CHAPTER VII
Liver and Intestine Transplantation

INTRODUCTION

Liver transplantation, like all solid organ transplantation, is characterized by progressive disparity between supply and demand, with ever increasing numbers of potential candidates and a significantly slower rise in the number of donor organs available. Despite using organs from older donors and donors with steatosis or evidence of current (e.g., hepatitis C positive) or prior (e.g., hepatitis B core antibody positive) viral hepatitis, the number of deceased donor organs has increased slowly. This shortage led to a marked increase in adult-to-adult living donor transplantation from 1998 to 2001. Though this trend was expected to continue to grow as it has in renal transplantation, a marked decrease in adult living donor transplants was seen in 2002, with the number of procedures decreasing by approximately 50% back to the level seen in 2000 (1). This trend likely reflects concerns about donor safety among programs, potential donors, and recipients following highly publicized adverse donor outcomes. Additionally, after several years the majority of patients on existing transplant waiting lists who were interested in and prepared for living donor transplantation had already undergone the procedure, thus leaving primarily the smaller pool of new listings as potential living donor candidates.

Given the decrease in living donor transplants and a more limited applicability of this modality than for renal transplantation, the need to maximize the utility of deceased donor organs is paramount. In response to the HHS final rule and the Institute of Medicine Report, the model for end-stage liver disease and pediatric end-stage liver disease (MELD and PELD) scores for prioritization of adult and pediatric liver transplant candidates were implemented to replace the prior allocation scheme with an objective severity-based allocation model. Initially designed to predict post-TIPS mortality, MELD was shown to be superior to Child-Pugh classification at predicting short-term patient mortality in diverse patient groups with end-stage liver disease, including transplant candidates**.** The system was fully implemented at the end of March 2002, making 2002 the first year to assess the impact of using the new allocation system. This report contains the first significant data using MELD/PELD, the implementation of which has resulted in decreased pretransplant mortality and some important shifts in which patients, particularly those with hepatocellular carcinoma, receive transplants. MELD and PELD are also addressed in Chapter X, "Improving Liver Allocation: MELD and PELD." However, waiting list mortality remains significant and has grown over the last decade while posttransplant survival has improved, making the survival benefit of transplant compared to waiting even larger.

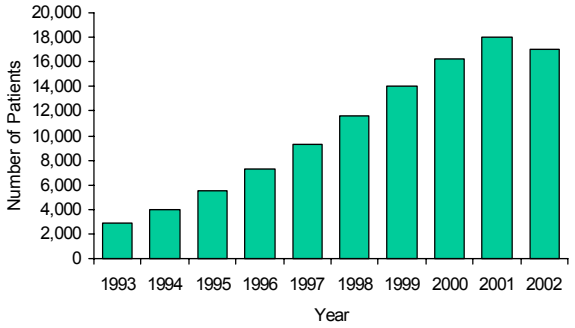
Intestine transplantation remains a lower-volume procedure limited to a small number of centers and still accompanied by high rates of death on the transplant waiting list and high rates of graft failure and death posttransplantation. It is hoped that continued advances in patient and donor selection, as well as immunosuppressive and perhaps immune tolerance protocols, will continue the advances in this field over the coming years.

LIVER TRANSPLANTATION

Liver Waiting List Characteristics

As in other fields of solid organ transplantation, the gap between the number of patients listed as candidates for liver transplantation and the number of transplants performed has grown over the last 10 years (through 2001). The waiting list increased more than sixfold in this time, from 2,902 patients in 1993 to 18,047 patients in 2001 (Figure VII-1) *[Table 9.1]*. The waiting list decreased in 2002 for the first time, dropping by 6% to a total of 16,974 patients waiting. Since the number of temporarily inactive patients increased (from 3,109 patients in 2001 to 3,866 in 2002), the net decrease in the active waiting list for 2002 was 12%.

Figure VII-1. Patients on the Liver Waiting List, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 9.1.

