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Evolution of Causes and Risk Factors for Mortality Post Liver Transplant: Results of the NIDDK Long Term Follow-up Study

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Abstract

Although mortality rates following liver transplantation (LT) are well described, there is a lack of detailed, prospective studies determining patterns of and risk factors for long term mortality. We analyzed the multi-center, prospectively obtained NIDDK Liver Transplantation Database of 798 transplant recipients from 1990–1994 (followup 2003). Overall, 327 recipients died. Causes of death >1 year: 28% hepatic, 22% malignancy, 11% cardiovascular, 9% infection, 6% renal failure. Renal related death increased dramatically over time. Risk factors for death >1 year (univariate): male gender, age/decade, pre-LT diabetes, post-LT diabetes, post-LT hypertension, post-LT renal insufficiency, retransplantation >1 year, pre-LT malignancy, alcoholic (ALD) disease and metabolic liver disease, with similar risks noted for death >5 years. Hepatitis C, retransplantation, post-LT diabetes, hypertension and renal insufficiency were significant risk factors for liver related death. Cardiac deaths associated with age, male gender, ALD, cryptogenic disease, pre-LT hypertension and post-LT renal insufficiency. In summary, the leading causes of late deaths after transplant were graft failure, malignancy, cardiovascular disease and renal failure. Older age, diabetes, and renal insufficiency identified patients at highest risk of poor survival overall. Diligent management of modifiable post-LT factors including diabetes, hypertension and renal insufficiency may impact long term mortality.

Introduction

Advances in medical management and surgical technique have resulted in step-wise improvements in early posttransplant survival rates. In the current transplant era, the overall 1 and 5 year survival rates after a liver transplant (LT) are 85% and 68% respectively, with a 10 year survival rate closer to 50% (http://www.unos.org). Improvement in early posttransplant patient survival has increased the importance of understanding the causes and risk factors for late posttransplant mortality. The few reports that have described longterm post-LT mortality of have been limited by a retrospective, single center design, small cohort size and/or inclusion of pediatric patients. (1–6)

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Available data on factors predictive of post-LT mortality are largely limited to the early posttransplant period and include perioperative factors and donor related factors which are not modifiable. (4,7) There are no reports of risk factors relating to specific causes of death after liver transplantation. The National Institutes of Health sponsored Long Term Follow Up Liver Transplant Database Study was designed to prospectively generate detailed survival data from a large multi-center cohort of liver transplant recipients. This database provides a unique opportunity to determine long term mortality rates and causes of death post transplant across multiple centers. This is the first analysis of patient related risk factors for death among adult patients dying beyond 1 and 5 years post-LT.

Methods

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplantation Database collection occurred from April 1990 to June 1994, with follow-up data obtained by January 2003 (median follow-up of 10 years) at three clinical centers: Mayo Clinic, MN, University of Nebraska, NE, and University of California at San Francisco (UCSF) with coordination through the University of Pittsburgh.(8) No followup beyond 2003 is available. 798 patients ≥ 18 years old who received their first transplant were included in our analysis. Mayo Clinic enrolled 30% (n=241), University of Nebraska 27% (n=216) and UCSF 43% (n=341). Immunosuppression protocols consisted of: 1. cyclosporine, prednisone, and azathioprine (Mayo), 2. cyclosporine and prednisone (University of Nebraska), 3. antilymphocyte globulin with cyclosporine, prednisone, and azathioprine (UCSF). All centers participated in the FK506 Primary Immunosuppression Trial, resulting in 92 recipients receiving a tacrolimus based regimen.

Cause of death was captured in the early (≤1 year) and late (>1 year, and >5 years) post-transplant periods. Patient related risk factors were analyzed for overall deaths as well as for each major cause of death >1 year and >5 years from transplant. “Hepatic failure” was not further characterized and included graft failure of any cause, including acute/chronic rejection and recurrent disease. 84 retransplantations were performed in the cohort during the followup. Causes of death are those listed as the primary cause of death by the physician involved in the care of the patient.

Pre-transplant malignancies were identified as those malignancies known prior to the transplant and those found only on pathologic evaluation of the explant (termed ‘incidental’). Diabetes mellitus (DM) was defined as a diagnosis that required treatment with insulin or oral hypoglycemics. Renal insufficiency/failure (RI) was defined as serum creatinine ≥ 2mg/dL. Hypertension (HTN) was defined as a sustained blood pressure >150/95 or the use of antihypertensive medication. DM, RI and HTN were determined both at the time of transplant and during the post-transplant period. Body mass index (BMI) was corrected for ascites at the time of transplant. Acute cellular rejection was diagnosed based on histologic criteria.

