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ORTHOTOPIC LIVER TRANSPLANTATION IN HIGH-RISK PATIENTS

RISK FACTORS ASSOCIATED WITH MORTALITY AND INFECTIOUS MORBIDITY

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Background. **One of the most controversial areas in patient selection and donor allocation is the high-risk patient. Risk factors for mortality and major infectious morbidity were prospectively analyzed in consecutive United States veterans undergoing liver transplantation under primary tacrolimus-based immunosuppression.**

Methods. **Twenty-eight pre-liver transplant, operative, and posttransplant risk factors were examined univariately and multivariately in 140 consecutive liver transplants in 130 veterans (98% male; mean age, 47.3 years).**

Results. **Eighty-two percent of the patients had postnecrotic cirrhosis due to viral hepatitis or ethanol (20% ethanol alone), and only 12% had cholestatic liver disease. Ninety-eight percent of the patients were hospitalized at the time of transplantation (66% United Network for Organ Sharing [UNOS] 2, 32% UNOS 1). Major bacterial infection, posttransplant dialysis, additional immunosuppression, readmission to intensive care unit (P=0.0001 for all), major fungal infection, posttransplant abdominal surgery, posttransplant intensive care unit stay length of stay (P<0.005 for all), donor age, pretransplant dialysis, and creatinine (P<0.05 for all) were significantly associated with mortality by univariate analysis. Underlying liver disease, cytomegalovirus infection and disease, portal vein thrombosis, UNOS status, Childs-Pugh score, patient age, pretransplant bilirubin, ischemia time, and operative blood loss were not significant predictors of mortality. Patients with hepatitis C (HCV) and recurrent HCV had a trend towards higher mortality (P=0.18). By multivariate analysis, donor age, any major infection, additional immunosuppression, posttransplant dialysis, and subsequent transplantation were significant independent predictors of mortality (P<0.05). Major infectious morbidity was associated with HCV recurrence (P=0.003), posttransplant dialysis (P=0.0001), pretransplant creatinine, donor age, median blood loss, intensive care unit length of stay, additional immunosuppression, and biopsy-proven rejection (P<0.05 for all). By multivariate analysis, intensive care unit length of stay and additional immunosuppression were significant independent predictors of infectious morbidity (P<0.03). HCV recur-**

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rence was of borderline significance ($P=0.07$).

***Conclusions.* Biologic and physiologic parameters appear to be more powerful predictors of mortality and morbidity after liver transplantation. Both donor and recipient variables need to be considered for early and late outcome analysis and risk assessment modeling.**

The number of cadaveric organ donors in the United States has remained relatively static while the candidate waiting list for solid organ transplants has grown exponentially (*1*). This growing disparity in supply and demand has catalyzed much debate regarding current allocation policies with views ranging from the utilitarian to the deontologic (*2–4*). One potential solution is readily evident in that the current potential pool of cadaver organs can probably meet the needs of those who are in the greatest need. Unfortunately, the average number of solid organ donors actually realized from this potential pool is less than one half (*5, 6*). Until this is rectified, the transplant community is faced with difficult selection and allocation decisions. Both the scarcity of donor organs and economic considerations have promulgated a number of investigators to examine preoperative, intra-operative, and postoperative risk factors in an effort to better predict outcome (*7–12*). Analyses have included both donor and recipient characteristics; however, a fully developed risk assessment model has not yet been realized.

One of the most controversial areas in patient selection and donor allocation is the high-risk patient (*2*). Several reports have concluded that transplantation of these patients is ill-advised, given the current economic climate and the current donor/recipient disparity (*3, 4*). This utilitarian stance has been challenged with several authors reporting acceptable outcomes including quality of life (*2, 13–16*).

Under primary tacrolimus (Prograf, formerly FK506)-based immunosuppression, we have had the opportunity to examine a unique high-risk group of consecutive United States veterans undergoing orthotopic liver transplantation. We analyzed a number of preoperative, intra-operative, and postoperative risk factors for both mortality and major infectious morbidity in an effort to better define predictors of outcome in the high-risk patient group.