The pediatric liver transplant waiting list increased more slowly over the last 10 years, from 427 patients listed in 1993 to 1,079 in 2001, with a drop in 2002 to 955, a decrease mirrored in the overall list. Since the adult

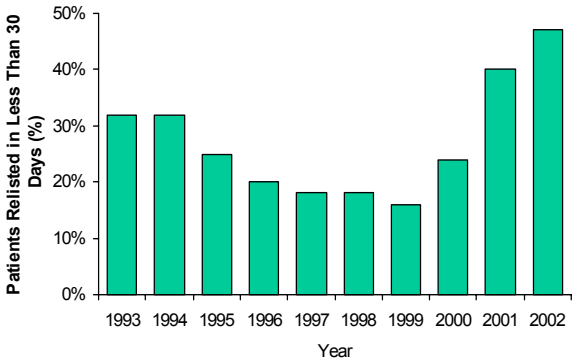
waiting list grew more quickly during the last decade, the percentage of pediatric patients on the waiting list decreased to 6% in 2002 from 15% in 1993 *[Table 9.1]*.

The racial distribution on the waiting list remained unchanged over the last 10 years. In 2002, 87% of the patients were white, while African Americans represented 7% and Asians another 4%. There has been a rise in the number of Hispanics on the waiting list from 11% in 1994 to 15% in 2002 *[Table 9.1]*.

Male candidates continue to outnumber female candidates on the waiting list. In 1993 male patients represented 53% of all registrants; this proportion rose gradually to 57% in 2002. Blood type O continues to be more prevalent on the waiting list than in the general US population. The distribution of ABO blood types among candidates remained unchanged over the last decade. In 2002, 51% of the patients had blood type O, 35% had blood type A, 11% had blood type B, and 3% were blood type AB. US residents represented 99% of the waiting list in 2002, and there was no change over the last decade *[Table 9.1]*.

In 1993, 8% of registrants on the waiting list had received a previous liver transplant. After a decline to 5% in 1999, this proportion rose to 7% in 2001 and 2002. More importantly, among such registrants, the proportion whose relisting occurred less than 30 days from the date of the prior transplant decreased from 31.9% in 1993 to a nadir of 15.6% in 1999, and then increased dramatically to 47.4% in 2002 (Figure VII-2). The reasons underlying this recent trend could include increased use of expanded criteria donor livers and split livers, both of which have increased rates of graft failure when compared to standard grafts (2-4).

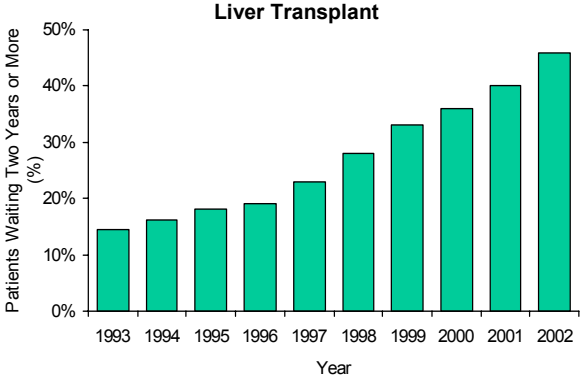
Figure VII-2. Patients Relisted in Less Than 30 Days



Source: SRTR analysis, August 2003.

Overall, the waiting time for liver transplantation continues to increase (Figure VII-3). In 2002, 7,857 out of 16,974 patients on the waiting list (46%) were waiting more than two years, compared with 7,221 (40%) in 2001 and 424 (15%) in 1993 *[Table 9.1]*. However, waiting time for patients transplanted in the 25th percentile actually decreased in 2002, down from 193 days in 2000 to 80 days in 2002 *[Table 9.2]*. This is due to the fact that sicker patients have faster access to transplant under MELD/PELD and that patients are no longer listed in order to acquire waiting time.

Figure VII-3. Patients Waiting Two Years or More for a Liver Transplant



Source: *2003 OPTN/SRTR Annual Report,* Table 9.1.