Numerical variables are summarized by means, standard deviations and ranges and categorical variables by counts and percents. Incidence of death by cause was determined using an extension of the Kaplan-Meier method accounting for these competing risks of death.(9) Risk factors relating to death overall all as well as specific causes were determined using Cox regression with two-sided 95% confidence intervals. The study was approved by the NIDDK as well as Mayo Clinic IRB.

Results

Demographics and underlying disease etiology are shown in Table 1. A total of 71 (8.9%) patients had malignancy in their explanted liver: 38 (28 hepatocellular carcinoma (HCC), 7 cholangiocarcinoma (CCA), 3 other) were identified prior to transplant and 33 (29 HCC, 4 CCA) were incidental cancers identified on the explant pathology report. The mean age of patients was 49.4 years (range 18.8 – 77.5). Hepatitis C was the most common primary cause of liver disease, occurring in 24% of recipients. Retransplantation was performed 84 times during the 12.6 year followup, with 54 of these within the first year of the primary transplant.

Overall patient survival at 1, 3, 5 and 10 years post-transplant was 87.0%, 78.6% , 74.9% and 59.4% respectively. The probability of death after transplant is depicted in Figure 1a. The probability of death exhibited a trimodal pattern, with the greatest risk during the first 6 months post transplant (11% mortality rate), decreasing and stable (2.5–5% / year) between 6 months and 8 years post-LT, and increasing to 6–7% / year thereafter.

327 patients died over the 12.6 years of followup (median=10 years). Of these, 78 (23.9%) died of hepatic causes, 207 (63.3%) of non-hepatic cause and 42 (12.8%) of unknown cause (Figure 2). Major causes of hepatic deaths were listed as recurrent disease (49/78, 62.8%) and ‘hepatic failure’ (29/78, 37.1%), of which 7/29 were rejection related. Of the patients who died of hepatic causes, 1 patient had coronary artery disease, 1 had pulmonary hypertension and 1 had seizures listed as contributing to death. Non-hepatic causes of death included: 61 (29.5%) malignancy, 52 (25.1%) infection, 40 (19.3%) cardiovascular, 14 (6.8%) renal, 6 (2.9%) neurologic, 5 (2.4%) gastrointestinal, 5 (2.4%) respiratory, and 19 other (multi-organ failure of unclear cause, trauma, suicide or other infrequent events). Malignancy deaths were attributed to the following: 8 lymphoproliferative disorder, 2 leukemia (1 additional leukemia “contributed to death” but was not listed as primary cause), 7 recurrent HCC, 5 recurrent CCA, 11 lung cancers, 4 oropharyngeal cancers, 8 colon cancer (including 1 small bowel), 2 esophageal cancer, 3 pancreatic carcinoma, 1 uterine cancer, 1 ovarian cancer, 1 melanoma, 1 oligodendroglioma, and 7 were unspecified (1 recurrent malignancy, 1 metastatic malignancy and 5 unspecified adenocarcinoma). Hyperkalemia and pulmonary hemorrhage were listed as contributing to death in 2 patients that died of malignancy. Infections causing death were: 20 “sepsis”, 22 “opportunistic infection”, 6 pneumonia, 3 bacterial peritonitis, 1 ascending cholangitis. Two patients had recurrent liver disease, 1 denovo hepatitis B, 1 red cell aplasia and 1 had Parkinson’s disease contributing to these deaths. Cardiovascular deaths were; 18 myocardial infarctions, 10 cerebrovascular accidents, 6 cardiac arrests, 5 heart failure/cardiomyopathy (1 with familial amyloidosis) and 1 myocarditis. Hypertension was the only contributor to death listed in these patients. Renal deaths were classified as “renal failure” as the primary cause of death. No other contributing cause was documented in 10/14 cases. Two patients had alcoholic cirrhosis, 1 patient had disseminated intravascular coagulation and 1 patient had congestive heart failure contributing to death. Contributing factors to ‘other deaths’ were noted to include 10 cardiovascular events, 1 recurrent hepatitis, 1 vasculitis, 1respiratory failure or 1 Alzheimer’s disease.

