RECURRENT HEPATITIS C CIRRHOSIS AFTER LIVER TRANSPLANTATION: A NATURAL HISTORY STUDY

By

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To Joe

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LIST OF ABBREVIATIONS

CBC	Complete Blood Count
CSA	Cyclosporin
HAI	Hepatic Activity Index
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
IFN	Interferon
INR	International Normalized Ratio
IVDU	Intravenous Drug Use
LT	Liver Transplantation
MELD	Model for End Stage Liver Disease
NR	Non-Responder to Interferon Therapy
PMN	Polymorphonuclear Leukocyte
RAPA	Sirolimus
RL	Relapse to Interferon Therapy
ROC	Receiver Operating Curve
SVR	Sustained Virologic Response
TAC	Tacrolimus
US	United States

Abstract of Thesis Presented to the Graduate School
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Hepatitis C virus infection is a significant public health problem. Chronic infection leads to cirrhosis and liver failure. Over the last 15 years, hepatitis C has become the most common cause of liver failure requiring liver transplantation in the United States. Hepatitis C virus re-infects the transplanted liver immediately, which causes hepatitis in the new allograft. Recurrent infection can lead to graft cirrhosis in up to 30% of patients within 5 years, which is much shorter than the time to cirrhosis in the immunocompetent population. The natural history of recurrent hepatitis C cirrhosis in the transplant population is not well defined. Limited data available are from Europe and suggest that after development of graft cirrhosis, decompensation and death occur rapidly. Therefore, the aim of this study is to define the natural history of recurrent HCV cirrhosis after LT in a US population and to identify risk factors for decompensation and survival.

All adult patients undergoing liver transplant for hepatitis C from 1991 to 2007 were prospectively monitored with protocol liver biopsies at month 4 and annually post-transplant. Cirrhosis was defined as fibrosis score 5 or 6 (modified Ishak scale) on biopsy. Antiviral therapy for hepatitis C was initiated when fibrosis score was >2. Demographic, clinical and histologic data were collected at time of cirrhosis and decompensation. Kaplan-Meier curves were used to

estimate probability of decompensation and patient survival. Cox regression analysis was used to determine risk factors of decompensation and survival.

Of the 1,085 adult liver transplants performed at the University of Florida from 1991 to 2007, 502 were performed for HCV cirrhosis. Eighty-eight patients had biopsy proven cirrhosis by a median time of 3.7 years after transplant, and 71 were clinically compensated at diagnosis. 26 patients had at least one episode of decompensation during follow up. The median time to the first decompensation event was 6 months. The cumulative probability of clinical decompensation after cirrhosis was 30% at 1 year and 39% at 3 years. A MELD score of ≥17 was predictive of decompensation (RR 7.28, 95%CI 2.58–16.9). A sustained virologic response to interferon treatment reduced the risk of decompensation (RR 0.03, 95%CI 0.006–0.4). Overall survival was 83% at 1 year, 61% at 3 years, and 41% at 5 years with a median survival time of 47.8 months. Survival was negatively affected by decompensation. Once decompensation occurred, 1 year survival was only 46%. Poor survival was predicted by MELD score ≥17, (RR 7.28; 95% CI 2.58–16.9), HCC (RR 4.14; 95% CI 1.42–14.9).

The results confirm a previous report of the accelerated natural history of hepatitis C cirrhosis in an immunosuppressed population. Successful antiviral therapy may protect against decompensation; however, once decompensation occurs, survival is negatively effected. Clinically, MELD is useful to predict decompensation events and survival. The finding that HCC negatively impacts survival is surprising, and deserves further study.

CHAPTER 1
INTRODUCTION

Hepatitis C viral infection is a significant public heath problem worldwide. The primary mode of transmission varies by location of cohort studied, but in general, it is transmitted by sharing infected blood.[1] In the United States, the most common mode of transmission is by intravenous drug use (IVDU), which is followed by those who were infected by contaminated blood products prior to blood bank screening. Sexual transmission is uncommon. Infection with hepatitis C (HCV) is largely asymptomatic, and many of those infected are diagnosed after only after routine blood chemistries are noted to be abnormal. Still others are not diagnosed until symptoms of liver damage become apparent.

Epidemiology of Hepatitis C

Approximately 3.2 million people in the US are chronically infected for an estimated 1.6% prevalence.[2] Data from NHANES III, which covered the years of 1988-1994, indicated the peak prevalence of infection occurred in those 30-39 years of age. The peak prevalence of infection shifted to ages 40-49 in a later NHANES cohort (1999–2002). When the prevalence of HCV was evaluated by year of birth in the early and late cohorts, the results were similar. The majority of people were born between 1945 and 1964, suggesting the shift in peak prevalence over time represented an aging cohort with a longer duration of infection. The prevalent cases are anticipated to decrease from 3 million to 2 million over the next 40 years.[3] The number of incident cases is also projected to decline largely because of a decrease in IVDU and in some small part because of blood bank screening. However, the damage to the liver from HCV is cumulative and slowly progressive. As a result of the long lag time from infection to the clinical manifestations of cirrhosis, the burden of end stage liver disease from HCV is just starting to be felt by the medical community. In 2000, there were less than 500,000 cases of cirrhosis in the

U.S. as a result of HCV. By 2020, the projected number of cases of cirrhosis from HCV will approach 720,000 and peak at 900,000 cases by 2030.[3]

Cirrhosis

The healthy liver is responsible for maintaining the body's metabolic homeostasis. This includes bile synthesis and excretion, which is important for digestion and absorption of dietary fats and vitamins. The liver also synthesizes proteins necessary for regulation of blood clotting, cholesterol levels, and clearance of metabolic waste products from the body. Cirrhosis is the final common pathway for all diseases that damage the liver and is not specific for HCV. Cirrhosis is a pathologic diagnosis based on liver histology where discrete nodules of liver parenchyma are surrounded by dense fibrous tissue. The parenchymal injury and resulting fibrosis extend throughout the entire liver creating a shrunken and hard organ.

The liver is able to maintain normal synthetic function in the early stages of cirrhosis despite having a significant amount of scar tissue present. The clinical consequences of the deranged metabolism are masked to some degree because of the large functional reserve of the liver. It is during this phase that patients are considered "compensated." As progressive liver injury accumulates, the synthetic capabilities diminish and the consequences of portal hypertension become evident. A transition occurs to a "decompensated" state once symptoms of liver failure are present, which include jaundice, ascites, encephalopathy, and esophageal variceal bleeding or hepatocellular carcinoma (HCC) develops. Jaundice is apparent clinically by yellowing of the skin and eyes and occurs as bilirubin accumulates to levels > 3mg/dL. Ascites is the accumulation of fluid in the peritoneal cavity as a result of portal hypertension and is clinically apparent by a swollen, often tense, distended abdomen. Esophageal varices are also a result of portal hypertension and are defined as abnormally distended veins in the esophagus. They pose a risk to rupture and cause catastrophic and life threatening hemorrhage. Hepatic

encephalopathy can be defined broadly as changes in mental status related to the inability of the liver to clear toxic metabolites from the blood. The clinical presentation of encephalopathy can be as subtle as insomnia or as overt as coma.

The rate of transition from compensated cirrhosis to decompensated cirrhosis is slow. As demonstrated by natural history studies of HCV cirrhosis, the cumulative probability of decompensation at 3 years is 12–17%. After 5 years from the diagnosis of cirrhosis, the probability of remaining compensated is approximately 80%.[4-6] The development of decompensation is clinically important because the prognosis is worse once this occurs. For those who remain compensated, survival 3 years from the diagnosis of cirrhosis ranges from 92% to 96%.[4-6] At 5 years, survival ranges from 82% to 90%.[4-6] Once an episode of decompensation occurs, survival deteriorates. The probability of remaining alive 3 years after decompensation is 57–60% and further decreases to 50–52% by 5 years.[4-6] Evaluation for liver transplantation is appropriate after the first episode of decompensation because of the expected decrease in survival related to liver failure.