PATIENTS AND METHODS

Between October 1989 and October 1995, 140 liver transplants were performed in 130 consecutive United States veterans under primary tacrolimus-based immunosuppression at the Veterans Administration Medical Center in Pittsburgh (one patient had a combined liver/kidney transplant). There were 128 (98%) males and 2 (2%) females with a mean age of 47.3 years (range, 22–70 years). There were 15 patients (11.5%) over the age of 60 (all male). The mean follow-up for survivors was 50±21.6 months (range, 15–88 months). The etiology of underlying liver disease is shown in Table 1. Pretransplant patient characteristics and morbidity are shown in Table 2. The immunosuppressive regimen has been described previously (*17*) with lower doses of induction tacrolimus and routine use of intravenous prostaglandin E-1 over the past 4 years.

Risk Factors Examined

Recipients. Pretransplant variables included age, diagnosis (including fulminant hepatic failure and hepatoma), United Network for Organ Sharing (UNOS*) status, need for mechanical ventilation, Childs-Pugh score, serum bilirubin, serum creatinine, need for hemodialysis, antibiotic therapy required within 4 weeks of transplant, weight >100 kg, multi-organ transplantation, and complications of portal hypertension.

Donor and intraoperative factors. Donor age, gender, ischemia time (time from cross-clamping to reperfusion), intra-operative blood loss, and recipient portal vein thrombosis were examined.

Posttransplant factors. These included length of intensive care unit (ICU) stay, need for ICU readmission, posttransplant surgery (abdominal), antibiotic therapy during the first 4 weeks, need for dialysis, subsequent transplantation, incidence of rejection and requirement for additional immunosuppression (steroid bolus, recycle, or OKT3), cytomegalovirus infection and disease, major bacterial and fungal infections (*18*), and hepatitis C recurrence.

Statistical Analysis

Clinical and laboratory data were entered into a data base (Prophet Statistics, BBN Systems and Technologies, Cambridge, MA). Categorized variably (mortality, infection) were compared using the

* Abbreviations: HCV, hepatits C virus; ICU, intensive care unit; UNOS, United Network for Organ Sharing.

TABLE 1. Indications for primary liver transplantation in United States veterans under primary tacrolimus (FK506, Prograf) immunosuppression[a]

	n	(%)
Viral hepatitis		
Hepatitis C	68	(53)
Hepatitis B	12	(9)
Alcoholic cirrhosis[b]	58	(45)
Cholestatic disease		
PBC	2	(2)
PSC	13	(10)
Metabolic disease	5	(4)
Cryptogenic cirrhosis	7	(4)
Hepatocellular carcinoma[c]	12	(9)
Polycystic liver	1	(1)
Total	130	

[a] Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

[b] Of the patients with alcohol-related disease, 29 had associated HCV, 32 had HCV and HBV, and 1 had HBV.

[c] Associated liver diseases included hepatitis B (2 patients), alcoholic cirrhosis (3 patients), cryptogenic cirrhosis (3 patients), hepatitis C (3 patients), and Wilson's disease (1 patient).

TABLE 2. Patient demographics and pretransplant risk factors[a]

Age (mean) (range, 22–69 yr)	47.3
Sex	
Male	98%
Female	2%
Childs-Pugh score (mean) (range, 6–15)	11.5
UNOS status	
3	2%
2	66%
1	32%
Bilirubin (mean mg/dl)	5.86
Renal function	
Creatinine (mean mg/dl)	1.43
Creatinine ≥2.0	16%
Dialysis	4%
Pre-OLTx antibiotics[b]	28%
Portal vein thrombosis	23%

[a] Abbreviations: OLTx, orthotopic liver transplant; UNOS, United Network for Organ Sharing.

[b] Antibiotic use within 4 weeks of OLTx.