95 patients died within 1–5 years of transplant. Known causes of death were: hepatic (28.4%), malignancy (24.2%), cardiovascular (13.7%), infection/sepsis (10.5%) and 12 unknown. 128 deaths occurred during the 5–12.6 years of followup. Late (>5years post-LT) causes of death were: hepatic (27.3%), malignancy (21.1%), renal failure (10.2%), cardiovascular (8.6%), and infection (8.6%).

The probability of death over time for the leading primary causes of death, are depicted in Figure 3. Infection related deaths occurred earlier in the post transplant setting. The greatest increase in frequency was observed for renal related mortality, which increased to 10.2% of deaths after 5 years.

Risk Factors for Death

Prevalence of comorbidity—Diabetes was present in 15% of patients prior to transplant (pre-LT), 25% of patients at 1 year post transplant (post-LT)and 33% of patients post-LT overall. Hypertension was present in 17% of pre-LT patients, 56% by 1 year post-LT and 67% of post-LT patients overall. Renal insufficiency/failure was present in 17% of pre-LT, 47% of post-LT by 1 year and 64% of post-LT patients overall. Renal failure requiring dialysis occurred in 6% by 1 year post-LT and 10% of patients overall. Rejection occurred in 65% of patients within 1 year and a total of 71% of patients over 10 years. A smoking history prior to LT was documented in 46% of patients. All HCC and CCA risk analyses reflect both known cancers and incidental cancers as the combination was more strongly predictive of outcomes.

Risk factors for overall death after 1 year, by univariate analysis, included (Tables 2 A&B): male gender, pre-LT age in decades, pre-LT HCC or CCA, pre-LT smoking history, pre-LT diabetes, post-LT diabetes, post-LT HTN, post-LT RI, alcoholic liver disease and metabolic liver disease. Retransplantation after 1 year was a risk for worse survival, but not retransplant within 1 yr. Cholestatic liver disease and acute liver failure were associated with a lower risk of death after 1 year of followup. Rejection, at any time, was not a risk factor for overall death (HR 1.20, p=0.22). Corrected BMI at the time of LT was not associated with overall risk of death (HR 1.11, p=0.1), nor was donor age (HR 1.01, p=0.82). Immunosuppression choice was not a risk factor for death (cyclosporin vs non cyclosporin HR 1.08, p=0.71, tacrolimus vs non-tacrolimus HR 0.94, p=0.71). Multivariate analysis (Table 3) showed age in decades (HR 1.23, p=0.0012), diabetes prior to LT (HR 1.48, p=0.023), RI at any time (time dependent) (HR 3.59, p<0.0001), CCA (HR 3.22, p=0.02), HCC (HR 1.76, p=0.01) and retransplant >1 year after primary transplant (HR 4.79, p<0.0001) to be associated with increased risk of death after 1 year post-LT. Cholestatic disease appeared protective (HR 0.46, p<0.0001) and retransplant within 1 year of the primary transplant did not impact long term survival (HR 1.52, p=0.12).

Metabolic risk factors for death >1 year post-LT were further analyzed in a time dependent analysis. Hypertension was associated with death post LT (HR 1.46, CI 1.08–1.97, p=0.011), as was diabetes (HR1.68, CI 1.28–2.19, p=0.0002). When pre LT diabetics are excluded, new onset diabetes (excluding transient diabetes within 6 months) is associated with a long term risk of death (HR 1.61, CI 1.05–2.48, p=0.039), and the risk of sustained diabetes post transplant (including pre LT diabetics, but excluding transient diabetes post-LT) was also significant (HR 1.87, CI 1.41–2.48, p<0.001). Similarly, RI was associated with increased risk of death (HR 4.10, CI 2.87–5.86, p<0.0001). New onset RI beyond 6 months post LT (excluding those with pre LT RI, and transient RI post-LT) was a risk (HR 4.48, CI 3.27–6.12, p<0.001) as was sustained RI post LT (excluding just transient RI post LT) (HR 3.82, CI 2.84–5.14, p<0.001). Renal insufficiency was analyzed by time to first diagnosis of renal insufficiency/failure (creatinine>2mg/dL) in Table 4.