Liver Transplantation for Hepatitis C Cirrhosis

As may be expected based on the epidemiology and natural history of the infection, HCV induced liver disease has become the most common indication for liver transplantation in the US. In 1991, only 16% of LT were performed for HCV, but by 2001, HCV was the indication for 55% of all LT.[7] The number of patients with decompensated disease who could be considered for liver transplantation will double over the next 30 years from 65,000 in 2000 to 145,000 in 2030.[3] In addition, the number of cases of HCC will also double from 7000 to 14000. To put these numbers in perspective, approximately 6000 liver transplants are performed annually in the U.S., and that number has not increased significantly over the past several years.[8] The rate limiting factor is the number of available donor organs. The increasing burden of HCV cirrhosis

with or without HCC will further pressure the already limited donor pool. In this light, the outcomes for LT for HCV will be carefully scrutinized as the transplant community decides the most ethical balance for organ allocation and distribution.

Recurrent Hepatitis C Infection

Transplantation relieves the symptoms of liver failure and cirrhosis, but it is not a cure for HCV. In fact, recurrence of HCV in the transplanted liver is expected, and most patients establish some degree of chronic hepatitis in the liver allograft.[9] The natural history of recurrent hepatitis C after LT is variable. An acute hepatitis occurs within 1–4 months of LT and is characterized by increased serum transaminases and levels of circulating virus.[10] Chronic hepatitis becomes established as HCV infection persists, which leads to progressive fibrosis in some patients. The development of fibrosis in the transplant population occurs at an accelerated rate (0.3–0.8 stage/year) compared to an non-immune compromised patient population.[11, 12] As a result, the estimated time from recurrent HCV infection to graft cirrhosis falls between 5 and 12 years, which is much faster than the >20 year progression to cirrhosis described in the non-transplant population.[1]

Multiple factors have been identified that are associated with disease progression, severity, and worse outcomes. As the demand for LT has increased, the donor pool of organs has not likewise expanded. Use of "marginal" organs, including those from donors >50 years old, has increased in order to meet demand. Multiple studies have now demonstrated that this may not be the best practice for patients with HCV since older donor age is a strong predictor of rapid fibrosis progression after transplant.[12-17] Immunosuppression management after transplant has also been implicated in progressive disease.[18, 19] Corticosteroids boluses used to treat acute cellular rejection in HCV patients lead to early disease recurrence and higher risk of progression to graft cirrhosis.[20, 21] The data on cumulative doses of corticosteroids used for maintaining

immunosuppression is less clear. Some authors advocate rapid tapering of steroids early after transplant; however recent data would suggest a longer steroid taper and lower overall immunosuppression may lead to better outcomes.[22, 23] Another strategy employed has been the complete avoidance of steroids, although the ideal immunosuppression protocol has not been established to help modify recurrence of HCV in the liver graft.[24]

Other variables that have been implicated to negatively impact HCV fibrosis progression include warm ischemia, graft preservation injury, presence of diabetes mellitus, donor steatosis, co-infection with CMV, and type of calcineurin inhibitor used.[14, 21, 25-27] Given the breadth of these findings, any single factor will not likely differentiate patients at risk for rapid progression of disease. Rational manipulation of the risk factors for fibrosis progression is important to prevent recurrent graft cirrhosis and graft failure since eradication of the virus after LT is challenging.[28-30]

Early data showed no negative impact on survival in those transplanted for HCV compared to other indications for transplant.[31] As experience with transplantation matured, decreased survival in those who were transplanted for HCV became evident.[32] At 5 and 10 years after transplantation, survival after LT for HCV reaches 61–75% and 68% compared with 76–85% and 78% for other indications.[33] The decreased survival after LT has been attributed to graft failure and cirrhosis from progressive HCV.[33] By analyzing LT cohorts by year of transplant, researchers showed 3-year survival improved for each consecutive time period for non-HCV indications. In contrast, survival in the HCV cohorts remained the same, and the survival benefit from improvements in immunosuppression and post-transplant care was mitigated by recurrence of disease.[34]

All patients transplanted for HCV cirrhosis face the prospect of recurrent disease and enduring treatment with interferon and ribavirin. Unfortunately, some of these patients also must cope with the eventual failure of the liver allograft as a result of chronic HCV infection. Recurrent graft cirrhosis occurs in 8–25% of those transplanted for HCV by a median of 3–4 years, with a 30% cumulative probability of developing graft cirrhosis by year five.[31, 35-39] The natural history of recurrent graft cirrhosis in the post-LT HCV patients is not well defined. A single study has shown survival one year after recurrent cirrhosis is 71%.[40] Decompensation occurs rapidly after the diagnosis of recurrent graft cirrhosis, with a 42% cumulative probability of decompensation at 1 year.[40] Furthermore, only 41% of patients are alive a year after decompensation in the post-LT population.[40] The data from this study originated from a single center in Spain who has reported poor outcomes in regards to recurrent HCV,[11] which suggest the results may have limited applicability for other transplant centers who fare better. Other limitations include a small study population (n=39) and short term follow up (1.1 year) after the development of cirrhosis. To date, these results have not been confirmed in a U.S. transplant population or by any other transplant center in Europe.

If recurrent graft cirrhosis has such an ominous prognosis, a better understanding of the natural history is important for both patients and clinicians as they face decisions in medical management and possibly even end of life care. In addition, the outcomes from recurrent HCV graft cirrhosis are meaningful to liver transplant centers as decisions are made regarding if and when a second liver transplant should be offered. Liver re-transplantation for graft failure is the only life saving option patients may have; however this practice is controversial. Initial single center reports of poor survival (mortality rates greater than 50%) after re-transplantation for HCV raised apprehension over the medical viability of this option.[41-43] Ethical concerns

regarding scarce resource utilization were also voiced within the liver transplant community. For these reasons and others, liver re-transplantation for HCV currently only accounts for 2–3% of all transplants annually.[44] A more recent multi-center study had equivalent 1 and 3 year survival in those re-transplanted for HCV compared to other indications for late graft failure, suggesting re-OLT may be an option in well selected patients.[45] As this clinical story develops, understanding prognostic factors for decompensation and survival will be critically important to determine the optimal timing of re-transplantation for HCV.

Study Aims

Therefore, the aims of this study were to determine the clinical course of recurrent graft cirrhosis from HCV and to identify prognostic factors for both decompensation and survival once cirrhosis occurs.

CHAPTER 2
MATERIALS AND METHODS

Patients

A total of 1,316 liver transplants were performed at the University of Florida from July 1991 to April 2007. In 502 adult liver transplants, the primary indication was HCV cirrhosis. Per institutional protocol for HCV transplant patients, liver biopsies were performed 4 months after LT and then yearly afterward. Biopsies were also done if clinically indicated. Each biopsy was scored for inflammation and fibrosis from recurrent HCV using the modified Knodell scoring system of Ishak[46]. All patients were evaluated for inclusion in the study if the following criteria were met: (1) at least one protocol biopsy following liver transplantation, (2) detectable HCV RNA after liver transplantation, and (3) biopsy proven cirrhosis defined by a fibrosis stage of 5 or 6. Patients were excluded for (1) evidence of cholestatic HCV, (2) fibrosis stage ≤4, (3) absence of a protocol liver biopsy, or (4) less than 4 months follow up after liver transplant.

Follow-up

All patients were evaluated in clinic once a year at the approximate anniversary of liver transplantation. At that time, the protocol biopsy was performed. Once cirrhosis was established by biopsy, a follow up liver ultrasound was performed, and at least one screening endoscopy was completed to evaluate for the presence of esophageal or gastric varices. In all patients, liver chemistries were assessed at 3 month intervals, and at the time of biopsy, an INR, platelet count, complete metabolic profile, CBC and HCV RNA were collected. Patients were also evaluated in clinic for complications of liver transplantation or recurrent disease.

Prior to 1997, standard immunosuppression consisted of Cyclosporine (CSA) in combination with prednisone. Target trough concentrations for CSA were 200–250 ng/ml for the first month post-transplant followed by 150–200 ng/ml thereafter. Now tacrolimus is used as the

primary calcineurin inhibitor for immunosuppression with target trough concentrations of 10–15 ng/ml for the first month post-transplant followed by 5–10 ng/ml thereafter. Typically, immunosuppression was tapered to monotherapy (TAC or CSA) within 4-6 months of transplantation as tolerated. Sirolimus was used as part of a renal sparing regimen as necessary when chronic renal insufficiency occurred during prolonged follow up after transplantation.