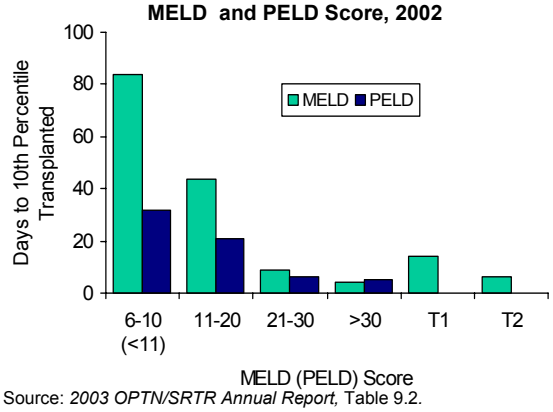
Out of the 16,974 candidates listed for liver transplantation at the end of 2002, 14,740 were listed according to the MELD score, 686 (4%) according to the PELD score and 22 (0.1%) were Status 1. The vast majority of the adult patients with chronic liver disease (82%) had a MELD score of 20 or less. These included 38% with a MELD score of 6-10 and 44% with a MELD score between 11 and 20. Patients with MELD 21-30 represented 4% and those with MELD scores above 30 made up 0.6% of the total waiting list. The pediatric patients on the waiting list had a similar distribution, but more patients waiting were in the lower PELD bracket: 77% of pediatric patients had a PELD score less than 11, 15% had a PELD score of 11 to 20, 6% had a PELD score of 21 to 30 and only 2% had a PELD score above 30 *[Table 9.1]*. The 10th percentile time to transplant for new waiting list registrants varied according to MELD and PELD scores *[Table 9.2]* and stage of hepatocellular carcinoma (median 82 days for those with Stage T1 tumors vs. 36 days for patients with Stage T2 tumors) (Figure VII-4). Implementation of the PELD score reduced the tenth percentile of pediatric time to transplant to 32 days for PELD scores less than 11, 21 days for PELD of 11-20, 6 days for PELD of 21-30, and 5 days for patients with PELD scores above 30.

Only 233 patients with hepatocellular carcinoma (1.4%) were on the waiting list at the end of 2002. Of these patients, 69 (0.4%) were staged T1 and 164 (1%) were staged T2 *[Table 9.1]*.

Waiting list registrations increased from 5,535 in 1993 to 11,132 in 2001, and then dropped to 9,651 in 2002.

The drop in waiting list registrations in the last year, which was seen across all age groups, was 13% overall *[Table 9.2]*. It is likely that decreased registrations are a result of the MELD system and decreased importance assigned to waiting time in organ allocation. Pediatric registrations were 8% of the total in 2002. The number of registrations of patients less than 1 year old increased from 276 in 1993 to 409 in 2001, then decreased to 349 in 2002. The number of registrations of all other pediatric candidates decreased slightly from 481 in 1993 to 455 in 2002. In the adult population there was an increase in registrations in all age groups, although this was more sustained in patients 35 years or older. In 2002, the 50-64 year age group had the most registrants (4,297).

Figure VII-4. 10th Percentile of Time to Liver Transplant by MELD and PELD Score, 2002



Source: *2003 OPTN/SRTR Annual Report,* Table 9.2.

New waiting list registrations increased by approximately 73% for both whites and African Americans. There was an increase in the listing of Asians from 170 in 1993 to 399 in 2002. Registration of Hispanics rose from 504 in 1993 to 1,433 in 2002 *[Table 9.2]*.

The number of annual registrations of female patients increased by 50% over the period, from 2,454 in 1993 to 3,690 in 2002. However, male patient registrations increased by 93%, from 3,081 in 1993 to 5,961 in 2002, thus increasing the male predominance on the waiting list.

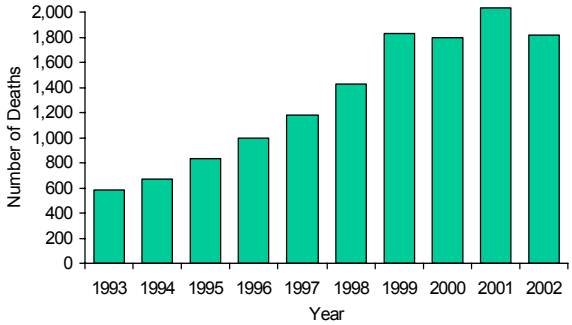
As mentioned above, patients registered for liver transplantation showed a distribution of blood types in which type O candidates were more common on the waiting list than in the United States population. Access to transplantation was better for type AB. The median waiting time for liver transplantation for type AB was 136 days. The median time exceeded one year in all other blood types. Out of 9,477 registrations, 119 (1.3%) were non-US residents. The absolute number of registrations of non-US residents dropped by 30% compared with 2001 *[Table 9.2]*.

In 2002, the median time from listing to transplant was 128 days for adults with a MELD score of 21-30 and 29 days for those with a MELD score of 31-40. In comparison, the median waiting time in 2001 for patients listed with medical urgency status 2A was 70 days and for status 2B was 301 days *[Table 9.2]*.

Waiting time for children was shorter than for adults. The median time from listing to transplant was 243 days for PELD scores of less than 11, 138 days with scores of 11-20, 125 days with PELD scores of 21-30, and 15 days with PELD scores of 31 and above.