Univariate risk factors specific for liver related death after 1 year included: hepatitis C (HR 2.53, p=0.0005), alcohol related disease (HR 2.26, p=0.005), male gender (HR 1.93, p=0.013), retransplantation >1 year post-LT (HR 10.0, p<0.0001), post-LT diabetes (HR 1.97, p=0.009), new onset post-LT diabetes (HR 2.58, p= 0.009), post-LT HTN (HR 1.82, p=0.038), and post-LT RI (HR 5.43, p<0.0001) and new onset post-LT RI (HR 6.39, p<0.001). Rejection was not a risk factor for overall liver related death (HR 1.09, p=0.77),

including the HCV population (HR 1.36, p=0.49). Donor age in decades was not a risk (HR 1.03, p=0.70). Neither HCC (HR 0.88, p=0.82), CCA (HR 2.6(CI 0.36–18.9), p=0.41) nor retransplant within 1 year (HR 1.41, p=0.52) were significant. Multivariate analysis (Table 3) showed HCV (HR 2.47, p=0.0005), retransplant > 1year post-LT (HR 8.5, p<0.0001), DM at any time (HR 1.80, p=0.022) and RI at any time (HR 5.55, p<0.0001) to be independently associated with liver related deaths after 1 year. HCC (HR 0.83, p=0.76), CCA (HR 2.18, p=0.44) and retransplant within 1 year (HR 1.44, p=0.48) were not.

HCC (HR 3.67, p=0.026) or CCA (HR 9.80, p=0.002) in the explant were associated with increased long term risk of malignancy related death. Age in decades (HR 1.53, p=0.002), ALD (HR 2.23, p=0.03) and post-LT RI (HR 2.92, p=0.006) were also risk factors on univariate analysis for malignancy related deaths. Smoking was not a risk factor for malignancy related deaths (HR 1.50, p=0.16). Table 3 shows the multivariate analysis.

Cardiac deaths > 1 year post-LT were associated on univariate analysis with age in decades (HR 2.28, p=0.0001), male gender (HR 2.63, p=0.028), ALD (HR 2.58, p=0.044), pre-LT hypertension (HR 3.21, p=0.01) and post-LT RI (HR 3.94, p<0.005). Neither diabetes nor smoking pre-LT was a significant risk for cardiac death (HR 1.70, p=0.26 and HR 1.71, p=0.20 respectively), as the numbers were small. Risk factors for renal related mortality on univariate analysis included age in decades (HR 1.82, p=0.027), pre-LT RI (HR 3.61, p=0.033), pre-LT diabetes (HR 7.44, p=0.0004), sustained post-LT diabetes (HR 4.18, p=0.012), rejection (HR 5.62, p=0.033), and ALD (HR 3.84, p=0.043). Multivariate analysis cardiovascular deaths is shown in table 3, but could not be performed on renal deaths as the number of events was too small.

Risk factors (univariate) associated with death > 5 years after transplant include: male gender (HR 1.54 (1.07–2.20), p=0.017), pre-LT diabetes (HR 1.70 (1.07–2.70), p=0.034), post-LT diabetes (HR 1.48 (1.03–2.12), p=0.036), hypertension post-LT (HR 1.64 (1.08–2.48), p=0.014), renal insufficiency post-LT (HR 3.65 (2.28–5.84), p<0.001), ALD (HR 2.38 (1.64–3.46), p<0.001), with PBC being protective (HR 0.42 (0.21–0.82), p=0.005). Multivariate analysis: age (decades) (HR 1.21 (1.02 – 1.44), p= 0.034), DM pre-LT (HR 1.58 (0.991– 2.529), p= 0.055), and RI at any time (HR 3.37 (2.10 – 5.40), p<.0001), ALD (with or without HCV) (HR 2.17 (1.48 – 3.16), p<.0001). Of note, neither pre-LT malignancy nor retransplantation was associated with mortality after 5 years post-LT (p=NS).

Discussion

Analysis of this unique multi-centered, prospectively obtained data set has generated several important observations. The first is that the relative frequency of specific causes of death evolves substantially over time, with marked increases occurring in hepatic and renal related deaths as the duration of follow-up increases. The second important new observation is that the risk of post-LT mortality exhibits a trimodal pattern, with the risk of mortality increasing with duration of follow-up. As outcomes have improved over time, we found that ~2/3 of all deaths occur after the first posttransplant year. This preponderance of late post-LT mortality highlights the importance of understanding longterm mortality. Finally, we have identified several potentially modifiable risk factors for longterm mortality.