Interferon Therapy for Recurrent Hepatitis C

Protocol biopsies were used to monitor for the development of fibrosis from recurrent hepatitis C. Combination therapy with interferon and ribavirin was initiated once patients developed significant fibrosis (Ishak fibrosis stage > 2) on protocol or indication liver biopsy. The duration of treatment was 48 weeks for genotype 1 and 24 weeks for genotype 2 and 3 if tolerated. Interferon (IFN) was initiated at half of standard dosing for 2 weeks, and if tolerated, a full dose was given. Ribavirin dosage was based on weight. Hemoglobin, white blood cell, and platelet counts were monitored weekly for the first four weeks and then monthly thereafter. Dose reductions for IFN were performed if PMN < 750 or platelets < 50,000/mL. If PMN < 500 or platelets < 30,000, therapy was stopped. If hemoglobin < 10 mg/dl, ribavirin was reduced to 600 mg/day. Ribavirin was discontinued if hemoglobin < 8 mg/dl. Therapy was discontinued in any patient who developed moderate to severe rejection, systemic bacterial infection, severe neuropsychiatric symptoms, or symptomatic anemia. Serum HCV RNA values were measured six months after completion of interferon-based therapy to asses for a sustained virological response (SVR) in those patients with a negative HCV at the end of treatment. Subsequently, HCV RNA titers were obtained annually.

Study Design and Data Collection

The study is a description of the natural history a small group of patients from a larger cohort of post-transplant HCV patients. Patients who developed recurrent graft cirrhosis were

identified from a post-LT database. Data was compiled retrospectively by reviewing computerized medical records, a separate electronic transplantation database, and paper charts. Clinical, laboratory, and biopsy data were recorded at time of study entry, which was defined as recurrent graft cirrhosis from HCV. Based on available laboratory data, a MELD score[47] (Model for Endstage Liver Disease) was calculated at study entry. Furthermore, patients were classified into one of four clinical stages of cirrhosis of increasing severity: (a) Stage 1 – no varices, no ascites (b) Stage 2 – varices, no ascites (c) Stage 3 – ascites ± varices (d) Stage 4 – bleeding ± ascites. Stages 1 & 2 were considered compensated cirrhosis, and stages 3 & 4 were considered decompensated cirrhosis[48]. During the subsequent follow up time, the development of the following clinical events was recorded: ascites, varices ± bleeding, encephalopathy, jaundice (bilirubin >3mg/dL), and hepatocellular carcinoma (HCC). Albumin, INR, platelets, creatinine, bilirubin, and MELD were also recorded at time of first decompensation.

Outcomes

The end points chosen were (a) clinical decompensation defined by ascites, bleeding esophageal varices, or encephalopathy, and (b) death or re-transplantation from recurrent HCV cirrhosis. The total time of observation was calculated from the date of cirrhosis until date of death, re-transplantation for HCV, or the end of the observation period (2/13/2008). The time to development of decompensated cirrhosis was calculated from the time of cirrhosis to the first development of clinical decompensation. If patients had more than one clinical event, then the date of the first event was used for time dependent calculations. Cause of death was categorized as related to graft failure or not. Patients were censored at time of death or end of the observation period. If patients were lost to follow up, they were censored at the date of last evaluation. Liver re-transplantation was considered as death for calculation of patient survival rates since the

overall aim of the study was to describe the course of events leading to the terminal event of either re-transplantation or death.

Prognostic Factors for Morbidity and Mortality

The following clinical and serologic variables at entry were evaluated as predictors of decompensation: age at diagnosis of cirrhosis, donor age, gender, MELD score, albumin, bilirubin, creatinine, INR, platelets, HCC at time of LT, Hepatic Activity Index (HAI), time from LT to cirrhosis, date of LT, immunosuppression regimen, and response to IFN treatment post-LT. A similar analysis was performed for predictors of survival using age, gender, MELD score, albumin, bilirubin, creatinine, INR, platelets, ascites, encephalopathy, jaundice, varices, time from LT to cirrhosis, date of LT, immunosuppression regimen, and response to interferon treatment post-LT in the groups presented compensated and decompensated.

Statistical Analysis

Categorical data were expressed as percentages, and continuous variables were presented as median with a range. The Chi-Square ($\chi 2$) or Fisher's exact test was used to compare categorical data when appropriate. The Kaplan-Meier method was used to establish the actuarial decompensation and survival curves that were compared with the log rank test. Multivariate Cox regression analyses were used to identify risk factors for time to decompensation and overall survival. Variables that retained significance ($p<0.05$) in the univariate analysis were retained in the multivariate analysis. ROC curves were generated to determine the accuracy of MELD at time of cirrhosis to predict 3 month and 1 year survival.

CHAPTER 3
RESULTS

A total of 1,316 liver transplants were performed at the University of Florida from July 1991 to April 2007. The primary indication was HCV cirrhosis in 502 patients. Patients were excluded if the fibrosis stage was ≤ 4 (n=328), no biopsy data was available (n=68), or if cholestatic HCV was present on biopsy (n=18). The final study cohort consisted of 88 patients with recurrent graft cirrhosis (Figure 3-1), which is 17.5% of those transplanted for HCV. Because retrospective studies are subject to bias, an evaluation of completeness of data ascertainment was undertaken. Thirty eight (43.2%) individuals missed no protocol biopsies. Twenty-three (26.1%) missed one biopsy, and 15 (17.1%) missed two protocol biopsies. Twelve (13.6%) of patients missed 3 or more biopsies. Importantly, only 12.5% (n=11) had greater than a 2 year period between a biopsy with fibrosis stage ≤4 prior to the biopsy with cirrhosis, suggesting that the timing of the onset of cirrhosis was captured with reasonable accuracy. Eleven patients (12.5%) were missing an INR, so a MELD score was not calculated. Nine patients (10.2%) were missing HAI grades. Otherwise, complete data was available for all other clinical and laboratory values.

Patient Characteristics

At the time of histologic diagnosis of cirrhosis, 80.7% of the patients (n=71) were clinically compensated. In this group, the median length of time from LT to recurrent graft cirrhosis was 3.7 years (range, 9 months–11.8 years). The average number of biopsies completed was 4.2, which is consistent with one per year. After the diagnosis of cirrhosis, the median follow up was 2 years (range, 0–6 years). At some point during the follow up after liver transplantation, treatment with IFN was attempted in a large proportion (71.8%) of the

compensated patients. An SVR was achieved in only 12.7% (n=9). Advanced fibrosis was present at time of treatment in each of these patients.

A smaller number of patients (19.3%) were decompensated at time of study entry. In this group, the length of time from LT to cirrhosis was 2.5 years (range, 4 months–8.1 years), and the number of biopsies completed was 3.4. After the diagnosis of cirrhosis, median follow up time was 5.1 months (range 0–3.6 years). In over half (52.9%) of these patients, IFN treatment was tried prior to decompensation, although SVR was achieved by only one person. The baseline clinical features of these two groups are compared in Table 3-1. The only significant differences found between the two groups were in albumin and creatinine. Accordingly, MELD scores were also significantly different between groups (11.2 vs 15.3, $p < 0.0001$). The clinical course for all patients with recurrent HCV graft cirrhosis (n=88) is summarized in Figure 3-2. For the overall cohort, the median time from LT to last follow up was 5.9 years (range 8 months–14 years). Less than half of the patients eventually developed signs of decompensated liver disease (n=26). At the end of follow up, 35 patients remained alive with compensated cirrhosis. The overall survival for both the compensated and decompensated patients at time of study entry is shown in Figure 3-3.

Patients with Compensated Cirrhosis at Baseline

Decompensation

Over a median follow up of 2 years (range 0 months–6 years) months, 63.4% (n=45) of the 71 compensated patients remained so. The other 26 patients developed signs of decompensated liver disease by a median time of 4.8 months (range 0–5.1 years) from the diagnosis of cirrhosis. The median MELD score and albumin at time of decompensation were 16 (range, 7–36) and 3.0 g/dL (range 2–4) respectively. Development of ascites was the most common clinical event (30.0%), followed by jaundice (19.7%) and encephalopathy (16.9%).