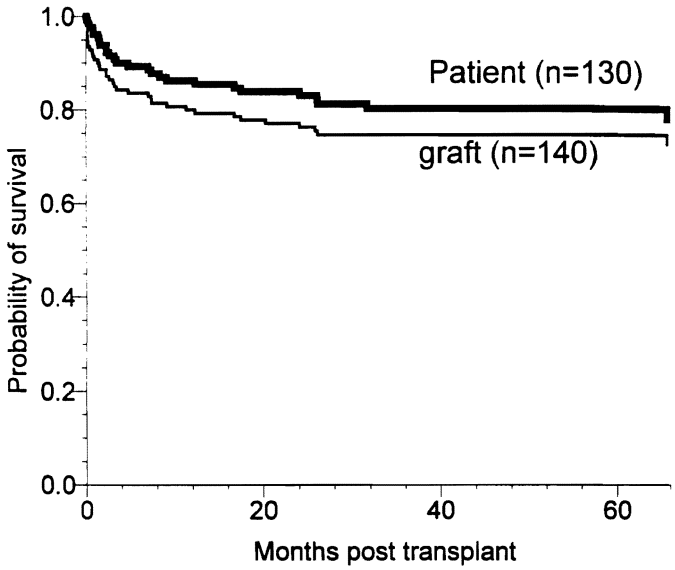

FIGURE 1. Kaplan-Meier patient and graft survival curves.

chi-square test or the Fisher exact test. Ordinal values such as UNOS or Childs-Pugh were compared using the Mann-Whitney *U* test. Kaplan-Meier probability survival curves were constructed using the date of first transplant as the starting point and loss of graft or death as the endpoints. Survival curves were compared using the Mantel-Cox log-rank test.

RESULTS

The underlying liver disease and demographic characteristics of the patients are reported in Tables 1 and 2. The overall actuarial patient survival rates were 90%, 87%, 85%, and 80% at 6, 12, 24, and 60 months, respectively (Fig. 1). Graft survival was 86%, 83%, 76%, and 70% at 6, 12, 24, and 60, months respectively. Ten patients (8%) received additional transplants, including 1 patient who received three grafts, with a long-term actuarial survival rate of 50%.

Risk Factors for Mortality

Univariate analysis. Patient mortality was associated with need for subsequent transplantation (22% vs. 4.7%, $P=0.016$), major bacterial (70% vs. 26%, $P=0.0001$) and fungal infections (30% vs. 6.6%, $P=0.003$), pre- and posttransplant dialysis (48% vs. 8.5%, $P=0.0001$), pretransplant creatinine (2.0 mg/dl vs. 1.3 mg/dl, $P=0.04$), donor age (40.5 years vs. 31.4 years, $P=0.01$), posttransplant abdominal surgery (43% vs. 18%, $P=0.0005$), requirement for augmented immunosuppression, number of rejection episodes (1.3 vs. 0.4, $P=0.009$), length of posttransplant ICU stay (25 days vs. 7.1 days, $P=0.004$), and readmission to ICU (52% vs. 25%, $P=0.0001$) (Table 3).

Underlying liver disease, need for mechanical ventilation, cytomegalovirus infection and disease, portal vein thrombosis, UNOS status, Childs-Pugh score, patient age, pretransplant bilirubin, donor sex, ischemia time, and operative blood loss and complications of portal hypertension were not significant predictors of mortality (Table 4). Several factors analyzed did not have sufficient numbers to define statistical significance. These include patient weight >100 kg (n=9), fulminant hepatic failure (n=0), multi-organ transplantation (n=1), and hepatoma (n=12). It is notable that patients with HCV had higher mortality ($P=0.18$) as did patients with posttransplant HCV recurrence ($P=0.185$), although statistical significance was not achieved.