Similar to previous reports, we found that liver-related causes were the most common etiology of death in the late transplant period, (4–6) closely followed by malignancy-related deaths. Infection is the most common cause of death prior to one year posttransplant. We found cardiovascular disease to be the third most common late cause of death, accounting for 12–16% of deaths (primary or major contributing causes). This may be an

underestimation as it is quite likely that some deaths characterized as ‘unknown’ included sudden cardiac deaths. Patients followed closely in a transplant center would be unlikely to have an ‘unknown’ liver or malignancy related death.

A novel observation in this multicentered study is the surge in renal related deaths with longer follow up. Other reviews have found renal failure to be a cause of 1–2% of deaths overall (4–6). Our study suggests that, with longer follow-up, renal failure is a major cause of death, with the inflection point for increasing frequency occurring at the sixth postoperative year. A weakness in this observation is the lack of clear definitions of renal failure as a cause of death. We are limited by the documentation of primary cause of death being simply “renal failure”. Supporting this finding, and even more importantly, is the analysis showing the risk of death from any cause is substantially impacted by renal insufficiency, with increased risk associated with later onset (>1 year post transplant) of renal insufficiency compared to early (<1 year) onset.

This study confirms a lower risk of death for cholestatic liver disease patients. It is thought that fulminant hepatic failure patients have an increased risk of mortality posttransplant, but our data suggests that if the patient survives the first year, they experience a lower risk of death thereafter. Alcoholic liver disease and metabolic liver disease are risk factors for long term mortality. A diagnosis of HCC or CCA at the time of transplant, whether previously identified or found incidentally on explant, portended a worse prognosis in this cohort of patients. The risk was higher when analyzed with all incidental malignancies included compared to only previously known malignancies, suggesting incidental cancers have an impact on long term mortality. This risk appears to be predominantly associated with malignancy related deaths, as they were not independent variables associated with other causes of death (although CCA had a HR 2.6 for liver related death suggesting a type 2 error). Care must be taken in interpreting this data as the difference in selection criteria for patients with malignancy as well as therapeutic management before and after transplant in the present era have undoubtedly affected the outcome in these patients.

Risk factors known to be associated with death early after LT include age, pre-LT renal insufficiency, and pre-LT diabetes are incorporated into survival adjustment calculations by the Scientific Registry of Transplant Recipients for center specific 1 year outcomes. These risk factors as well as hypertension also contribute independently to an increase the risk of death in the *late* posttransplant period. This is the first large multi-centered study to identify patient related risk factors for death and cause specific death. It has been suggested that patients transplanted with pre-existing diabetes have worse 1, 3, and 5 year survival after a transplant (11,12). New onset diabetes is reported in 10–35% of liver transplant patients (13–15). One case control study suggested no increased risk of 1, 3, or 5 year mortality for patients with sustained new onset diabetes after transplant (15) whereas another retrospective study with 10 year analysis suggested increased mortality for patients with sustained new onset diabetes (13). In our study, both pretransplant and posttransplant diabetes (whether new onset or sustained diabetes), in addition to posttransplant hypertension and renal insufficiency, were predictors of longterm death, as well as specifically cardiovascular and renal deaths. Body mass index at the time of transplant was not associated with longterm mortality, consistent with previous findings(16). Surprisingly, smoking was a risk factor for overall death, but not cardiovascular or malignancy deaths specifically, but this may be due to small numbers of smokers in the cause specific analysis. Regardless of the era of transplant, these risk factors remain major issues in the care of post transplant patients and may be targets to improve overall outcomes.

Retransplantation > 1 year from the primary transplant is associated with increased risk of death overall, primarily due to markedly increased risk of liver related death (independent

HR 8.5). Retransplantation within the first year of primary transplant was not associated with an increased risk of death long term (>1 year). This may reflect the era of transplantation and may not be applicable to the current era as survival after retransplantation has improved since the early 1990's (10).

Liver-related deaths accounted for almost 1/3 of all deaths. Risk factors for liver-related death included underlying hepatitis C, an established risk factor, as well as posttransplant diabetes, hypertension, and renal insufficiency, which have not previously been associated with liver related deaths. It should be noted that this cohort of patients were transplanted in the early 1990s which preceded the likelihood of early antiviral treatment for their recurrent hepatitis C after transplant. The impact of HCV on longterm outcomes in this cohort has been described previously(17). The association of diabetes with liver related mortality fits with the current knowledge that insulin resistance posttransplant has been shown to be associated with more rapidly progressive fibrosis and hepatitis C recurrence, intuitively increasing the risk of liver-related mortality(18).

