ORIGINAL STUDIES

Outcome of Liver Transplantation in a Hispanic Population: 100 Liver Transplants in Puerto Ricans

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***Background*: The residents of Puerto Rico (PR) had limited access to liver transplantation (LTx) prior to 1996. LTx remains locally unavailable and success rates for LTx for patients from PR have never been published. The outcome of the first 100 LTx recipients from PR transplanted at our center is analyzed.**

***Methods*: 100 consecutive patients transplanted between 3/1997 and 1/2005 were evaluated.**

***Results*: Hepatitis C was the indication for LTx in 44%. Overall patient survival at 1, 3 and 5 yrs was: 94.0%, 81.4% and 75.7%, respectively, while for hepatitis C, it was 90%, 73% and 73%, respectively. At mean follow up of 44 mo., 80% of patients were alive (66% HCV were alive vs 91% non HCV, p< 0.01).**

***Conclusions*: Access to LTx in Puerto Rico has dramatically improved since 1996. The government-sponsored fund has provided access to indigent patients. Decreased survival in this minority population was not observed at 1, 3 and 5 years. Long term survival was most affected by recurrence of HCV.**

Key words: Access to liver transplant, Hispanics, Outcome liver transplant

Liver transplantation (LTx) is the only life-saving treatment for end stage liver disease. It is also indicated in enzymatic (metabolic) liver disorders, hepatocellular carcinoma and fulminant hepatic failure. Prognostic models such as the MELD (Model End Stage Liver Disease), incorporating serum total bilirubin, creatinine and INR, estimate the pre transplant mortality and is used to prioritize patients on the waiting list. Over 6,000 liver transplants are performed annually in the United States and approximately the same number in the rest of the world. The one year patient survival has improved to 87%. Five year patient survival averages 75%. There is no information on liver transplantation services offered or outcomes achieved for citizens from the Commonwealth of Puerto Rico prior to 1997. This report is the first one, encompassing a multi-institutional effort over the last decade.

Minorities in the United States have less access to healthcare (1), including transplantation. The relative rate of kidney transplants in African-Americans is significantly lower than in whites, 16.9% versus 52% (2). Disparity between African-Americans and whites has also been observed for LTx according to United Network Organ Sharing (UNOS, the organ transplant regulatory agency) data for 1994 to 1998, in which transplant ratios were lower, and mortality in the waiting list was higher for blacks (3). The proportion of Hispanics in the LTx waiting list is similar to their proportion in the US population, suggesting access may not be a limiting factor in this ethnic minority. Transplantation rates for 2006 (cadaveric and living donors) were 60.6% for whites, 68.19 % for African Americans and 55.0% for Hispanics. For 2005, median time to LTx after listing was significantly longer for Hispanics (782 days) than for whites (290 days) and African Americans (195 days) (4). According to UNOS data, there were 15.9% Hispanics on the LTx waiting list in 2006, and 13.6% underwent transplants. Annual death rates in the waiting list were also higher for Hispanics (137.9/1000 patient-years) and African-Americans (138.8/10000 pt-yrs) than whites (111.0/1000 pt-yrs) in 2006 (4).

Puerto Rico has a high prevalence of chronic liver disease and viral hepatitis-related deaths. As there is no local LTx center, factors such as geography, culture, and economics have had limited impact on access to liver transplant in the past. In 1997, the LifeLink Healthcare Institute (LLHCI) and Tampa General Hospital (the transplant center) transplanted their first patient from Puerto Rico. Following this, referrals from Puerto Rico for LTx increased. During this time, the Government of Puerto Rico established the Puerto Rico Catastrophic Fund (PRCF) to cover expenses

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of catastrophic remediable diseases that would otherwise not be treated for indigent patients or those with insufficient coverage for medical expenses. LTx was included in the procedures covered by this fund, thus facilitating access to this therapy. In 1999, the Division of Gastroenterology and Liver Diseases of the University of Puerto Rico School of Medicine (UPR) became affiliated with LLHCI to establish a LTx Evaluation Clinic. A detailed analysis of the clinic's first four years of operation has been previously published (5).