Registrations of patients with medical urgency status 1 decreased by 25% from 678 in 1993 to 510 in 2002. Some of this reflects a change in the eligibility criteria for Status 1 listing over time rather than trends in listing for acute hepatic failure in the earlier part of the study interval. In 2002, the median waiting time to transplant was 11 days for patients in this category. The median waiting time to transplant for patients with hepatocellular carcinoma in 2002 was 82 days with T1 tumors and 36 days with T2 tumors *[Table 9.2]*.

Figure VII-5. Deaths on the Liver Waiting List, 1993-2002

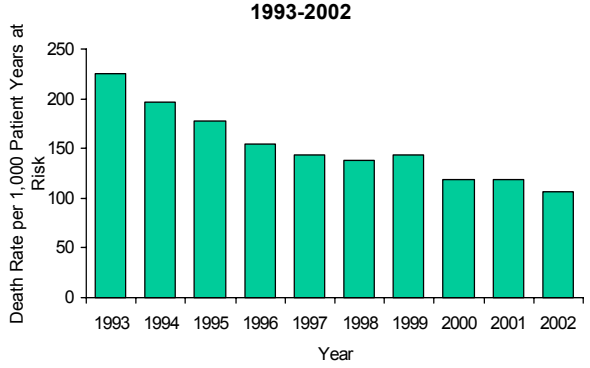


Source: *2003 OPTN/SRTR Annual Report,* Table 9.3.

The number of deaths on the waiting list increased more than threefold, from 579 in 1993 to 2,034 in 2001. However, in 2002 there was an 11% decrease in the number of deaths to 1,818 (Figure VII-5) *[Table 9.3]*. A possible explanation for this decline is the implementation of the MELD/PELD allocation system that preferentially directs livers to patients with the most imminent risk of death. The number of liver transplants increased by 2% from 2001 to 2002. However, until 2001 the number of deaths on the waiting list continued to increase despite annual increases in the number of transplants performed — likely an impact of the MELD/PELD allocation system. The MELD/PELD effect is discussed in detail Chapter X, "Improving Liver Allocation: MELD and PELD." In addition to a drop in the absolute number of deaths on the liver waiting list, the rate of death continues to decline, reflecting either

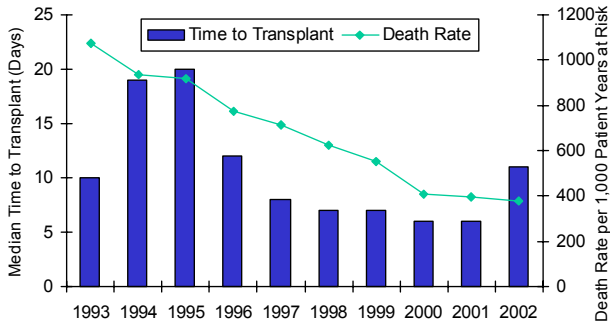
continued improvements in pretransplant care or a continued increase in the number of patients on the waiting list with low short term mortality risk (Figure VII-6) *[Table 9.3]*. Although the MELD/PELD system did not alter the allocation system for Status 1 patients, the mortality rate continued to fall for this group as well in 2002 *[Table 9.3]*. The decline in mortality rate for Status 1 patients occurred despite an increase in the median time to transplant (Figure VII-7) *[Table 9.2]*. This suggests that the continued downward trend in waiting list mortality may be related, in part, to improvements in pre-transplant care as well as to improved access to livers for those with an urgent need for transplant. Deaths on the pediatric waiting list have been very low, reflecting the intended design of the system, which predicts lower mortality risk at any given PELD score compared with the equivalent MELD score.

Figure VII-6. Death Rate per 1,000 Patient Years at Risk, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 9.3.

Figure VII-7. Waiting List Death Rates Per 1,000 Patient Years at Risk and Time to Transplant for Status 1 Liver Patients, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Tables 9.2, 9.3.

Another important waiting list trend is the dramatic decline (the first ever) in the time to transplant for new waiting list registrants. The tenth and twenty-fifth percentile of the time to transplant for new liver registrants fell from 29 days and 169 days in 2001 to 14 and 80 days, respectively, in 2002 *[Table 9.2]*. Again, this is likely an effect of the MELD allocation system, since patients who are listed when they are very ill no longer have to accrue substantial waiting time before being allocated a liver and patients are no longer being listed simply to accrue waiting time.

