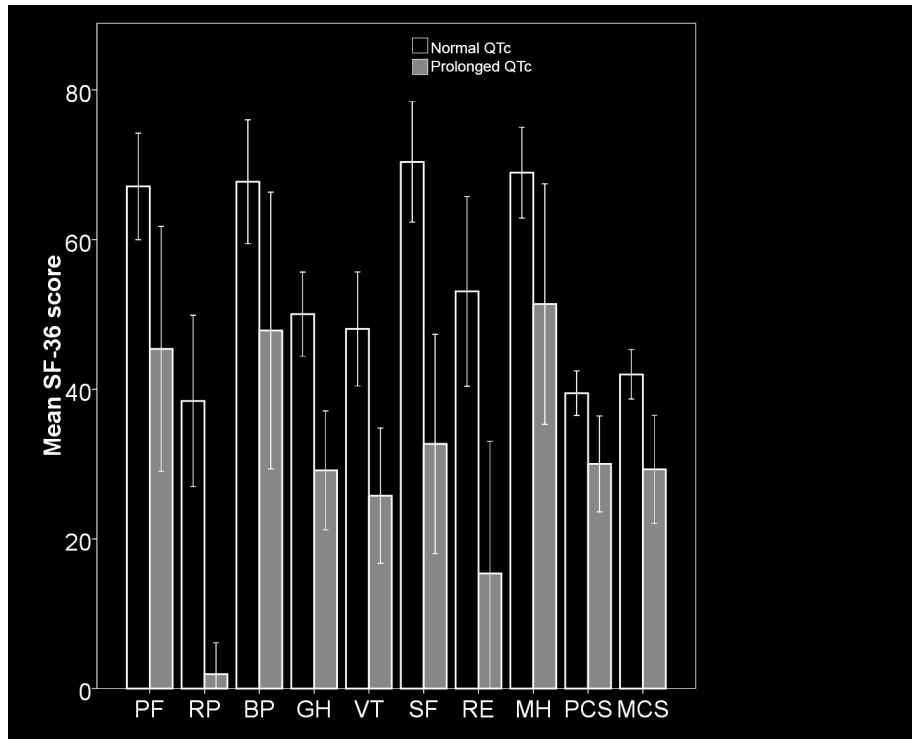


Figure 4. SF-36 scores and QTc time $p < 0.05$ for all, Error bars indicate 95% confidence interval. PF - Physical functioning, RP - Role-Physical, BP - Bodily Pain, GH - General Health, VT - Vitality, SF - Social Functioning, RE - Role-Emotional, MH - Mental Health, PCS - Physical Component Summary, MCS - Mental Component Summary

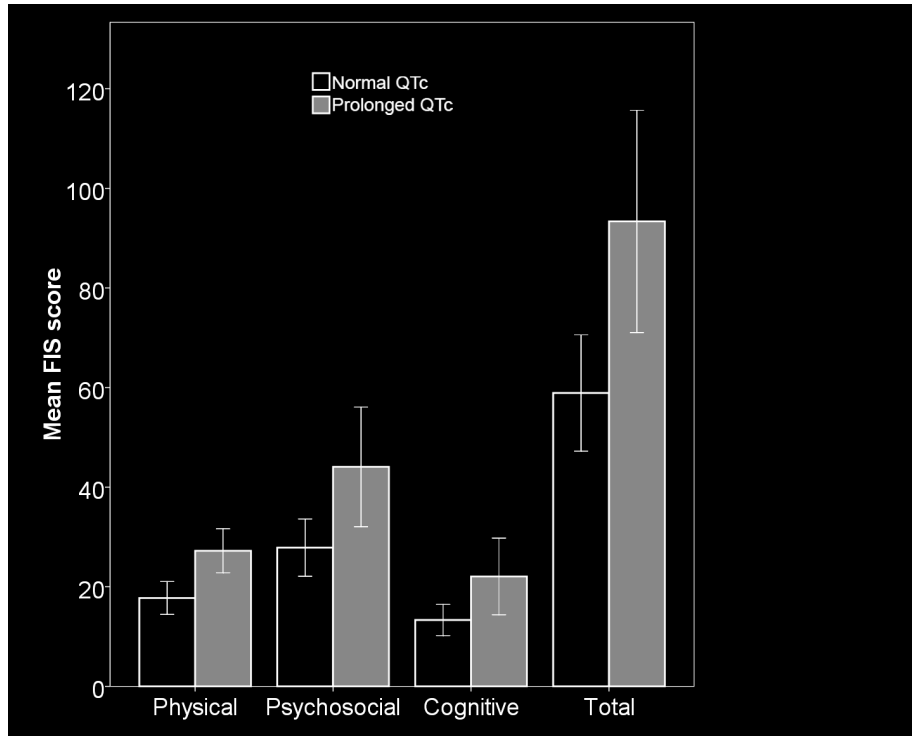


Figure 5. *QTc* and FIS score, $p < 0.05$ for all. Error bars indicate 95 % confidence interval.