In the past, patients and families had to travel to the United States in the early transplant evaluation phase. The establishment of the UPR Evaluation Clinic allowed the majority of these patients to remain in Puerto Rico under the care of their physicians. Since its adoption in 2001, MELD, which prioritizes patients for transplantation, has been used as a guide to determine the timing for moving transplant candidates to the Unites States.

We report on the experience with the first 100 LTx recipients from Puerto Rico transplanted at the LLHCI and Tampa General Hospital, including only those patients that resided in Puerto Rico at the time of the referral for LTx. This is a unique group affected by many factors which are described here. The data provides a description of the outcome of liver transplantation in a minority population with limited access. The results can also be used to compare liver transplant utilization in Puerto Rico to other Latin American countries and other minorities in the United States and provides a model that may be applicable to other underserved populations.

Methods

Data was collected on the first 100 consecutive patients from Puerto Rico transplanted between March of 1997 and January of 2005, out of a total of 488 patients transplanted at LLHCI during this time period. No patients were excluded. Information was compiled by review of medical charts and liver transplant flow sheets, and by communication with the physicians caring for the patient. Assessment was made of the patients' overall health and current problems. The status of each of the 100 patients is known. Individual data included demographic information, etiology of liver disease, donor and recipient age, blood utilization, the patient's current location, morbidity, survival, and Hepatitis C-related outcome. The study was approved by the Institutional Review Board of the Medical Sciences Campus of the UPR.

From December of 1996 to September of 1999, the majority of patients from Puerto Rico were referred directly to the transplant center by community physicians, gastroenterologists, or hepatologists. Since September of 1999, most of the referrals originate from the UPR LTx Evaluation Clinic. Initial evaluation at the clinic includes determining if the patient is a candidate for a transplant evaluation. Patients that are determined to be candidates and who are either indigent or have insufficient funding for LTx are referred to the PRCF. After the transplant evaluation is completed, the patients are referred to LLHCI and the referrals are reviewed by the transplant surgeon (AA). Those with low MELD scores, not likely to be transplanted in the near future, are given appointments for evaluation by the transplant surgeon at the UPR Clinic. Those with higher MELD scores, other medical factors or exceptional conditions are given an appointment at the transplant center. Final evaluation for listing is carried out after the patients are evaluated in Tampa, insurance approval is confirmed, and adequate coverage for immunosuppressants is obtained. The decision for listing is then made by the Liver Transplantation Selection Committee at the transplant center. Hepatocellular carcinoma and other unusual serious conditions, such as hepatopulmonary syndrome, porto-pulmonary hypertension, and others receive prompt referral to the transplant center.

All transplants were carried out at Tampa General Hospital in standard orthotropic fashion, most with veno-venous bypass. Immunosuppression consisted of tacrolimus-based maintenance in 95% of cases, in combination with prednisone +/- mycophenolate mofetil. In the majority, prednisone was weaned by six months. Induction agents were rarely used. Rejection episodes were treated with 1 gm methylprednisolone and a five-day taper; and, in refractory, cases with Muromonab OKT3 (Ortho Biotech, Bridgewater, NJ) until 2000 and rabbit anti-thymocyte globulin (Genzyme Corp, Cambridge, MA) from 2000 to present. Histologic confirmation of progressive Hepatitis C recurrence was treated with standard interferon and ribavirin until 2001, and pegylated interferon and ribavirin since 2001. Follow-up was carried out at the LLHCI in Tampa until the patient was stable and returned to Puerto Rico, at which point medical care was continued at the UPR Clinic or by the referring community gastroenterologist/hepatologist. Annual long-term follow-up in Tampa was also carried out for most patients. Statistical analysis was performed utilizing Chi-square and Kaplan Meier analysis.