Overall annual death rates per 1,000 patient years at risk dropped progressively from 225 in 1993 to 119 in 2001 and 106 in 2002 *[Table 9.3]*. However, infants less than 1 year old show a progressive increase in mortality over time. Annual death rates per 1,000 patient years at risk increased from 502 in 1993 to 572 in 2001 and 766 in 2002. In all other age groups the annual death rates per 1,000 patient years at risk decreased by more than half during the last decade *[Table 9.3]*.

In 2002, the annual death rate per 1,000 patient years at risk was highest for African Americans (153), followed by whites (103), then Asians (84). Hispanics had 113 deaths per 1,000 patient years at risk *[Table 9.3]*. There was no difference in death rates between female and male patients on the waiting list (101 and 109 respectively). The annual death rates per 1,000 patient years at risk varied minimally by blood type: 108 for type O, 100 for type A, 119 for type B and 95 for type AB *[Table 9.3]*.

The annual death rate per 1,000 patient years at risk was higher in patient groups with higher MELD scores, as expected. The annual death rates per 1,000 patient years at risk in 2002 were 52 in patients with MELD scores of 6-10, 121 with scores of 11-20, 666 with scores of 21-30, and 3,029 for patients with MELD scores of 30 and above. This has been seen despite the fact that the waiting time for transplant was much shorter in the higher MELD score groups *[Table 9.3]* and reflects the ability of MELD to predict short-term mortality accurately. The risk of death on the waiting list by MELD still varies by region and blood type**.** Though organ distribution issues remain controversial, future research is needed to attempt to equalize the risk of dying on the waiting list**.**

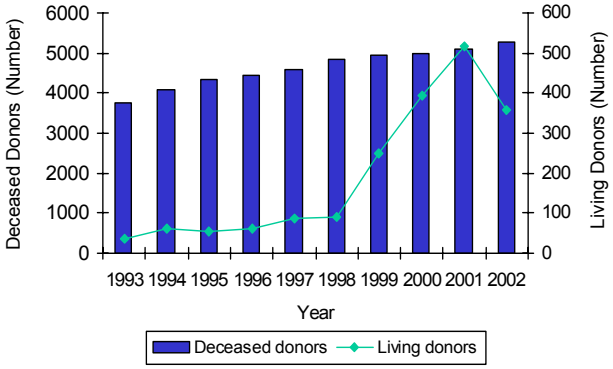
Patients on the waiting list with hepatocellular carcinoma had a higher annual death rate per 1,000 patient years at risk in 2002, with 163 for T1 tumors and 165 for T2 tumors. *[Table 9.3]*.

Liver Transplant Recipient Characteristics

There has been a steady increase each year in the number of liver transplants being performed with deceased donor organs, from 3,399 in 1993 to 4,962 in 2002 *[Table 9.4a]*. Several factors contribute: more patients on the waiting list, an increase in the number of deceased donors, and the use of expanded donor livers

(5). In 2002, 5,369 livers were recovered from 6,182 deceased donors (Figure VII-8) *[Tables 1.1 and 1.2]*, meaning 87% of deceased donors were liver donors; however, 407 (8%) of these livers were discarded, so that ultimately 80% (4,962/6,182) of the deceased donor livers were transplanted *[Tables 1.1, 1.2, and 9.4a]*. The number of transplants in recipients younger than 18 was similar in 2001 and 2002, with virtually all of the increase in the number of transplants occurring in the age groups 35-49, 50-64, and older than 65 years, a steady trend over the past decade *[Table 9.4a]*. The majority of patients transplanted (53%) were 50 years or older. Most of the patients transplanted in 2002 were 50-64 years old (46.2%), and 7% were 65 or older. The percentage of recipients aged 50-64 rose from 37% in 1993 to 46% in 2002 *[Table 9.4a]*. The increasing age trend in transplant recipients most likely reflects the growing number of older patients on the waiting list, which is multifactorial, including increased willingness of centers to transplant older individuals, longer waiting times, and the increasing median age of the hepatitis C cohort, which was largely infected in the 1960s and 1970s.