Cardiac biomarkers

Patients with an increased NTproBNP (possible or likely heart failure) compared to those with normal NTproBNP levels had lower physical functioning SF-36 domain scores (36.5 (SD 24) vs. 68 (SD 28), $p < 0.05$) but the two groups did not differ significantly in any other SF-36 or FIS domain ($p > 0.05$, data not shown). After adjustment for liver cirrhosis severity (Child-Pugh score), age and gender, the relationship with physical functioning did not remain significant ($p > 0.05$). Patients with increased high-sensitive troponin T levels did not differ significantly in any SF-36 or FIS domain scores compared to the rest of the cohort ($p > 0.05$ for all, data not shown).

Serum adiponectin levels were not significantly related to either FIS or SF-36 ($p > 0.05$ for all domains). Serum adiponectin levels were correlated to liver disease severity and serum NTproBNP as well as serum high-sensitivity troponin T but not to LVDD, HFNEF or other cardiac alterations. In linear regression analysis, serum

adiponectin was only related to liver disease severity, expressed as the Child-Pugh score (beta=2.81, p=0.041).

5 DISCUSSION

Cardiac complications are common following liver transplantation and seem to be associated with post-transplant morbidity and mortality. Cardiac complications amongst liver transplant patients are also a long term problem after the initial discharge from the immediate inpatient period. In this thesis we also present certain risk factors at pre-transplant evaluation that may aid in the risk stratification of patients at that time for cardiac complications post-transplantation, including ECG alterations. However cardiac dysfunction in liver transplant candidate does not seem to be of major importance for health related quality of life or fatigue.

5.1.1 Cirrhotic cardiomyopathy

Even though there are no consensus criteria for the diagnosis of cirrhotic cardiomyopathy we analyzed several factors considered to be features of cirrhotic cardiomyopathy. A prolonged corrected QT time, which is a part of the suggested criteria, was found in 32 % and 16 % of our cohorts. Systolic dysfunction (defined as an EF < 50 %) on the other hand, was not as common (3 % and 0 % respectively). However, left ventricular diastolic dysfunction was more prevalent, observed in 18 % and 31 %, respectively. Cardiac biomarkers were only available in paper IV where a Troponin T was above the reference in 19.5 % patients and a NTproBNP was normal in 86 % of patients. Other structural abnormalities were also quite common in both our cohorts and ECG abnormalities were even more common. A common pre-transplant echocardiographic abnormality that was more common in patients with vs. those without post-transplant cardiac events was an enlarged left atrium, mainly due to its relation to arrhythmias, in particular atrial fibrillation.

Previous studies have assessed the occurrence of heart failure post-transplant in patients with both acute and chronic liver disease, reporting an incidence of pulmonary edema of 31-47 % post-operatively.^{144, 145} However, only a minority of these patients was regarded as having overt heart failure, which was assessed in a subjective manner.^{144, 145} We assessed the frequency of heart failure according to the Boston classification which is objective and has been validated against NTproBNP with high sensitivity and specificity.^{146, 147} The frequency of highly possible heart failure peri-transplant in our study (27 %) is similar to that of abnormal cardiac response (22.5 %) (defined as a decrease in left ventricular stroke work index despite a rise in pulmonary wedge capillary pressure 10 min after reperfusion) in patients undergoing liver transplantation, which may be an indicator of patients with cirrhotic cardiomyopathy.⁹⁸ This frequency of heart failure was similar to another study in which patients underwent echocardiography about six months after transplantation