Results

Demographics

Recipients included 32 females and 68 males, with a mean age of 48 years (range 19-67). The mean donor

age was 36 years. Average blood utilization during surgery, including 5 urgent retransplant operations, was 9 units of packed red blood cells (range 1-32) and 22 units of fresh frozen plasma (range 0-63). The mean waiting time from listing to liver transplantation in the pre-MELD era (until February of 2000) was 7.2 months, decreasing to 2.8 months in the MELD era. The etiology of liver diseases for all LTx is listed in Figure 1. Hepatitis C-related disease was the indication for LTx in 44% of patients. Referrals originated from the UPR Clinic in 52% of the cases, community hepatologists in 26%, and community gastroenterologists in 23%. Since 2001, 72% of referrals were from the UPR, increasing to 80% in 2004. Candidacy for LTx was more likely if referral origin was from UPR (156/180, 86%), than from another sources (40/91, 44%); p<0.001. The patient's current location post-transplantation is as follows: 54 have returned to Puerto Rico, 41 remain in Tampa, FL, 4 in Orlando, FL, and 1 other location. Five patients have dual residence.

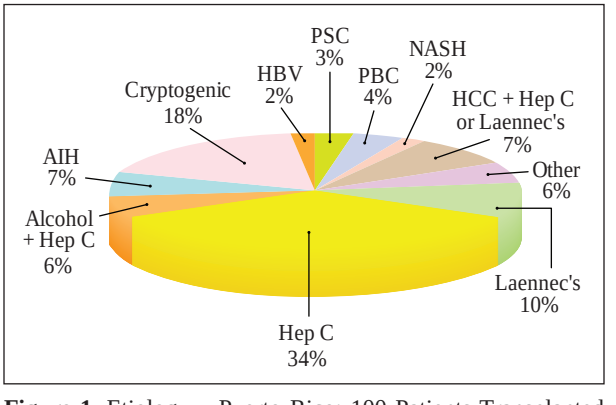

Figure 1. Etiology – Puerto Rico: 100 Patients Transplanted Abbreviations: Hep C, hepatits C; AIH, autoimmune hepatits; HBV, hepatits B; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma

Morbidity

Re-transplantation was carried out as a status 1 (urgent) in 5 patients (5%), 3 for primary graft non-function, 1 for hepatic artery thrombosis, and 1 for acute cellular rejection. All five patients were alive one year post LTx. Biliary complications occurred in 11 patients (11%), 8 of which are currently alive. Hepatic artery thrombosis occurred in one patient (1%) who was successfully retransplanted. Five (5%) patients have developed end stage renal disease, 4 of which are alive, and 2 of which have undergone subsequent kidney transplantation. Acute cellular rejection was observed in 25% of patients in the first year and in 3% the following year (Table 1).

Table 1. Complications

Re-transplantation	5%
Biliary	11%
Hepatic artery thrombosis	1%
End stage renal disease	5%
Acute cellular rejection, 1st year	25%

Survival

Actuarial patient survival at 1, 3, and 5 years was as follows (95% confidence interval): 94% (0.98-0.89) at one year, 83.9% (0.91-0.76) at three years, and 80.9% (0.89-0.72) at five years, respectively. This is compared to the national adjusted overall survival of 87.1% at one year, 79.10 at three years and 73.4% at five years (4-5)(7) (Figure 2). Similar data for Hispanics across the nation is 87.3% at 1 year, 80.5% at 3 yrs and 75.0% at 5 years (Table 2). Seventy-nine (79%) of the patients are currently alive at a mean follow-up of 44 months (range 12-101). There were 21 deaths, listed in Table 3. Two deaths were attributed to noncompliance. In the Hepatitis C group, actuarial patient survival at 1, 3, and 5 years was as follows (95% confidence interval): 90.4% (0.99-0.81), 73.8% (0.89-0.53), and 73.8% (0.89-0.58). However, only 33% (15/45) of patients with Hepatitis C related liver disease were alive at the end of follow-up versus 89% (49/55) non Hepatitis C (P=0.01). Seventy one percent (15/21) of all deaths occurred in the Hepatitis C cohort, 53% of these (8/15) were related to Hepatitis C recurrence.