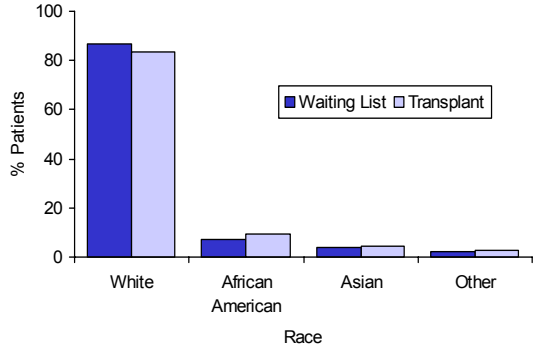
Figure VII-8. Deceased and Living Liver Donors, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 1.1.

The recipient race was 83% white, 10% African American, 4% Asian, and 3% other/multi-racial *[Table 9.4a]*. These percentages are similar to the characteristics of the waiting list patients, of whom 87% were white, 7% African American, 4% Asian, and 2% other/multi-racial (Figure VII-9) *[Table 9.1]*. Ethnicity was similar between the waiting list patients and transplant recipients for the Hispanic/Latino population (15% and 13%, respectively) and for the non-Hispanic/non-Latino population (84% and 87%, respectively) *[Tables 9.1 and 9.4a]*. The percentage of white recipients decreased from 86% in 1993 to 83% in 2002, with a concurrent rise in African American recipients from 8.7% to 9.6% and of Asians from 2.6% to 4.3% *[Table 9.4a]*. The proportion of patients of Hispanic ethnicity increased from 10% to 13%. There continued to be a trend toward a greater percentage of men being transplanted (66% in 2002) *[Table 9.4a]*; this may reflect the distribution of diseases between men and women, disease severity, and size considerations. The blood type distribution for recipients in 2002 was type O 42%, type A 39%, type B 13%, and type AB 6% *[Table 9.4a]*. This matches the overall estimates of blood types in the US population (and thus the donor population) and has not changed since 1993. The percentage of blood type O among recipients is lower than that of the patients waiting for transplantation *[Table 9.4a]*. Approximately 9% of liver transplant recipients in 2002 had a prior liver transplant, the lowest to date, down from 17% in 1993 and 10% in 2001 *[Table 9.4a]*. The absolute number of retransplantation procedures was 571 in 1993 and has since remained between 425 and 467 per year. US residents made up 99% of the recipients.

Figure VII-9. Liver Waiting List and Transplants by Race, 2002



Source: *2003 OPTN/SRTR Annual Report,* Tables 9.1 and 9.4.

The MELD/PELD system of recipient prioritization was implemented on February 27, 2002, so that data from 2002 includes transplant recipients transplanted under the MELD/PELD system (n= 3830, or 77%) and the old Status 2, 2A, 2B, 3, and 7 system (n= 652, or 13%) *[Table 9.4a]*. The Status 1 system was unaffected by MELD/PELD, and 480 (10%) Status 1 patients were transplanted in 2002, compared with 601 in 2001. In 2002, "not hospitalized," "hospitalized," and "in intensive care unit" (ICU) recipients made up 69%, 15%, and 15%, of the total, respectively, with the most substantial change being a decrease in the ICU-bound recipients from 27% in 2001 (relatively steady over the past decade) to 15% in 2002 *[Table 9.4a]*. Only 7% of recipients were on life support at transplant, compared with 11% in 2001. One of the anticipated benefits of the MELD/PELD system is that sicker patients will be transplanted before they progress to a more grave ICU-bound status. This was seen in New England, where implementation of a point system based on disease severity prior to MELD/PELD resulted in the sicker 2B

patients being transplanted before they progressed to 2A (6). Of note was the increase in the "not hospitalized" recipients, from 58% in 2001 to 69% in 2002 *[Table 9.4a]*. This trend is likely multifactorial, resulting from a higher percentage of stable hepatocellular carcinoma patients transplanted after implementation of the MELD/PELD system, decreased severity of illness due to preemptive transplantation, improved pretransplant care, and decreased use of the ICU to maintain patient medical urgency status. Whether these trends will continue remains to be seen. The MELD scores at which adult recipients received transplants in 2002 included the following percentages: 6-10 (4%), 11-20 (24%), 21-30 (15%), and >30 (10%). The PELD scores for children included the following percentages: <11 (1.7%), 11-20 (1.1%), 21-30 (0.7%), >30 (0.1%). Patients with hepatocellular carcinoma T1 tumors made up 2.7%, hepatocellular carcinoma T2 tumors 13.3%, other exceptions 5.5%, and Status 1 9.7%. The remaining 13.1% were transplanted under the old medical urgency status system during the first two months of 2002 *[Table 9.4a]*.