(24 %). In this study, mean arterial pressure was also a riskfactor for developing heart failure postoperatively. However they also found that diastolic dysfunction was a riskfactor, a finding we could not confirm.¹⁴⁸ Recent studies have also suggested that patients undergoing liver transplantations may develop an acute stress induced cardiomyopathy, theoretically similar to takotsubo cardiomyopathy. These studies suggest that 1.5-3 % of patients are affected, however not all patients in the studies were screened for the condition so the numbers are uncertain.^{149, 150} In another study, 88 % of patients did an echocardiogram about 2 months after liver transplantation and 10 % of the patients had developed heart failure.¹⁵¹ In this study, similar riskfactors as in our paper I could be seen such as prolonged QTc time on ECG, renal failure, and lower mean arterial pressure.¹⁵¹

Taking all factors into account, cirrhotic cardiomyopathy probably affected a significant proportion of our patients. A prolonged QTc time and diastolic dysfunction were independently related to several outcomes in our study implicating that cirrhotic cardiomyopathy is an important factor for post-transplant outcome. However it does not seem to have any major effects on the quality of life in these patients. Prolonged QTc time was related to a lower score in all SF-36 domains in univariate analysis and a lower physical component of the FIS.

However, a remaining difficulty in assessing the true impact of cirrhotic cardiomyopathy is the lack of a clear definition of this condition and our studies were not designed to conclusively assess the impact of cirrhotic cardiomyopathy on Quality of life and outcome post-transplant. Dobutamine stress echocardiography has been suggested as a diagnostic tool for cirrhotic cardiomyopathy²⁷, Future studies could perhaps employ this technique to divide cirrhotic into patients with and without cirrhotic cardiomyopathy. We could not show an association between cardiac biomarkers and quality of life but a recent study has shown that the markers may be of prognostic value.¹⁵²

5.1.2 ECG and outcome

Rate corrected QT time was of significance for a number of outcome measures in our studies. Among the factors that affected QTc time, possible QT prolonging drugs, alcoholic cirrhosis, age, mean arterial pressure (higher pressure decreased QTc time), and propranolol (decreased QTc time), only mean arterial pressure can serve as a marker of portal hypertension, suggesting that liver disease severity seems to play a role to some degree. It is possible QTc time prolongation is a result of the

development of hepatic decompensation and is therefore potentially a prognostic marker, which is however purely speculative.

ECG abnormalities were common among our patients, as 73% of these patients had at least one abnormality at the pre-transplant evaluation. Besides a prolonged QTc interval, which is common in cirrhotics^{47, 49, 51, 52, 54, 153-156}, about one fifth of patients had QRS-axis deviation or findings compatible with the presence of CAD. Our data indicate that most predictors of ECG features of CAD are known risk factors of CAD (such as smoking, older age, arterial hypertension, and male gender).¹⁵⁷ MELD was also found to be a predictor of ECG features of CAD. The ECG abnormalities observed in our studies could potentially be related to cirrhotic cardiomyopathy, which may have an impact on transplantation outcome.^{145, 158} Furthermore, a prolonged QTc interval was associated with older age and alcoholic liver disease while beta blockers were a protective factor: this has also been shown in other studies.^{47, 55, 56, 61} In addition, prolonged QTc interval was also associated in multivariate analysis with peri-transplant heart failure and cardiac events following transplantation and in univariate analysis associated with overall mortality, cardiac event free survival, and cardiac events, both ACS and arrhythmias but the lowest p value was noted for atrial arrhythmias.

To our knowledge, we are the first group to show that other ECG abnormalities such as the presence of a Q wave, may be related to post-transplant cardiac events. The majority of patients suffering post-transplant cardiac events (69 %) had at least one ECG abnormality. Although we cannot claim that an independent relationship exists between pre-transplant ECG abnormalities and post-transplant cardiac events, it may be of importance for selecting patients to screen for CAD prior to transplantation.

Prolonged QTc time was also associated to all domains in SF-36 and FIS which remained significantly related only to the mental component summary (Beta=-9.7, p=0.009) and the physical FIS domain score (beta=10.5, p=0.004).

5.1.3 Diastolic dysfunction

In our cohorts, the frequency of diastolic dysfunction was 18 % and 31 %, which is comparable to or slightly lower than in other studies.^{32, 34, 159}

Older age and lower hemoglobin levels were related to diastolic dysfunction in the current studies, which is in keeping with findings in non-cirrhotic populations as both factors could contribute to myocardial hypertrophy¹⁶⁰. In addition, use of beta blockers at pre-transplant evaluation were related to a lower incidence of diastolic dysfunction. Adiponectin was not related to diastolic dysfunction which has been

implicated in non-cirrhotic individuals¹⁶¹ suggesting that the pathogenesis of diastolic dysfunction in cirrhotics may be different from that in non-cirrhotic patients. One study has also shown a relationship with lower liver function and increasing diastolic dysfunction,¹⁶² a finding that we could not confirm in our papers.