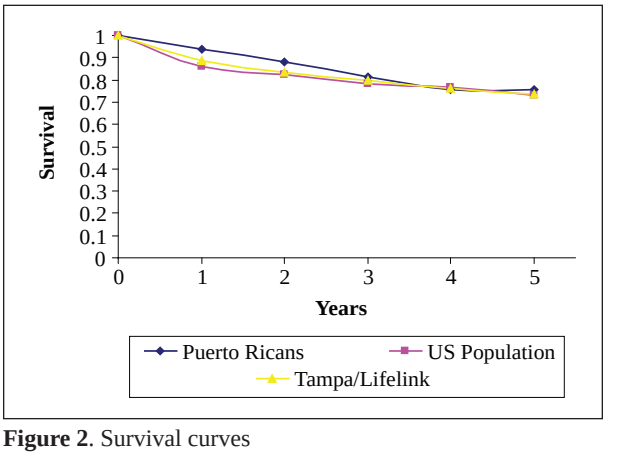

Figure 2. Survival curves

Table 2. Patient Survival

Year	Puerto Rico	US Average UNOS	Hispanics UNOS
1 year	94%	87.1%	87.3%
3 year	83.9%	79.1%	80.5%
5 year	80.9%	73.4%	75%

Table 3. Deaths

Early	Intracerebral hemorrhage
< 3 mo	Sepsis (3)
Late	Mesenteric thrombosis
	Lung Ca
	Rectal Ca
	Tuberculosis
	Recurrent Hepatocellular Carcinoma
	Liver failure
	Sepsis
	Varicella pneumonia
	Recurrent Hepatitis C (8)

Discussion

In Puerto Rico, many factors affect access and are hurdles to liver transplantation, including geographical isolation, language, culture, family dynamics, socioeconomic structure, psychological and substance abuse issues, health insurance, access to immunosuppression therapy, ensuing complications of liver disease and development of untransplantable hepatocellular carcinoma. Awareness and access to LTx in Puerto Rico increased after establishment in 1996 of the LLHCI in Tampa and creation of the UPR LTx Evaluation Clinic in 1999. In the past, patients of low socioeconomic status and the medically indigent were expected to die without being considered for LTx. Few patients traveled to transplant centers in the mainland US. Access for these patients dramatically changed after establishment of the PRCF in 1996. The Fund has partially covered transplant medical expenses in approximately 50% and totally in approximately 25% of the 100 patients here described. Strong working relationships within the UPR, LLHCI, and Tampa General Hospital as well as with the PRCF have been maintained since its inception.

The local LTx Evaluation Clinic at UPR has ameliorated language barriers and cultural fears, and has facilitated future candidate's access to the evaluation process. Psychological and social worker evaluations are performed at the clinic. A local support group has been established and assists and educates patients during the evaluation process prior to relocation to the mainland. Healthcare providers at the UPR Clinic maintain frequent communication with the transplant center. Achievement of candidacy and eventual LTx was found to be more likely when the patients originated from the UPR Clinic. This most likely is the result of applying consistent well-defined evaluation and transplant criteria, multidisciplinary assessment of candidates, and constant access to the transplant center for expedited management. Another factor may be that community physicians are now referring patients to the UPR Clinic instead of directly to the transplant center.

Deaths from chronic liver disease and cirrhosis is higher in Puerto Rico than in the US (12), 19.6 per 100,000 population, and it is the 10th leading cause of all deaths. It is the 5th leading cause for ages 30 to 39, 4th in the 40 to 64 age group and accounted for nearly 2.2-3.1% of all deaths reported in Puerto Rico over the last two decades (6). A decline in age-adjusted death rates for liver disease and cirrhosis were observed for the US and Puerto Rico from 1980-1998 (6). This decrease was not sustained after 1994, mainly attributed to viral hepatitis and hepatocellular carcinoma (7-8). Vital statistics for 2007 show an age adjusted death rate for cirrhosis and chronic liver disease of 9.3 per 100,000 for the US and 5.9 per 100,000 for Puerto Rico (9).

Deaths related to viral hepatitis in Puerto Rico increased six fold from 1982-1999, with a marked increase after 1995, reaching 2.1 per 100,000 population in 1998 (6). A population study in adults living in metropolitan San Juan, PR found a prevalence of hepatitis C antibodies of 6.3% (10). A significant number of these will go on to cirrhosis, decompensated liver disease, hepatocellular carcinoma and death. Puerto Rico faces a serious problem with morbidity and mortality from chronic liver disease over the next two decades.