Malignancy is the second most common cause of death in the long term followup of these patients. It is no surprise that patients transplanted with HCC or CCA are at higher risk of death from a malignancy. Protocols and allocation policies are different from 1990-94 and therefore this data may not apply to the current transplant era. However, more patients died of denovo than recurrent malignancy and risk factors exist including ALD and older patients which are unrelated to the era of transplant. Interestingly, PSC and smoking history were not statistically associated with increased malignancy-related death despite a higher frequency of malignancy in PSC patients (20). A detailed analysis of malignancy posttransplant in this population is now published elsewhere (20). Rigorous screening programs for prevention and early detection of malignancy in the post transplant should be studied.

Renal insufficiency/failure occurred in over 68% of patients in the posttransplant period and was shown to be an important risk factor for late death. Renal failure is an important cause of death in a small but increasing number of patients late posttransplant. Older age, pre-LT RI, pre and post-LT diabetes and ALD are strongly associated with renal related death and should be factored into identifying recipients who may benefit from combined liver kidney transplantation.

An obvious limitation of this study is its historical nature. The lack of clarity on the specific causes of liver related deaths (recurrence of disease vs rejections or other cause) or renal deaths is a limitation and allows for only generalizations regarding risk factors for these deaths. We must also keep in mind that the risk factors identified may be associated with contributing causes of death and not necessarily the listed cause. Certainly survival after primary transplantation or retransplantation has improved over the years. While this impacts the interpretability of some of the data presented, it is also the driving factor to understand more about long term mortality. This study, allows insight into *cause-specific* risk factors, helping us to identify those risk factors that may or may not change within multiple eras of transplant. Metabolic complications after transplant arise in a large percentage of the transplant population in every era and this study provides awareness into the impact of these complications on longterm survival. Continued data of cause-specific risk factors for longterm mortality are needed.

Summary

Hepatic etiologies are the most frequent cause of death in the late posttransplant setting. Immunosuppression changes and antiviral treatments in the current era of transplantation may impact the frequency of liver related deaths. In addition to malignancy and cardiovascular disease, renal failure is an important and escalating cause of death in the late

posttransplant setting. Diabetes and renal insufficiency both pre-LT and post-LT are key factors in long-term survival after liver transplantation. Understanding risk factors for cause-specific mortality can provide targets for therapeutic interventions that may impact long-term mortality. Investigations into the effects of diligent medical management of diabetes, hypertension, and renal insufficiency on long-term morbidity and mortality in the current era of liver transplantation are needed.

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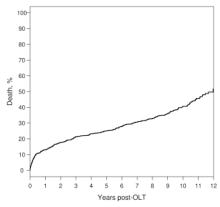

Figure 1. Kaplan-Meier Mortality Curve

The probability of death after liver transplant exhibited a trimodal pattern, with the greatest risk during the first 6 months post transplant, decreasing and remaining stable for 8 years post-LT, and increasing thereafter.

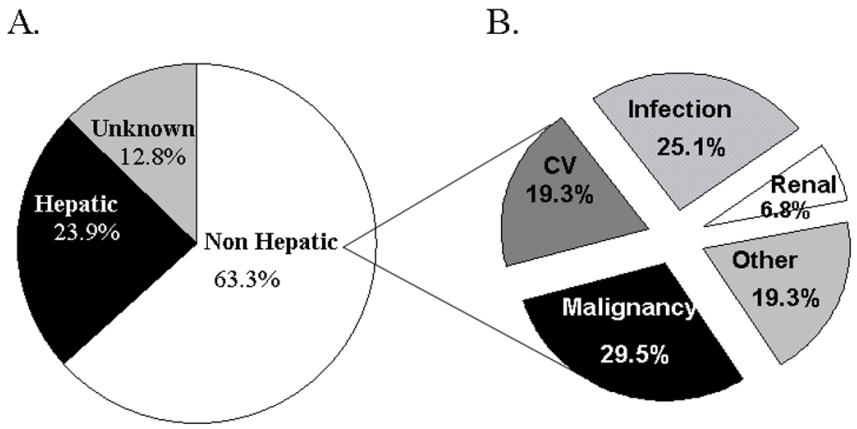

Figure 2.
A. Causes Death Overall, N=327. B. Non-Hepatic Causes of Deaths, N=207. CV=Cardiovascular.