We were the first group to show that diastolic dysfunction is related to lower long-term graft survival post-transplant. This is in keeping with previous studies showing that diastolic dysfunction is associated with reduced survival in patients with liver cirrhosis undergoing transjugular intrahepatic portosystemic shunt.^{32, 34} But studies are not consistent. A subsequent study has confirmed our result that diastolic dysfunction is a factor that affects mortality following transplantation but it may also be of importance to developing rejection.¹⁶³ However two recent studies could not confirm that outcome was associated with diastolic dysfunction.^{159, 164} Another study also investigated the impact of left ventricular hypertrophy, a common factor leading to diastolic dysfunction, on transplant outcome. The results indicate that left ventricular hypertrophy was associated with a lower survival post-transplant, both in the short and long term.¹⁶⁵ Left ventricular mass and diastolic dysfunction worsens after transplantation was shown in one study: these results conflict with previous studies but are nevertheless interesting as they may explain why diastolic dysfunction seems to have an effect on outcome even in long term (late graft mortality) after transplantation as we have shown in paper I.¹⁶⁶

5.1.4 Risk stratification

In paper I-III we identified several negative prognostic findings which may help in identifying high-risk patients and possibly aid in reducing the risk for patients. Some findings can also be used as a prognostic tool following transplantation such as the Boston score, discussed below in the section “Clinical implications of the thesis”.

Several of the factors associated with a negative outcome presented in this thesis are not identifiable at pre-transplant evaluation, though others are readily available. In summary, the main factors that we identified as risk factors for several outcomes at pre-transplant evaluation: diastolic dysfunction, hepatocellular carcinoma, history of arterial hypertension, prolonged QTc interval, Q wave, ECG features consistent with coronary artery disease, lower baseline mean arterial pressure, age above 52 years, and renal impairment (and history of hepatorenal syndrome). Two factors were also identified as protective; use of beta blockers and cholestatic disease.

A lower mean arterial pressure, which we found to be a riskfactor for adverse outcome, is frequently a result of portal hypertension.⁶ One of the most important

factors responsible for vasodilatation in portal hypertension is nitric oxide (NO)⁶ which has also been suggested to be an important pathophysiological mediator in cirrhotic cardiomyopathy.¹⁵⁸ This suggests that cirrhotic cardiomyopathy and nitric oxide as a potential pathogenic factor is contributing to peri-transplant heart failure and post-transplant outcome.

Other studies have also attempted to identify pre-transplant risk factors for adverse outcome. One showed that the third leading cause of death was cardiac related and risk factors included age, history of coronary artery disease, pre-transplant requirement for vasopressors, MELD score, and development of acute kidney injury.¹⁶⁷ Another study using similar definitions for cardiac events found the following risk factors; older age, male sex, diabetes, hypertension and use of mycophenolate mofetil.¹⁶⁸ In addition another study also showed age as a factor and features of prior cardiac disease.¹⁶⁹ Furthermore, we could also confirm results from previous studies showing that beta-blocker use was associated with better 30-day patient survival post-transplant.¹⁷⁰ Despite the lack of large randomized placebo controlled trials, a potential effect of beta blockers on diastolic dysfunction has been suggested in non-cirrhotic populations.³⁸ Several factors in these studies are consistent with our findings indicating that our results may be generalizable.

Renal impairment is a known risk factor for cardiovascular morbidity and mortality in non-cirrhotic individuals^{138, 171, 172} and is associated with post-transplant mortality.^{173, 174} According to data from the UNOS database, mortality following liver transplantation was more commonly due to cardiac causes among patients with severe pre-transplant renal impairment (GFR < 20ml/min) compared with patients with normal renal function.¹⁷³ We could show that renal impairment was associated with more cardiac events following transplantation. Another study has shown that renal impairment was associated with more cardiovascular events post-transplant.¹⁷⁵ However, in this report no survival or regression analyses were performed and it is somewhat unclear what the definitions of cardiovascular events were.¹⁷⁵ A link that may explain our finding is the presence of the cardiorenal syndrome.⁸⁶

The current methods of risk-stratifying a patient prior to transplantation is suboptimal. A method suggested for pre-operative evaluation of cirrhotics is dobutamine stress echocardiography to predict patients at high risk for post-operative cardiac events. However negative predictive values for dobutamine stress echocardiography was 89 % in one study and in another it was even lower as many cirrhotics have chronotropic incompetence.^{167, 176} In a review of dobutamine stress echocardiography at pre-transplant evaluation in cirrhotics had a negative predictive value of 75 %.¹⁷⁷ This suggests that screening for coronary artery disease may be suboptimal with dobutamine stress testing alone. Our risk model may assist in detecting patients that need further evaluation.