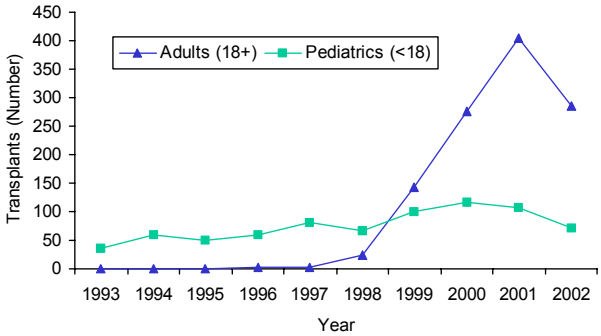
The primary diagnosis groups of deceased donor liver transplant recipients in 2002 included non-cholestatic cirrhosis as the most common (61%), followed by cholestatic liver disease/cirrhosis (10%), acute hepatic necrosis (8%), biliary atresia (3%), metabolic diseases (3%), malignant neoplasms (7%, compared with 3.5% in 2001), and other (8%) *[Table 9.4a]*. According to additional SRTR analysis, the frequency of hepatitis C as the primary diagnosis for transplant recipients has grown over the decade, from 21% in 1993 to 31% in 2002.

The spectrum of liver disease etiology has gradually changed over the last decade. The absolute number of patients with cholestatic liver disease transplanted decreased from 594 (18%) in 1993 to 485 (10%) in 2002, parallel to an increase in the number of transplants for non-cholestatic liver disease from 1,959 patients (58%) in 1993 to 3,004 (61%) in 2002. Acute hepatic necrosis increased from 218 cases in 1993 to 441 in 2000, but since then, the number of transplants performed for this etiology declined to 388 (12%) *[Table 9.4a]*. Increased waiting time may play a role in this trend with an increased proportion of patients with acute liver failure who either recover or develop contraindications to transplantation.

Between 2.7% and 3.5% of transplants were performed for malignancy between 1993 and 2001. Under MELD/PELD in 2002, the number of transplants for malignancy increased more than twofold but still represented only 7% of the transplants performed. There was a gradual decrease in the number of patients with biliary atresia transplanted, from 240 in 1993 (7%) to 164 in 2002 (3%) *[Table 9.4a]*.

The incidence of liver transplantation steadily increased from 13 per million population in 1993 to 18 in 2002. The highest incidence was seen in recipients 50-64 years old (54 per million), which was consistent across racial and ethnic groups *[Table 9.5]*.

Figure VII-10. Living Liver Donor Transplants, Adults vs. Pediatrics, 1993-2002

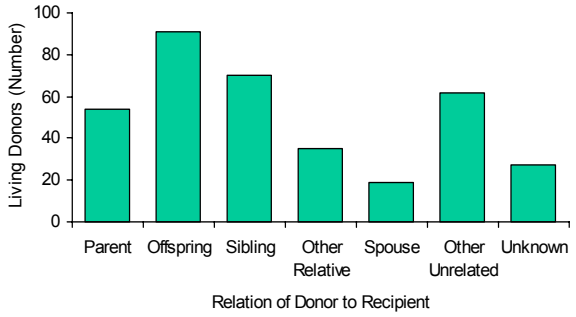


Source: *2003 OPTN/SRTR Annual Report,* Table 9.4.

There was a steady increase in living donor liver transplants, from 36 in 1993 to 84 in 1997. A more rapid increase occurred from 92 in 1998 to 511 in 2001 primarily because of an increase in adult living donor liver transplants; 97% of living donor recipients were younger than 18 years in 1997 compared with 20% in 2002 (Figure VII-10). However, a decrease to 358 was noted in 2002 *[Table 9.4b]*. This sharp decrease in living donor liver transplants may have been related to increased concern about donor safety after a widely publicized donor death, as well as published reports of significant donor morbidity and mortality (7,8). Recipient race and ethnicity were similar to deceased donor transplants, but there was a trend in 2002 toward a greater percentage of women receiving living donor liver transplants (43%) compared with deceased donors (34%), possibly because of size considerations *[Tables 9.4a and 9.4b]*. A greater proportion of living donor recipients were blood type O (55%) compared with deceased donors (42%), probably reflecting the markedly longer waiting times for deceased donor organs among blood type O candidates and a tendency, therefore, to opt for living donor transplantation *[Tables 9.2, 9.4a, and 9.4b]*. Only 2% of recipients were retransplants *[Table 9.4b]*, and 2% were non-US residents. There was a trend toward living donor recipients being less ill: 79% were not hospitalized compared with 69% for deceased donor recipients, and only 8% were in an ICU compared with 15% of deceased donor recipients *[Tables 9.4a, 9.4b]*. Similarly, the MELD scores for the adult recipients were lower: 6-