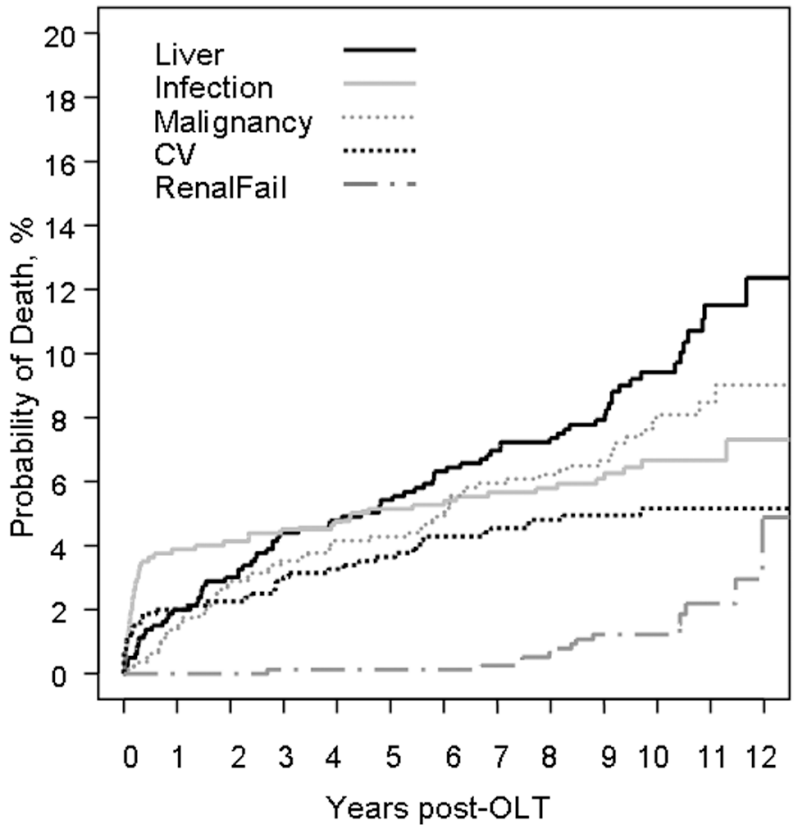

Figure 3. Cause Specific Probability of Death Over Time (by Primary cause)

Infection is the leading cause of death over the first 3 years, with majority occurring in the first 6 months. Liver related causes of death are the most common cause of death thereafter and overall, with increased frequency after 8 years. Renal related deaths increase in probability after 8 years of followup, with a sharp rise after 10 years. Cardiovascular deaths are under-reported – see text (10 deaths had major contributing cardiovascular cause not captured in graph).

Table 1

Patient Demographics, N=798

Male	55.5%	
Caucasian/AA/Hispanic/Asian	80 / 4 / 10 / 4%	
Age (years)	49.4 (mean) (18.8–77.5 range)	
Underlying etiology (n, %)		
Hepatitis C	139	(17.4)
Hepatitis C/ alcohol	54	(6.7)
Alcohol	102	(12.8)
Hepatitis B	37	(4.6)
Autoimmune hepatitis	46	(5.8)
Primary Sclerosing Cholangitis	129	(16.2)
Primary Biliary Cirrhosis	100	(12.5)
Cryptogenic	85	(10.7)
Fulminant Hepatic Failure	44	(5.5)
Metabolic*	23	(2.9)
Other	39	(4.9)
Malignancy**	71	(8.9)
HCC (known/incidental)	28 (3.5) / 29 (3.6)	
CCA (known/incidental)	7 (0.9) / 4 (0.5)	
Other	3	(3.8)

AA = African American.

* inherited disorders

** incidental cancers are found on explant only

Table 2a/b

Univariate Analysis: Risk Factors Associated with Increased **Overall Mortality** beyond 1 Year Post Liver Transplant (LT).

A			
Risk Factor	**HR**	**CI**	**P value**
Male Gender	1.65	1.26 – 2.18	**<0.001**
Age in decades	1.22	1.08–1.38	**0.002**
Donor Age in Decades	1.01	0.93–1.10	0.824
Cyclosporine use	1.08	0.71–1.65	0.717
Tacrolimus use	0.94	0.68–1.30	0.711
History of smoking	1.41	1.08–1.85	**0.010**
Diabetes pre-LT	1.94	1.40–2.68	**<0.001**
Hypertension pre-LT	1.31	0.94–1.81	0.107
Renal insufficiency pre-LT	1.35	0.97–1.89	0.078
Diabetes post-LT**	1.87	1.41–2.48	**<0.001**
Hypertension post-LT	1.46	1.08–1.97	**0.010**
Renal insufficiency post-LT	4.10	2.87–5.86	**<0.001**
Rejection post-LT	1.20	0.89–1.61	0.220
Retransplant < 1 year	1.52	0.90–2.56	0.12
Retransplant > 1 year*	4.79	2.72–8.43	**<0.001**