5.1.5 Clinical implications of the thesis

We have identified several pre-transplant risk factors for having peri- and post-transplant cardiac events, listed above. Even though most of our data needs to be validated in an external cohort they may help in selection liver transplant candidates and identifying high-risk individuals who may benefit from additional cardiac evaluation at pre-transplant evaluation. A high Boston score post-transplant seems to be a prognostic tool, both for mortality and morbidity. Cardiac abnormalities in cirrhotics, however, do not seem to be of major importance for quality of life or fatigue.

Heart failure, as assessed by the Boston classification, in the peri-transplant period was found to be related to peri-transplant patient mortality. Even though only one patient died of cardiac related causes, it is conceivable that patients with overt heart failure may be frailer when they develop serious postoperative complications and thus more likely to have a fatal outcome. The score might be of use in the peri-operative period for identifying patients at risk for a poor outcome.

Diastolic dysfunction is related to compromised long-term graft survival post-transplant. To date there are no consistent data on effective treatment for diastolic heart failure but recommendations include control of hypertension and decongesting patients with pulmonary edema and peripheral edema^{178, 179}. The recommendations could be used in our population as pre-transplant optimization but it is uncertain if patients with cirrhosis might benefit from this.

Prolonged QTc time was associated with a worse outcome for several endpoints (see above). Even though it is uncertain if the QTc prolongation *per se* is responsible for the worse outcome, patients should be screened for reversible causes of QT prolongation. In order to reduce the risk associated with QT prolongation, it is important to avoid medications without a good indication, avoid electrolyte imbalance, and the patients should be considered for beta blocker therapy if there are other indications which have only been considered as relative. Other ECG abnormalities as described in paper III should also serve as an incitement to further evaluate a patient at pre-transplant evaluation. For example, any ECG abnormality consistent with coronary artery disease should prompt a diagnostic test for coronary artery disease.

The risk stratification tool in paper II may be used to identify patients at risk for cardiac complications following transplantation and patients who fall into categories “high” or “very high” should be evaluated extensively before transplantation regarding their cardiac workup.

Following transplantation all patients should receive optimal primary prophylaxis for cardiac disease as we could conclude that patients being transplanted have a 14-fold increased chance of having a cardiac event compared to the general population after transplantation which is far more than a previously reported,⁹⁵ especially our data regarding the high frequency of acute coronary syndromes up to 9 years after transplantation.

In non-cirrhotic individuals, heart failure is related to poor QoL^{118, 119} although published data are not unanimous.¹⁸⁰ In our study, no cardiac structural abnormalities were related to decreased QoL, which is in line with a previous smaller report.¹³⁵ This finding is somewhat surprising as cardiac dysfunction is related to poor survival both pre- and post-transplant.^{34, 181} However, previous reports have shown discrepancies between objective markers of liver disease severity and subjective determinants of QoL, with subjective symptoms being equally or more important than liver disease severity or complications to patients with cirrhosis, having an impact on QoL.¹²³ Even if QoL is not related to cardiac function in cirrhotics, it is commonly impaired among cirrhotics and every effort should be taken to increase it by addressing reversible factors such as ascites and encephalopathy.

5.1.6 Limitations

Our studies have certain limitations. All studies had a retrospective design. Thus, although echo- and electrocardiography were routinely performed at pre-transplant evaluation, not all data was available in all patients. This can be seen in the papers where cohorts have been limited by the availability of data. Glomerular filtration rate, echocardiographies, and electrocardiographies were the main limiting factors and in paper IV the access to frozen serum was also a limiting factor. The patients were not actively screened on a daily basis for cardiac complications but only on clinical suspicion which also may have underestimated the frequency of cardiac complications in paper I-III.