Multivariate analysis. Variables found to be significant in the univariate analysis were utilized for stepwise logistic regression analysis. Donor age ($P=0.04$), any major infection ($P=0.02$), additional immunosuppression ($P=0.01$), posttransplant dialysis ($P=0.006$), posttransplant surgery, biopsy-proven rejection, and need for subsequent transplantation

TABLE 3. Risk factors associated with mortality: univariate analysis[a]

Risk factor	Dead (n=23)	Alive (n=106)	*P*
Pre-OLTx			
Need for dialysis	13%	6.6%	0.04
Serum creatinine (mean)	2.0	1.3	0.04
Donor age (mean)	40.5	31.4	0.01
Post-OLTx			
Need for dialysis	48%	8.5%	0.0001
Surgery (abdominal)	43%	18%	0.0005
Augmented	78%	33%	0.0001
Immunosuppression			
No. of steroid boluses (mean)	1.7	0.4	0.001
No. of steroid re-cycles (mean)	0.65	0.19	0.01
Biopsy-proven rejection (mean no.)	1.3	0.4	0.009
Major infections			
Bacterial	70%	26%	0.0001
Fungal	30%	6.6%	0.003
ICU LOS (mean no. of days)	25	7.1	0.004
Readmission to ICU	52%	25%	0.0001
Subsequent transplantation	22%	4.7%	0.016

[a] Abbreviations: ICU, intensive care unit; LOS, length of stay; OLTx, orthotopic liver transplant.

TABLE 4. Risk factors not associated with mortality[a]

Risk factor	Dead (n=23)	Alive (n=106)
Liver disease[b] (%)		
Hepatitis (viral)		
C	65	50
B	13	84
Ethanol	43	45
Cholestatic (PSC/PBC)	4	13
Metabolic	0	5
Cryptogenic	9	5
Hepatoma	13	8
Portal vein thrombosis	30	22
UNOS status (%)		
3	0	3
2	70	65
1	30	32
Childs-Pugh score (mean)	11.9	11.4
Patient age (mean)	45.7	45.7
Donor sex (%)		
Male	78	76
Female	22	24
Pre-OLTx Female bilirubin (mean mg/dl)	4.9	6.0
Ischemia time (mean hr ± SD)	12.7±4	13.5±3
Operative blood loss (no. of PRBCs)	15	12.5

[a] Abbreviations: OLTx, orthotopic liver transplant; PBC, primary biliary cirrhosis; pRBC, packed red blood cells; PSC, primary sclerosing cholangitis; UNOS, United Network for Organ Sharing.
[b] Some patients have more than one underlying disease.

($P=0.02$) were identified as significant independent predictors of mortality (Table 5).

Risk Factors for Infectious Morbidity

Univariate analysis. Donor age, recipient pretransplant creatinine, need for mechanical ventilation, need for post-transplant dialysis, operative blood loss, ICU length of stay, biopsy-proven rejection, augmented immunosuppression, and HCV recurrence were associated with increased major infectious morbidity (Table 6).

Multivariate analysis. By multivariate analysis, ICU length of stay, and additional immunosuppression were significant independent predictors of infectious morbidity ($P<0.03$) for all variables. HCV recurrence was of borderline significance ($P=0.07$) (Table 7).

Subsequent Transplantation

Overall, 10 patients underwent retransplantation. Subsequent transplantation occurred within 2 weeks of the original transplant in seven patients (median=5 days). Recipient portal vein thrombosis ($P=0.01$) and median blood loss (25 units of packed red blood cells vs. 12 units of packed red blood cells, $P=0.004$) were statistically significant factors for subsequent transplantation. Requirements for subsequent transplantation in patients with portal vein thrombosis were not associated with problems of portal in-flow or other vascular complications.