Esophageal varices were present in 25.6% of patients, although only one bleeding event occurred. Only one patient developed de novo hepatocellular carcinoma. The cumulative probability of clinical decompensation was 23% at 6 months, 30% at 1 year, and 39% at 3 years after cirrhosis developed (Figure 3-4). The probability of remaining compensated at 5 years was 53%.

Death or re-transplantation

Twenty three patients reached the outcome of death or re-LT. Nineteen patients died and four were re-transplanted for HCV. The median time from LT to re-LT was 3.9 years (range, 1.9–8.3 years). Three of the re-transplanted patients are still alive. The other patient died of a cerebrovascular accident after re-LT. In the other 19 patients, the most common cause of death was graft failure (79%) secondary to recurrent HCV.

Patient survival

From the time of diagnosis compensated cirrhosis, the cumulative probability of survival was 83% at 1 year, 61% at 3 years, and 41% at 5 years with a median survival time of 47.8 months. As shown in Figure 3-5, cumulative survival is worse in those who decompensate when compared to patients who remain compensated ($p<0.001$). When considering survival from the time of decompensation, survival is poor as shown in Figure 3-6. The probability of survival one year after decompensation is 46%. The median time from decompensation to death was 11.1 months.

Risk factors for decompensation and mortality

Factors in a univariate analysis for predictors of decompensation are shown in Table 3-2. The factors with significance were albumin, MELD score, and two of the individual components of the MELD, bilirubin and INR. In addition, in those who had a rapid course of recurrent HCV

cirrhosis, the relative risk of decompensation was 3.20 (95% CI 1.31–7.80). The risk of decompensation increased as the MELD score increased with the highest risk in those with score MELD ≥ 17 (RR 7.28; 95% CI 2.41–22.0) as seen in Figure 3-7. A SVR to IFN decreased the risk for decompensation (RR 0.05; 95%CI 0.04–0.42). In the subsequent multivariate analysis, MELD ≥ 17 (RR 3.88; 95% CI 1.12–13.45) had the greatest risk for decompensation and was the only variable that retained significance. Albumin approached significance (p=0.54) and was protective (RR 0.49; 95%CI 0.24–1.01). The impact IFN treatment had on decreasing the risk of decompensation lost significance in the multivariate model (RR 0.37; 95%CI 0.5–3.0).

Similar factors were used in a univariate analysis for overall survival as shown in Table 3-3. Two of those remained significant in the multivariate analysis. The largest risk for mortality was from a MELD ≥ 17 (RR 13.6; 95% CI 2.7–68.1). HCC at time of LT also conferred a risk for decreased survival (RR 4.14; 95% CI 1.42–14.9).

Patients with Decompensated Cirrhosis at Baseline

This small group of patients (n=17) presented initially with clinical signs of decompensation, and cirrhosis was confirmed by subsequent biopsy. Ascites was the presenting symptom in 15 patients (88.2%), whereas jaundice (n=1) and variceal bleeding (n=1) accounted for the other patients. Four patients (24%) developed encephalopathy and seven became jaundiced (41.2%). Nine (47.1%) patients had varices, but only two patients had a variceal bleed. Twelve patients reached the outcome of death or re-LT for HCV. Two patients were transplanted, and are still alive at time of last follow up. The cause of death was graft failure in 7 of 10 patients. Cumulative probabilities of survival were 75% at 3 months, 55% at 6 months, and 41% at 1 year with a median survival time of 6.8 months.

MELD Score as a Predictor of Mortality

Complete laboratory data were available to calculate a MELD score at study entry in 77 of 88 (87.5%) patients. Overall, there were 43 deaths; 7 occurred within 3 months and 19 occurred within one year. The c-statistic for prediction of 3 month and 1 year survival by the MELD score was 0.84 (95% CI 0.69–0.99, $p=0.003$) and 0.87 (95% CI 0.72–0.93, $p<0.001$), respectively.

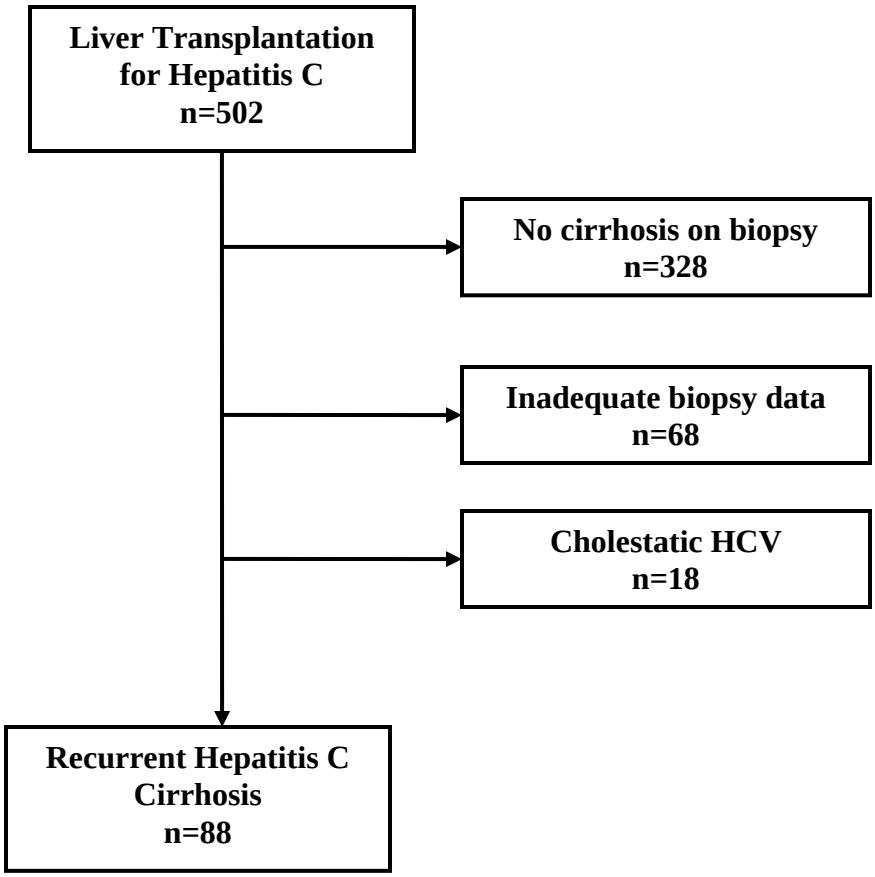

Figure 3-1. Exclusion criteria. 502 patients were transplanted for HCV. Only 88 patients developed cirrhosis and were included in the study.

Table 3-1. Baseline characteristics of patients with compensated and decompensated recurrent HCV graft cirrhosis

Patient Characteristics			
Variables	Compensated n=71	Decompensated n=17	P value
Age in years (mean)	53.5	50.5	ns
Sex (%male)	63.4	52.9	ns
Race			
% Caucasian	77.5	88.2	ns
% African American	7.0	5.9	
% Hispanic	15.5	5.9	
Age at OLT (mean)	49.4	47.4	ns
Donor Age (mean)	43.5	50.9	ns
Donor Sex (%male)	47.9	47.1	ns
HCC at OLT (%)	14.1	0.0	ns
Genotype (%)			
1	70.4	64.7	ns
2/3	7.0	11.8	
4	1.4	5.9	
Albumin (g/dL)	3.6	2.9	0.0001
Bilirubin (mg/dL)	1.9	4.4	ns
Platelets (1000/mm^3)	115.7	117.2	ns
Creatinine (mg/dL)	1.2	1.7	0.0001
INR	1.1	1.2	ns
HAI at time of cirrhosis	5.1	5.0	ns
HAI average from all biopsies	4.1	4.4	ns
Steroid treatment for rejection	52.1	43.8	ns
No IFN treatment post-OLT (%)	28.2	47.1	ns
SVR to IFN (%)	12.7	5.9	ns
Treatment Failure to IFN	59.2	47.1	ns
Immunosuppression			
Cyclosporine	40.8	23.5	ns
Tacrolimus	74.6	82.4	
Rapa	8.5	5.9	
OLT before 12/31/1998	43.7	35.3	ns