B			
Underlying disease			
Acute Liver Failure	0.42	0.17–1.02	**0.027**
ALD or ALD+HCV	1.82	1.36–2.44	**<0.001**
ALD only	1.73	1.22–2.44	**0.004**
Autoimmune	0.68	0.36–1.27	0.198
Cholestatic	0.41	0.29–0.58	**<0.001**
Cryptogenic	1.40	0.95–2.06,	0.099
Hepatitis B	1.63	0.90–2.92	0.130
Hepatitis C	1.33	0.99–1.78	0.064
Metabolic	2.25	1.19–4.25	**0.026**
Other	1.15	0.64–2.06	0.651
Malignancy – HCC^	2.16	1.42–3.28	**0.001**
- CCA^	2.80	1.04–7.5	0.08

** diabetes posttransplant excludes transient diabetes within the first 6 months of transplant ALD = alcohol related disease, HCC = hepatocellular carcinoma, CCA = cholangiocarcinoma

^ denotes including incidentally identified HCC or CCA.

* Retransplant >1 year after primary transplant.

Table 3

Multivariate Analysis: Risk Factors Associated with Increased Mortality beyond 1 Year Post Liver Transplant (LT).

Overall Death			
Risk Factor	**HR**	**CI**	**Pvalue**
Overall Death ^			
Age in decades	1.24	1.09–1.41	**<0.001**
Diabetes pre-LT	1.48	1.06–2.08	**0.023**
Renal insufficiency pre or post-LT*	3.59	2.50–5.16	**<0.001**
Cholestatic Disease pre-LT	0.45	0.32–0.65	**<0.001**
HCC	1.76	1.13–2.72	**0.011**
CCA	3.22	1.17–8.81	**0.023**
Retransplant > 1year ^^	5.04	2.83–8.96	**<0.001**
Liver-related Death			
HCV diagnosis	2.61	1.57–4.35	**<0.001**
Renal insufficiency pre or post-LT*	5.10	2.41–10.77	**<0.001**
Diabetes pre or post LT*	1.85	1.21–3.05	**0.016**
Retransplant > 1year ^^	8.50	3.77–19.16	**<0.001**
Cardiovascular Death			
Age in decades	2.12	1.34–3.36	**0.001**
Cryptogenic cirrhosis pre-LT	5.59	2.04–15.29	**<0.001**
Alcoholic liver disease pre-LT	4.79	1.73–13.27	**0.003**
Malignancy Death			
Age in decades	1.46	1.11–1.93	**0.007**
Cholestatic disease pre-LT	0.47	0.23–0.98	**0.043**
Renal insufficiency pre or post-LT*	2.66	1.35–5.25	**0.005**
HCC	2.80	1.30–6.01	**0.008**
CCA	12.48	3.65–42.69	**<0.001**

^ Multivariate analysis for Overall death after 5years showed similar HR, see text.

* Time dependent factor analysis

ALD = alcohol related disease, HCC = hepatocellular carcinoma, CCA = cholangiocarcinoma

^^ Retransplant >1 year after primary transplant.

Note: Renal related deaths were too few to perform multivariate analysis

Table 4

Timing of Development of Renal insufficiency (RI) Predicts Risk of Long-term Mortality After Liver Transplant

Time	HR	CI	Pvalue
Compared to no Renal insufficiency			
Pre Transplant	2.51	1.69–3.75	**<0.001**
Post Transplant 0–1 year*	2.41	1.73–3.36	**<0.001**
1–5 years*	6.58	3.66–11.81	**<0.001**
>5 years*	7.49	4.01–13.97	**<0.001**
Compared to RI 0–1 year Post-LT			
Post Transplant 1–5 years*	2.73	1.56–5.69	**0.0004**
>5 years*	3.10	1.70–5.69	**0.0002**
Compared to RI 1–5 year Post-LT			
Post Transplant >5 years*	1.14	0.51–2.53	**0.75**

*similar HR when analyzed when all patients with pre-LT RI are excluded.