The need for LTx in Puerto Rico appears to be high. Extrapolating data from other countries, such as Israel (10-15 LTx per million population) (11), or Canada (15.4/ million) (12), this would translate to 60 LTx per year for Puerto Rico. The need in the United States is higher (21/million) (13). Referrals from Puerto Rico for LTx to our center alone exceeded 50 in 2006, and there are at least three other centers in the Southeast of the United States evaluating and performing LTx for patients from Puerto Rico in an organized fashion. Data from the UPR Clinic indicated that 70% of patients referred for LTx consideration by community physicians were candidates to begin an evaluation process and 47% completed the evaluation, or approximately 1/3 of those referred (5). Approximately 1/3 of those referred have been transplanted and 50 remain with low severity end stage liver disease. In our center alone, 3.5 patients per million/Puerto Rico population received a LTx. The current average in the US is 5 patients/million. This is higher than the average of 2.3 LTx/ million reported for Latin America (14).

Success rates for LTx for patients from Puerto Rico have never been published. The outcome for these patients prior to 1996 is unknown and there is no accurate way to gather this data. Analysis of the OPTN/UNOS Liver Transplant Registry, as well as one report comparing transplant outcomes by race, have noted a decreased graft and patient survival in African-Americans but comparable outcomes

for Hispanics versus non-Hispanic whites (15-17). In our series, decreased patient survival was not observed. The results in this minority population were better than expected. Waiting time for transplantation was much shorter than the national median for Hispanics, and 5 yr adjusted survival was also better than the national median. Determinants of outcome may be a well-organized referral and evaluation process, and post-transplant care. In addition, the patients benefit from transplantation in UNOS Region 3, known for high transplantation rates, shorter waiting times, and lower MELD scores. Time to LTx in our minority group was extremely short in the MELD era. Compliance with post-transplant clinic visits and medications has also been involved in graft and patient survival. A study of 601 transplant recipients, including blacks and Hispanics, showed that the higher rate of noncompliance in the minority patients was related to lower socioeconomic status and not to race (18). Although the population we report in this study has a significant portion of low income patients (as evidenced by the 25% funded fully by the Government and 50% additional requiring at least partial Government assistance), non-compliance was extremely low. The presence of a stable social environment, with support from the family, and a culturally sensitive health environment, both in Puerto Rico and in the transplant center, may have influenced this behavior. From 2006 to 2008, 56 additional Puerto Ricans have been transplanted under this program, of which 52 are alive, for a 93% over-all survival in this group.

In summary, we present a series of 100 consecutive liver transplant recipients from a Hispanic population with limited access to transplantation, and demonstrate a similar or better outcome than the general population in the Unites States in spite of the socioeconomic, cultural and geographic limitations imposed on these patients. An important factor adversely affecting the outcome is Hepatitis C. Long-term survival was affected by recurrence in the allograft and not by long-term access to medical care or immunosuppression. Our experience supports the efforts to increase access to transplantation in minorities, as justified by the favorable short and long term results. An analysis of the Hepatitis C cohort is warranted and well underway.

Resumen

Hasta el 1996, los residentes de Puerto Rico tenían acceso limitado a trasplante de hígado. El procedimiento no estaba disponible en Puerto Rico, y los resultados de trasplante en puertorriqueños no habían sido reportados. En este estudio, presentamos los primeros 100 pacientes de Puerto Rico trasplantados en nuestro centro. Métodos: Se revisaron los expedientes de los primeros 100 pacientes trasplantados. Resultados: Hepatitis C fue la indicación para trasplante en 44%. La tasa de sobrevivencia de pacientes a 1, 3 y 5 años fue: 94.0%, 81.4% and 75.7%, respectivamente, mientras que para hepatitis C fue 90%, 73% and 73%, respectivamente. A seguimiento promedio de 44 meses, 80% de los pacientes sobrevivieron (66% de los de Hepatitis C vs. 91% no Hepatitis C, $p< 0.01$). Conclusiones: El acceso a trasplante de hígado en PR ha mejorado dramáticamente desde el 1996. El Fondo Catastrófico gubernamental ha provisto acceso a pacientes sin recursos. La tasa de sobrevivencia en esta población de minoría fue comparable con la nacional a 1, 3 y 5 años. La sobrevivencia a largo plazo fue afectada principalmente por la recurrencia de Hepatitis C.

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