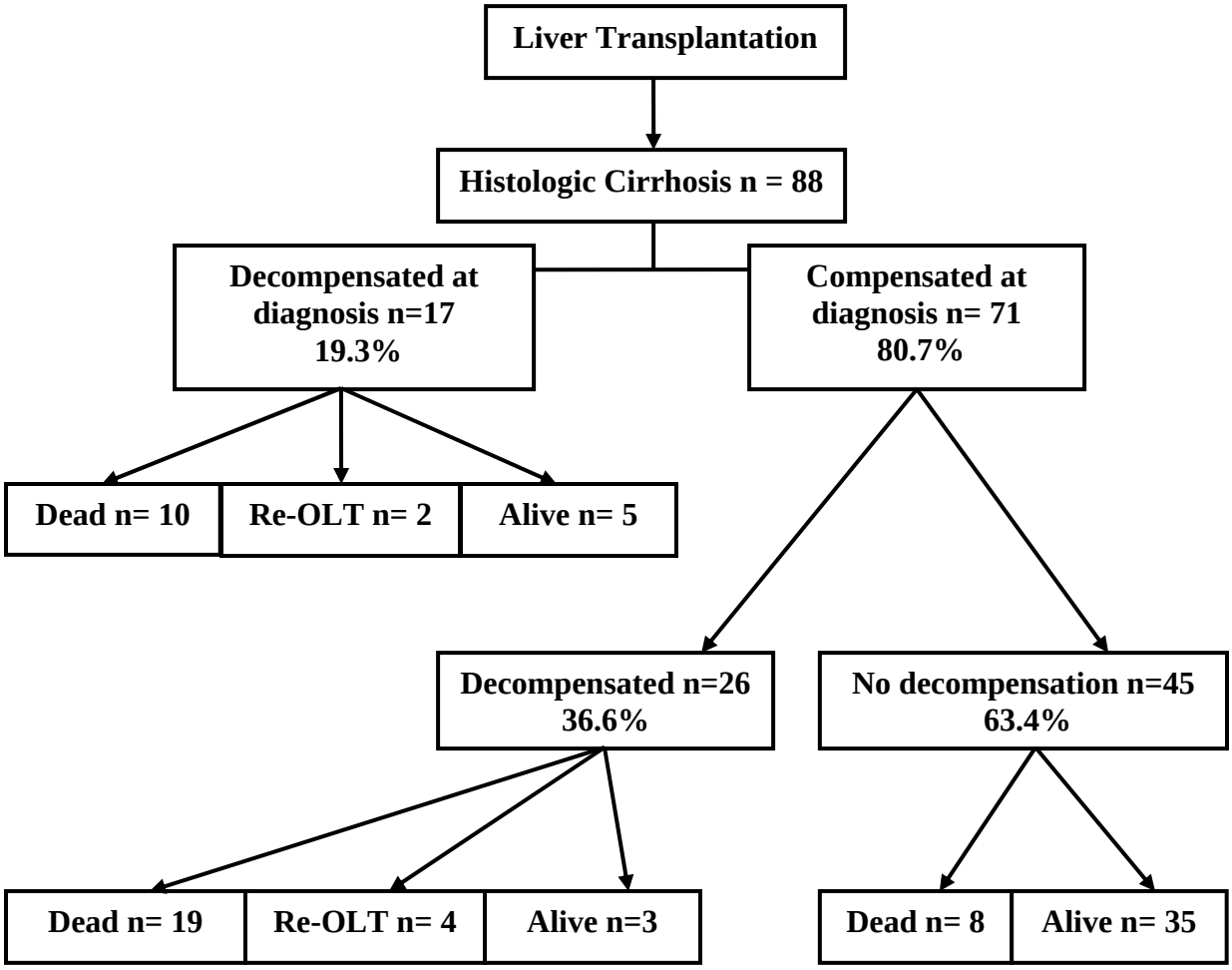

Figure 3-2. Clinical outcome from time of study entry until death or last follow-up.

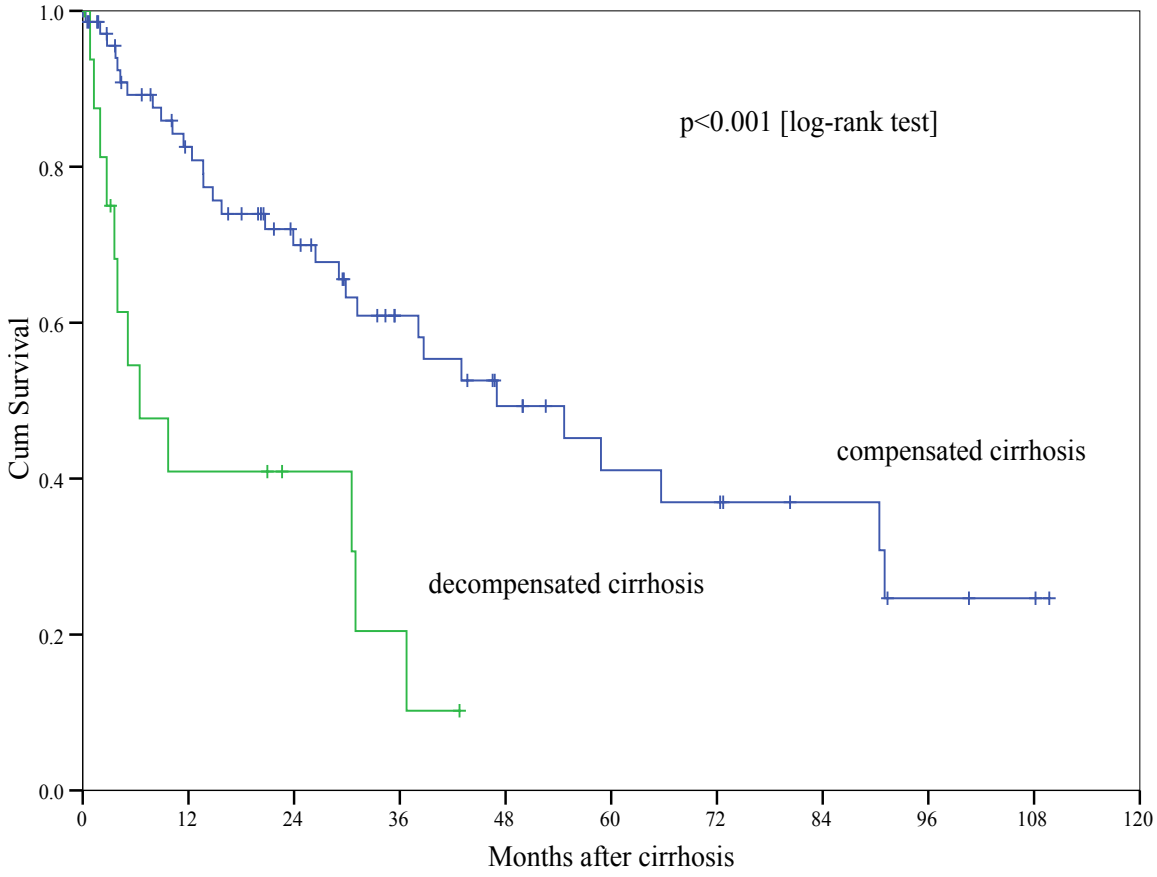

Figure 3-3. Overall survival of the entire cohort (n=88) from time of study entry stratified into compensated cirrhosis (n=71) and decompensated cirrhosis (n=17). Survival is significantly worse in those who are decompensated at diagnosis (41% vs. 83% at 1 year). Median survival is also shorter (6.8 months vs. 47.8 months).