Patient selection in both cohorts in Paper I-IV may theoretically have excluded some cirrhotics who were excluded from liver transplant evaluation and subsequent transplantation for having a complicated cardiac comorbidity. Therefore this might have underestimated the incidence of cardiac complications. However regarding paper I-III and cardiac complications following liver transplantation, we think the generalizability may be better as exclusion of patients on the basis of their other comorbidities is common. The patient selection in paper IV also has some selection issues. The study was made to assess the impact of fatigue and quality of life in cirrhosis, by only using a cohort which has already been assessed as fit enough to undergo liver transplant evaluation. Thus some patients with a complicated cardiac

comorbidity would not have been referred for evaluation. Finally, our data only reflect our center and the generalizability is uncertain.

However, all available echocardiographies reviewed by an experienced echocardiography technician and all electrocardiograms were reviewed by two of the investigators (Fu and Josefsson). Both techniques are observer dependent which is an issue that may be of importance in our studies.

For determining heart failure we used three different methods, echocardiography, NT-proBNP and the Boston classification. NT-proBNP was only available in paper IV which would have been of use in paper I. All papers in the thesis used echocardiography, though in paper I the only method that we had available for diagnosing heart failure postoperatively was the Boston classification. This has not been validated in the peri-operative setting and thus the frequency of heart failure may, in theory, have been over- or under-estimated. However it has been validated with reasonable accuracy to NTproBNP in an emergency setting¹⁴⁷. When we assessed peri-operative heart failure we did not register the amount of fluids and blood transfused in paper I which, if large volumes are used, may induce symptoms of heart failure, but all patients were treated at the same institution by the same team of hepatologists, transplant surgeons and anaesthesiologists adhering to the same local routines and practices. Also, a previous study has not shown any relationship with fluid replacement and pulmonary oedema in the liver transplant setting⁹⁷.

We used E/A ratio as a marker of diastolic dysfunction. This has some limitations and thus we may not have diagnosed all cases with diastolic dysfunction in our cohorts. Increased left atrial size was common in our cohorts and may be a sign of heart failure with normal ejection fraction but may also indicate increased left atrial pressure. The use of tissue Doppler imaging could have eliminated this problem³¹. Unfortunately the echocardiograms in our studies were not done using this technique. E/A ratio can also “pseudonormalize” in patients with pronounced diastolic dysfunction. This problem can also be eliminated using tissue Doppler imaging. End diastolic ventricular volume was similar between the two groups suggesting that the cardiac volume was not significantly different, potentially ruling out a reduced preload as a cause of the reduced E/A ratio in both cohorts of this thesis. Reversal of the E/A ratio from >1 to ≤ 1 is common in a populations older than 70 years of age¹⁸². Though only 4 patients in the cohort of paper I-III and only 3 patients in paper IV were older than 70 and most were at least 10 years younger. Heart rate may also affect the E/A ratio but there was no significant difference in heart rate between the two groups in both cohorts.

To assess whether patients with cirrhosis more frequently had ECG alterations than others we used a healthy control group without other chronic illness. It may be more appropriate to use an additional control group with another chronic illness. Similarly a control group might have been included undergoing another major non-cardiac surgery for the incidence of post-transplant cardiac events. However, studies on non-cirrhotic patients undergoing liver resection surgery have reported an incidence of peri-operative cardiac events, ranging between 0.5-4.5 %, ^{183, 184} which is far lower than in our population - 15.5 %. An external validation is necessary for the risk model we propose in paper II, even if an internal validation is valuable, an external is needed as the c-statistic may be lower in other patients.

All patients were thoroughly evaluated at pre-transplant evaluation for comorbidities, including a cardiac evaluation but some limitations must be considered. We did not have access to serum cholesterol in paper I-III which is a risk factor for coronary artery disease in general. Not all patients underwent screening for coronary artery disease, however the patients with certain risk factors did undergo screening, therefore limiting the patients with non-diagnosed coronary artery disease. In paper IV it would also have been useful if all patients had undergone some cardiac stress investigation to possibly uncover a latent heart failure, such as in cirrhotic cardiomyopathy.

6 CONCLUSIONS

- Liver transplant candidates have a high prevalence of post-transplant heart failure and cardiac events
- Cardiac events seem to be even more prevalent than previously reported.
- Several factors such as renal impairment, prolonged QTc time and older age are associated with a higher prevalence of cardiac events post-transplant
- Cardiac dysfunction *per se* does not seem to be a major factor for quality of life in patients with cirrhosis

7 FUTURE PERSPECTIVES

Future studies should focus on therapies of minimizing the incidence of cardiac complications and further investigating the pathogenesis of cirrhotic cardiomyopathy for potential therapeutic targets.

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