TABLE 6. Risk factors for infectious morbidity: univariate analysis[a]

Risk factors	Infection (n=58)	No infection (n=71)	P
Pre-OLTx			
Donor age (mean)	36	30.5	0.03
Serum creatinine (mean)	1.7	1.2	0.04
Operative			
Blood loss (median no. of pRBCs)	15.5	10	0.02
Post-OLTx			
Need for mechanical ventilation	69%	28%	0.003
Need for dialysis	29%	4.2%	0.0001
ICU LOS (mean no. of days)	15.3	6.1	0.001
No. of steroid boluses (mean)	1.0	0.2	0.001
No. of steroid recycles (mean)	0.4	0.1	0.015
Biopsy-proven rejection (mean no.)	0.8	0.3	0.001
HCV recurrence	36%	14%	0.003

[a] Abbreviations: HCV, hepatitis C virus; ICU, intensive care unit; LOS, length of stay; OLTx, orthotopic liver transplant.

TABLE 7. Risk factors for infectious morbidity: multivariate analysis[a]

Risk factors	Odds ratio	(95% CI)	P
ICU length of stay	1.08	(1.0–1.16)	0.03
Augmented immunosuppression	3.18	(1.3–7.83)	0.01
HCV recurrence	2.57	(0.93–7.09)	0.07

[a] Abbreviations: CI, confidence interval; HCV, hepatitis C virus; ICU, intensive care unit.

DISCUSSION

Orthotopic liver transplantation was originally conceived and developed for patients with end-stage liver disease who had little hope for survival otherwise. Refinements in surgical technique, immunosuppression, and peri-operative management had expanded the indications for transplantation. As a result, the number of candidates for liver transplantation has grown rapidly, while the organ pool has remained relatively stagnant. This supply and demand disparity has led to much controversy regarding organ allocation (*2*, *3*, *4*, *15*). Many have argued that liver transplantation should be performed in patients who are less ill, citing better survival rates and lesser costs (*3*, *4*). A recent report from the University of Wisconsin showed no significant difference in long-term survival with UNOS status 4 patients (old classification) (*11*). This is consistent with our observations in this select group of veteran patients. We and others have found that these desperately ill patients can be treated with acceptable 1- and 3-year survival rates with the most dramatic gain in life-years compared with the low-risk patient (*15*). Recent data on patient outcome and graft survival have suggested that UNOS status is a somewhat artificial classification and physiologic variables appear to be more powerful predictors of outcome (*7*, *10*, *12*, *19*). We would suggest that the high-risk patient group (currently designated as UNOS 1 and 2, or hospitalized patients) needs to be defined more precisely to aid the transplant physician to better decide which high-risk patients can be salvaged with reasonable outcome. How shall we further define the high-risk patient? The Blue Cross/Blue Shield consortium have classified high-risk recipients according to diagnosis, prior operative procedures and patient condition (*20*). Several of these risk factors such as portal vein thrombosis and previous right upper quadrant surgery have not, however, been shown to result in significantly poorer survival rates (*16*). Other physiologic parameters have been shown to be better predictors of outcome for early and late (greater than 6 months) outcome (*7*, *18*).

Severity of liver dysfunction as reflected by degree of hyperbilirubinemia and coagulopathy have been shown to be significant predictors of mortality in patients requiring ICU care for end-stage liver disease (*7*, *10*, *19*). An analysis of a series of patients in the University of Wisconsin era has indicated that requirement for mechanical ventilation and elevated bilirubin are significant independent predictors of graft failure (*19*). Eckhoff et al. (*13*) found that prolonged partial thromboplastin time was a significant independent risk factor for mortality in UNOS 4 patients. Advanced disease as evident by requirement for ICU support (UNOS 4) and Childs class C have also been associated with higher mortality. We did not find these factors to be predictive of mortality or infectious morbidity. However, this is likely a result of the skewed nature of our patient population; the mean Childs-Pugh score of our patients was 11.5, 70% were Childs class C and the vast majority (98%) were hospitalized at the time of transplantation. Graft dysfunction requiring

TABLE 5. Risk factors associated with mortality: multivariate analysis[a]

Risk factor	Odds ratio	(95% CI)	P
Donor age	1.04	(0.5–6.9)	0.04
Post-OLTx dialysis	8.065	(1.9–39.9)	0.006
Augmented immunosuppression	5.91	(1.4–24.6)	0.01
Major infection	8.15	(1.5–45.1)	0.02
Subsequent transplant	9.54	(1.4–63.5)	0.02

[a] Abbreviations: CI, confidence interval; OLTx, orthotopic liver transplant.

retransplantation was a significant independent predictor of patient mortality, and this is consistent with the literature (*7, 9, 11, 19*).