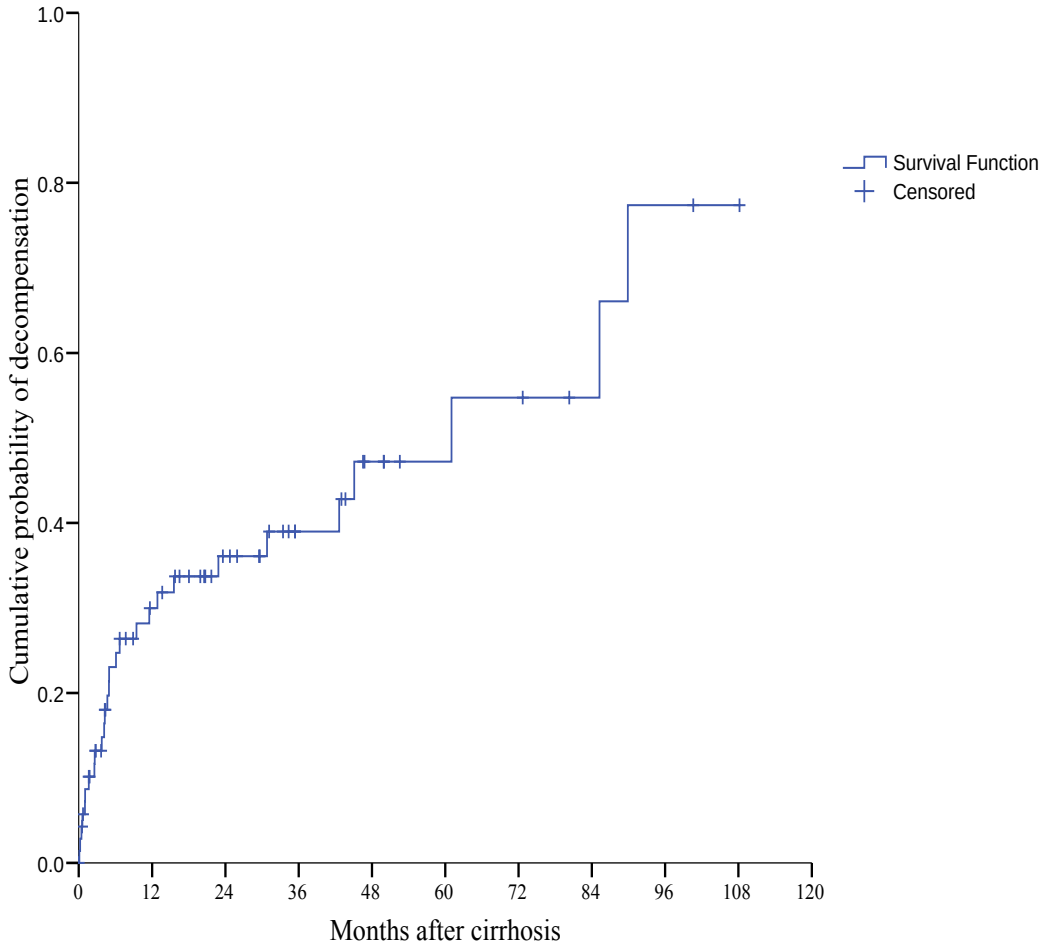

Figure 3-4. The cumulative probability of decompensation is 30% one year after the diagnosis of cirrhosis. The probability of decompensation at 5 years is 47%.

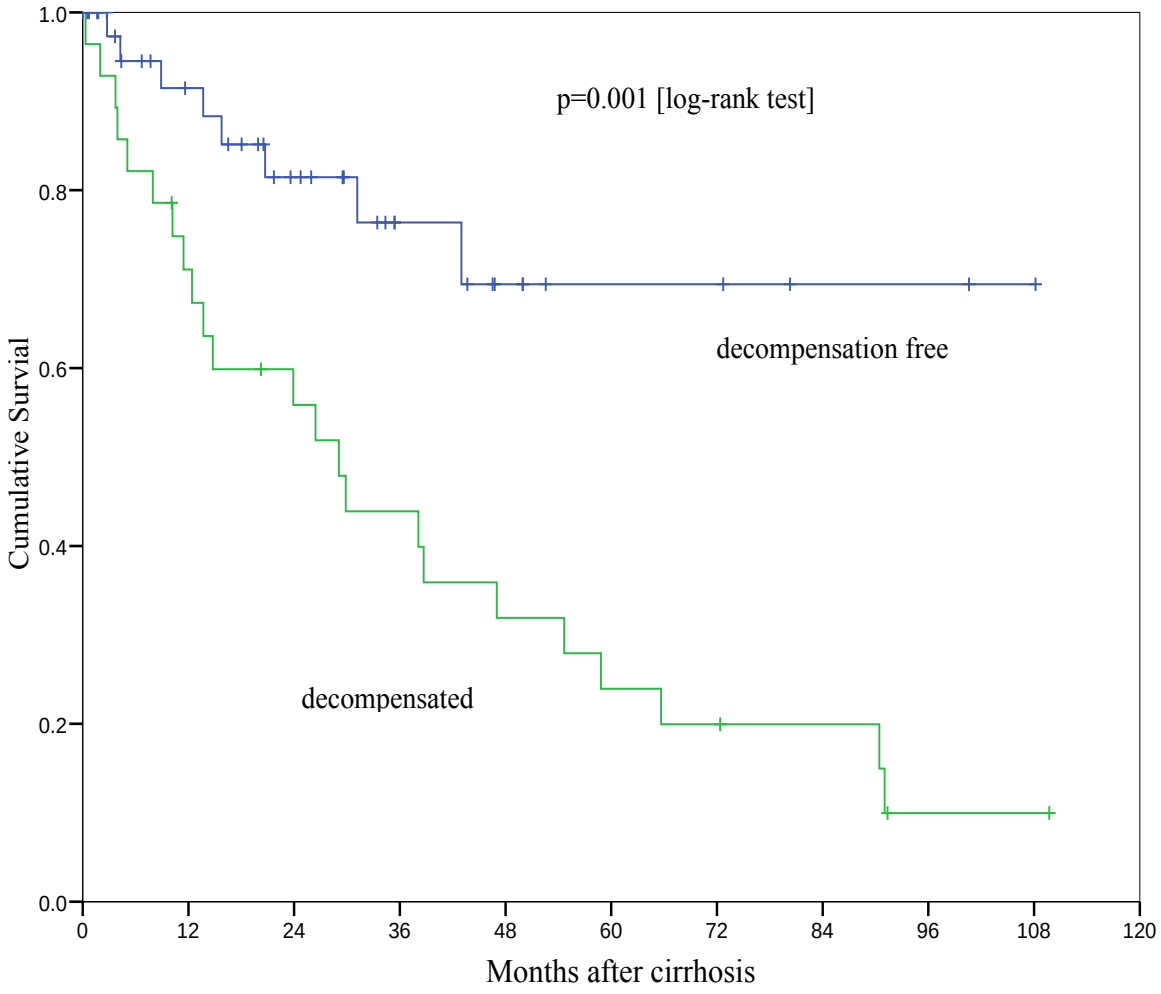

Figure 3-5. Overall survival from diagnosis of cirrhosis. Survival is significantly better in those who remain compensated ($p<0.001$).

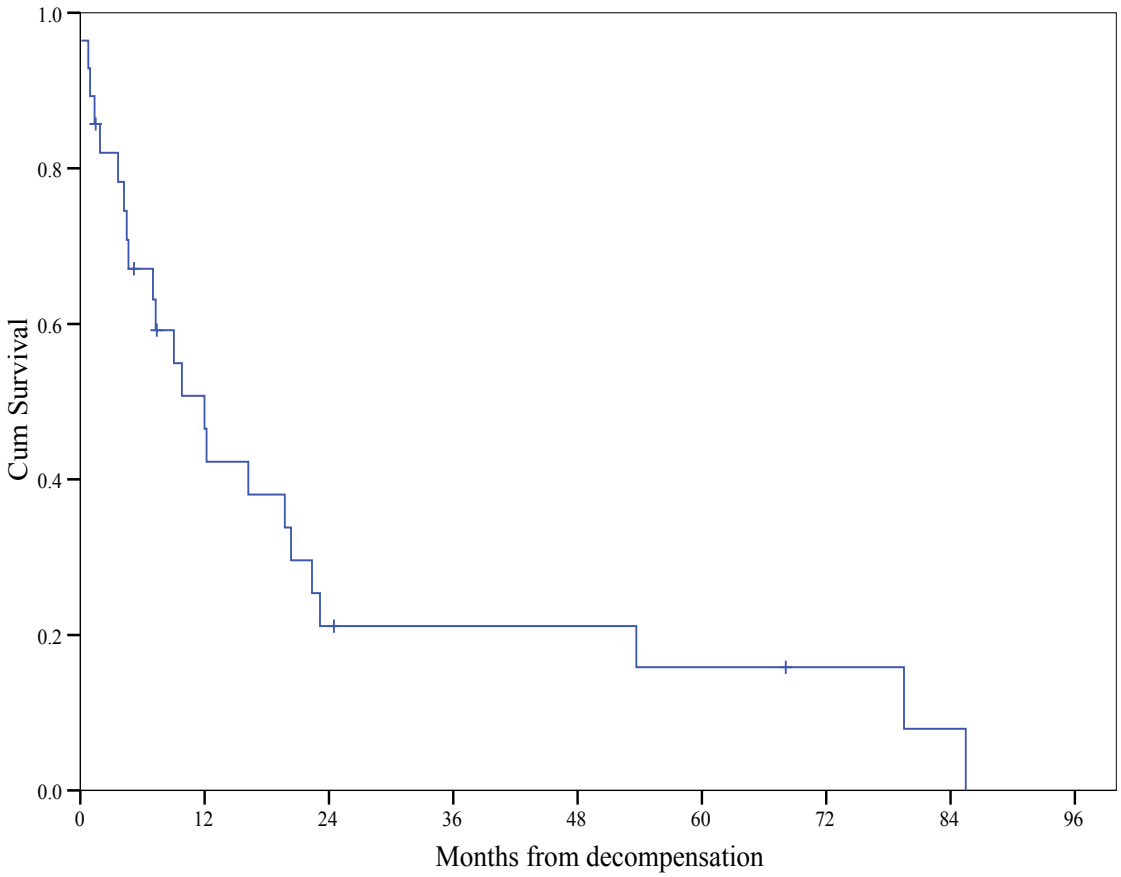

Figure 3-6. Cumulative survival from time of decompensation. The median time from decompensation to death is 11.8 months. Probability of survival once signs of liver decompensation develop is 46% at 1 year.

Table 3-2. Univariate analysis of predictors of decompensation after recurrent graft cirrhosis

Predictors of Decompensation			
Variables	RR	95% CI	*p*
Age at post-OLT cirrhosis	0.98	0.93-1.03	ns
Age at OLT	1.00	0.95-1.05	ns
Male gender	0.74	0.34-1.61	ns
Donor gender male	1.67	0.77-3.63	ns
Donor age at OLT	0.99	0.97-1.01	ns
Genotype 1	0.94	0.41-2.20	ns
HCC at OLT	1.30	0.38-4.43	ns
MELD	1.28	1.13-1.45	0.0001
Albumin at cirrhosis (g/dL)	0.45	0.23-0.92	0.03
Bilirubin (mg/dL)	1.17	1.07-1.28	0.001
INR	3.51	1.44-8.60	0.006
Creatinine (mg/dL)	0.91	0.29-2.87	ns
Platelets ($1000/mm^3$)	1.00	0.99-1.01	ns
HAI score at cirrhosis	1.06	0.77-1.47	ns
OLT to cirrhosis < 2 yr	3.20	1.31-7.80	0.01
OLT before 12/31/1998	0.75	0.34-1.67	ns
CSA	0.53	0.23-1.21	ns
TAC	1.96	0.76-5.03	ns
RAPA	0.98	0.29-3.38	ns
Graft rejection	0.57	0.25-1.31	ns
Steroid RX for graft rejection	0.87	0.40-1.89	ns
Response for interferon post OLT			
Treatment failures	0.28	0.12-0.64	0.003
Sustained response	0.05	0.04-0.42	0.006

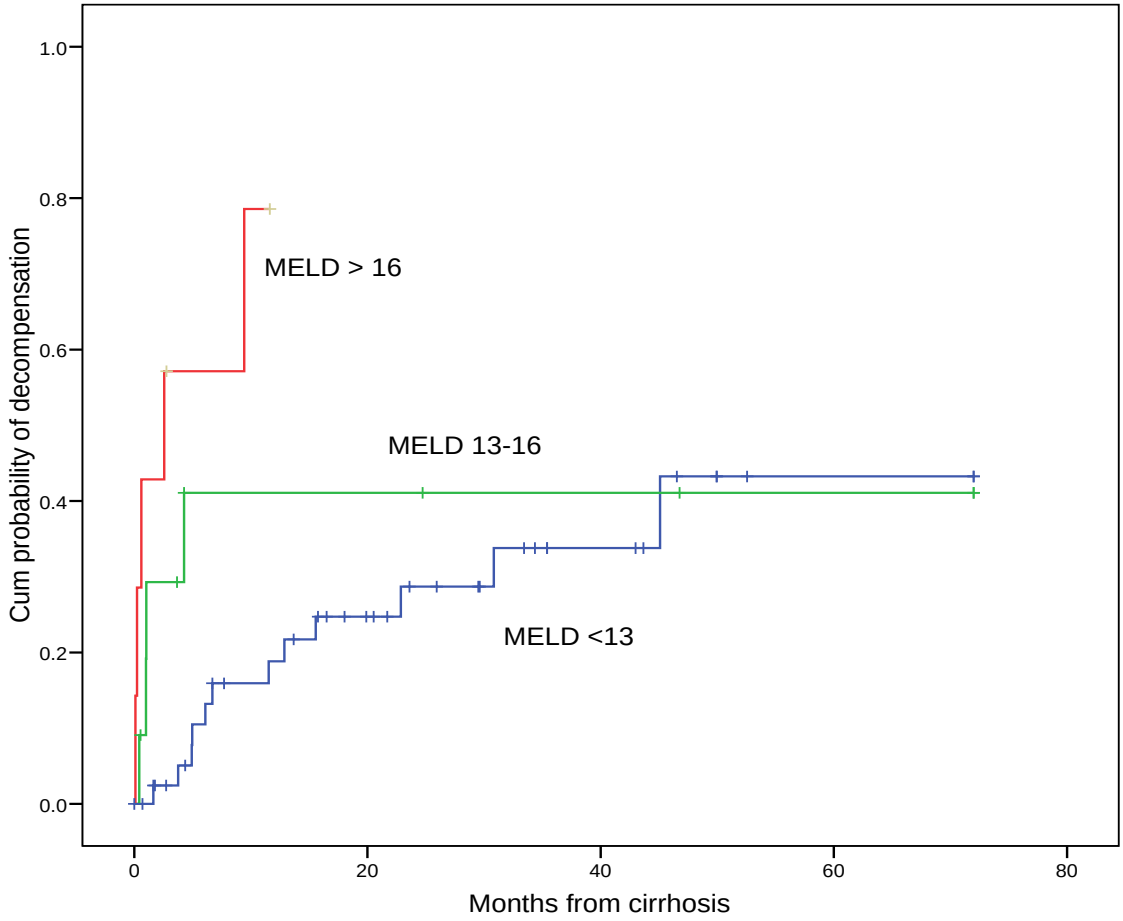

Figure 3-7. Decompensation by MELD score. As the MELD score increases, the probability of clinical decompensation becomes significantly higher ($p<0.001$).

Table 3-3. Univariate analysis of predictors of survival after recurrent graft cirrhosis

Predictors of Survival			
Variables	RR	95% CI	*p*
Age at post-OLT cirrhosis	1.00	0.96-1.05	ns
Age at OLT	1.02	0.97-1.06	ns
Male gender	0.70	0.34-1.46	ns
Donor gender male	1.00	0.48-2.07	ns
Donor age at OLT	1.00	0.98-1.03	ns
Genotype 1	0.61	0.29-1.29	ns
HCC at OLT	3.50	1.29-9.53	0.01
MELD	1.32	1.15-1.51	0.0001
Albumin at cirrhosis (g/dL)	0.36	0.16-0.77	0.009
Bilirubin (mg/dL)	1.21	1.10-1.33	0.0001
INR	1.78	1.41-2.26	0.0001
Creatinine (mg/dL)	0.61	0.21-1.70	ns
Platelets ($1000/mm^3$)	1.00	0.99-1.01	ns
HAI score at cirrhosis	1.22	0.92-1.63	ns
OLT to cirrhosis < 2 yr	2.02	0.89-4.73	ns
OLT before 12/31/1998	1.20	0.56-2.53	ns
CSA	0.52	0.25-1.12	ns
TAC	1.11	0.51-2.41	ns
RAPA	0.56	0.17-1.91	ns
Graft rejection	0.56	0.24-1.27	ns
Steroid RX for graft rejection	0.90	0.44-1.88	ns
Decompensation in < 1 year	5.29	2.23-12.5	0.0001
Response for interferon post OLT			
Treatment failures	2.31	1.08-4.93	0.03
Sustained response	0.15	0.02-1.17	0.07