Renal insufficiency has been implicated as a harbinger of not only mortality, but increased infectious morbidity in both patients waiting for transplantation, as well as those undergoing transplantation (*10, 12*). A recent report examined the impact of renal insufficiency (defined as creatinine >1.6 mg/dl) on outcome (*21*). A lower patient and graft survival was noted in patients presenting with fulminant hepatic failure. Renal insufficiency did not, however, affect patient survival in patients with cirrhosis, except in those requiring dialysis or combined liver-kidney transplants. Other notable observations were longer hospital and ICU length of stay, adding to overall costs of transplantation in these patients. Our results differ in that not only patients requiring dialysis but all patients with renal insufficiency had a significantly higher mortality. In addition, Brown et al. (*21*) did not examine the impact of renal insufficiency on infectious morbidity and a multivariate analysis was not performed. We agree with the approach of Baliga et al. (*10*) that instituting aggressive volume support and assessment with invasive monitoring in an attempt to reverse any prerenal component, as well as other studies to rule out hepatorenal syndrome or glomerulonephropathies is indicated. Although we concur with the conclusions of Baliga et al., it is important to note that they only assessed hospital mortality and their criteria for infections were not as rigorous as those used in our report. From our data, renal insufficiency both before and after transplantation would appear to have farther reaching consequences in terms of mortality and infectious morbidity. Ideally, intervention with liver transplantation is desired before progression to full renal support.

Donor age was a significant independent predictor of mortality in our patient population. This is consistent with observations in a much larger series of patients examining graft failure defined as patient death or retransplantation (*7, 19*). Conversely, donor sex and ischemia time did not impact significantly on mortality or infectious morbidity, and this is likely due to our much smaller number of observations in this group of hospitalized patients. This serves to illustrate again that we must be cognizant of donor, as well as recipient factors when attempting to predict outcome or likelihood of success.

Our observation of increased mortality in patients requiring augmented immunosuppression is neither surprising nor unique (*22–24*). It is also not surprising that patients experiencing a major infection or requiring posttransplant abdominal surgery are at higher risk for mortality. These occurrences are not predictable preoperatively, and do not add to our ability to predict outcomes in the high-risk patient. These observations do, however, serve to illustrate that immunosuppression should be administered judiciously and technical imperfections are not tolerated well by the recipient.

Augmented immunosuppression and ICU length of stay were significant predictors of infectious morbidity. Major infections are not unexpected sequelae associated with these risk factors. Recurrent HCV hepatitis also appears to impact adversely upon infectious morbidity. HCV is thought to have immunomodulatory properties and perhaps recurrent HCV may facilitate infections from pathogens associated with depressed cell-mediated immunity (*25, 26*).

In conclusion, biologic and physiologic parameters appear to be better predictors of mortality and morbidity after liver transplantation. More subjective and artificial categorizations such as UNOS status were not important factors in our patient population. This is perhaps explained by the skewed nature of our high-risk patient group; nearly all patients required hospitalization at the time of transplantation. Our data indicate that donor age and renal failure (with or without the need for dialysis) are markers for mortality and infectious morbidity. It is notable that in spite of this risk profile, the overall patient survival is excellent and adds further testimony to the salvageability of high-risk patients in need of liver transplantation. These observations merit further investigation in a larger series of high-risk patients to realize a more accurate risk assessment model to optimize the allocation of a presently scarce resource.

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