CHAPTER 5
DISCUSSION

At the University of Florida, Hepatitis C is the most common indication for liver transplantation, accounting for almost half of all transplantations that have been performed to date. HCV recurrence in the graft is inevitable. Treatment after transplantation to eradicate HCV is often attempted, but it is poorly tolerated secondary to side effects. Rates of SVR after transplant are approximately 30%, which is less than would be expected in a non-immunocompromised population.[49, 50] These factors combined with the increase in number of patients being transplanted for HCV cirrhosis leave transplant centers faced with continued growth in the number of post LT patients with recurrent HCV graft cirrhosis. For this reason, better insight into the natural history of recurrent HCV graft cirrhosis is needed. Much of the current understanding is based on a single center's experience from Spain which reported a rapid progression to decompensation and death once cirrhosis is present.[40] By focusing on a similar group of patients, the goal of this study was to evaluate the long term outcomes after the development of cirrhosis in a U.S. population. Decompensation and survival were the primary outcomes and predictive factors for each of these events were also evaluated. The results reported here represent the largest series to date of patients with recurrent HCV graft cirrhosis.

The key findings in this study can be summarized as follows: (1) Short term survival one year after the diagnosis of cirrhosis is good (83%) but falls to 41% by 5 years; (2) the probability of decompensation one year after cirrhosis is 30% and remains less than 50% at five years; (3) survival is poor once decompensation develops; (4) MELD score $\geq$ 17 and transplantation for HCC are predictors of poor survival. These results confirm the aggressive nature of HCV after LT as the probabilities of decompensation and survival are less than what is reported in immunocompetent HCV populations.

Ascites was the most common decompensating event, occurring in 30% of patients. Encephalopathy, jaundice, and GI bleeding also occurred in similar proportions to previous reports. Only one case of de novo HCC occurred, which is quite different from the reported natural history prior to transplant. In a large cohort of patients with HCV cirrhosis, HCC was the most common complication. It occurred in 32% of the population, and was the major contributor to mortality.[51] The reason for lack of observed HCC in this study population is unknown, but it can be postulated to partly be a time dependent phenomenon. The probability of developing cancer increases with time. The estimated annual incidence of HCC is 3–4%, with the cumulative probability of 15–20% at five years.[6, 51] The cumulative probability of survival in this study cohort at five years was 41%. Simply put, patients may not live long enough after recurrent graft cirrhosis to have time to develop HCC. The small number of patients in the study may also be a factor in the lack of incident cases.

Although the general conclusions made from this study are similar to those of Berenguer et. al[40], the results suggest differences in the time frame in which complications develop. The median time from LT to development of cirrhosis was longer (3 vs. 2 years), and survival at one year was higher (83% vs. 72%). The lower probability of decompensation is the likely explanation, since decompensation negatively influences survival (Figure 3-5). Antiviral treatment with IFN is one possible explanation for the slower rate of decompensation, since roughly two thirds of the patients were treated in an attempt to eradicate HCV. In the univariate analysis, IFN treatment reduced the risk of decompensation in patients who achieved an SVR. This finding is consistent with the only randomized controlled trial of IFN treatment after LT.[52] The investigators reported a reduction in the hepatic venous pressure gradient (HVPG) in those who achieved an SVR. This study did not evaluate the affect of decreased HVPG on

decompensation or survival outcomes, but the investigators had previously showed an elevated HVPG is predictive of severe recurrent HCV and decompensation.[53] The results of the current study provide evidence that SVR may improve clinical outcomes, not just surrogate markers like fibrosis progression. The findings are comparable to a recent study that showed achieving an SVR significantly reduced the risk of liver failure in patients with advanced fibrosis or cirrhosis.[54] Although significance of IFN treatment was lost in the multivariate analysis because the total number who achieved an SVR was so small, it is an interesting finding that needs to be confirmed by others in the post transplant setting. The results strengthen the argument for aggressive treatment of those with recurrent HCV after LT, even if advanced disease is already present.

Other possible reasons for the lower probability of decompensation are related to baseline differences in the two cohorts of patients that cannot be measured. The cirrhotic cohort in the Spanish study had a CP score of 5 (range, 5–11) and an albumin of 3.8g/L at baseline, whereas the patients in the current study had a MELD of 11 (range, 6–33) and an albumin of 3.6g/L. A direct comparison in the severity of illness cannot be made since we did not use Child-Pugh (CP) scores. Because of the retrospective nature of this study, an accurate assignment of CP scores was not possible. Instead, a MELD score was calculated based on objective lab data done at the time of the biopsy. If anything, the slightly lower albumin would suggest a higher probability of decompensation in the current study since it was identified as an independent predictor of decompensation by the Spanish group and approached significance in the current analysis.

Regardless of the overall probability of decompensation, this study confirms that decompensation is a watershed event in recurrent HCV graft cirrhosis. The one year survival after clinical decompensation was only 46%, which is very similar to the Spanish study. For

comparison, the probability of survival after the onset of the first major complication in a general HCV population is 50% at 5 years.[4] The influence decompensation has on survival is best seen when survival is stratified by decompensation. One year survival in compensated patients is 91% compared to 71% in decompensated patients. The difference is more pronounced at 5 years, where cumulative survival is 69% in those that remain compensated and only 24% in the decompensated group. Interestingly, a group of patients had clinical signs of decompensation which led to a biopsy confirming cirrhosis. The worst survival was seen in these patients, with a 41% one year survival rate, compared to 85% and 92% in the other two groups. Importantly, this survival at one year is similar to that seen after decompensation occurs in the compensated group.

The focus of this study was not to identify the factors associated with recurrent graft cirrhosis, but known risk like donor age, steroid treatment for rejection and others were included in the analysis for predictors of decompensation and survival. None were significant predictors of risk. The MELD score was used as a continuous variable and was predictive of both decompensation and survival. A score ≥ 17 conferred the highest risk of decompensation and thus survival. The finding that HCC at time of transplant negatively impacted survival is unexpected. LT is widely accepted as therapy for HCC when stringent selection criteria are used. To qualify for transplantation, a single tumor nodule must be less than 5cm in size or up to three nodules can be present if all are less than 3 cm. The initial study was followed by others that demonstrated excellent survival.[55, 56] In this highly selected study population of those with the recurrent graft cirrhosis, the decreased survival is not related to recurrent cancer. In fact, since tumor is removed at time of transplant, something about its absence may accelerate the progression of recurrent HCV.

Limitations of this study are its retrospective nature which potentially introduces several confounding factors. The patients were transplanted over the course of many years, and immunosuppression regimens and other clinical management protocols have changed with time. To asses for any impact that changes in clinical management may have occurred with time, the cohort was divided into two groups by year of transplantation. The later group was used as a referent for those transplanted prior to December 1998, and no significant differences were found. The only potential for selection bias was in those patients who were treated with IFN. By protocol, all patients were eligible, but some were deemed to sick to tolerate the treatment. This could exaggerate the effect of IFN treatment on preventing decompensation and survival if at baseline those not treated were sick. For that reason, treatment failures were compared only to those who achieved an SVR. Lead time bias was minimized because of the nature of the protocol biopsies yearly.

In conclusion, recurrent HCV cirrhosis is a growing problem faced by liver transplant centers. Survival short term after cirrhosis is excellent, but decreases over time related to decompensation and graft failure. Once decompensation occurs, survival is poor and repeat liver transplantation should be considered to improve survival.

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BIOGRAPHICAL SKETCH

Virginia Clark received her undergraduate degree from the University of Georgia in 1996. Her medical degree is from Emory University, and she completed training in internal medicine at Vanderbilt University in 2003. She completed subspecialty training in gastroenterology at the University of Florida in 2007. Her masters degree in clinical investigation was completed during her time as a gastroenterology and hepatology fellow. She joined the College of Medicine at the University of Florida as faculty in the Division of Gastroenterology, Hepatology, and Nutrition.