10 (14%), 11-20 (41%), 21-30 (3.9%). Furthermore, fewer patients were transplanted for hepatocellular carcinoma (1.4% T1 and 0.8% T2), likely due to the increased points received by HCC patients after the implementation of the MELD system. PELD scores for pediatric living donor recipients were: <11 (5%), 11-20 (3%), 21-30 (2%), and >30 (0.3%) *[Table 9.4b]*. The primary diagnoses were similar to deceased donor recipients except for a slight trend toward more cholestatic disease/cirrhosis and fewer malignant neoplasms in the living donor recipients *[Table 9.4b]*. Parents made up 15% of donors, offspring 25%, sibling 20%, other relative 10%, spouse 5%, and other unrelated 17% (Figure VII-11) *[Table 9.4b]*. The increase in unrelated donors has occurred since the introduction of adult-to-adult living donor liver transplant despite the risks to the donors. This increase undoubtedly reflects the tremendous pressures that the shortage of deceased donor livers and long waiting times are putting on patients and their friends and relatives.

Figure VII-11. Relationship of Living Liver Donors and Recipients, 2002

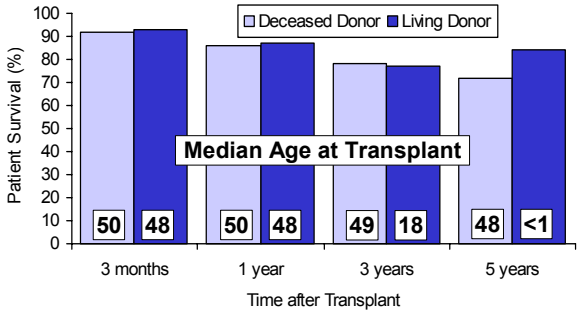


Source: *2003 OPTN/SRTR Annual Report,* Table 9.4.

Liver Transplant Patient Survival

Unadjusted patient survival among deceased donor liver transplant recipients was 92% at three months, 86% at one year, 78% at three years, and 72% at five years posttransplant *[Table 9.11a]*. Among living donor transplant recipients, unadjusted survival was slightly higher at all time points except three years posttransplant (Figure VII-12) *[Table 9.11b]*. Differences in unadjusted patient survival between groups of patients at each time period were significant at $P \leq 0.05$ for comparisons based on race, whether the patient was on life support, ICU status, and donor age. Adjusted one-year deceased donor patient survival (adjusted for population parameters in 2001) increased from 83% in 1992 to 88% in 2001 *[Table 1.13a]*.

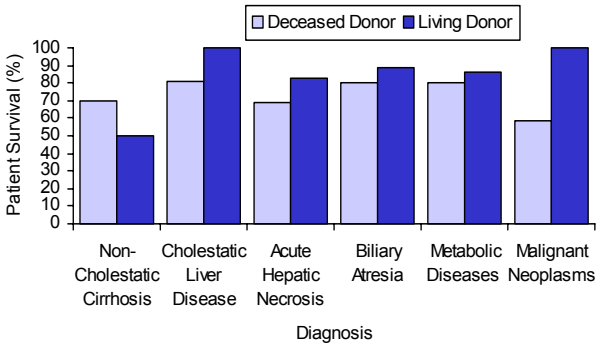
Figure VII-12. Unadjusted Patient Survival Among Liver Transplant Recipients, Living vs. Deceased Donor



Source: *2003 OPTN/SRTR Annual Report,* Table 9.11. Cohorts are for transplants performed during 2000-2001 for 3 month & 1 year; 1998-1999 for 3 year; and 1996-1997 for 5 year survival.

Patient survival for deceased donor recipients varied significantly with recipient age. Five-year survival was 84% in the 6-10 year old group but only 62% in recipients over 65 years *[Table 9.11a]*. African Americans' patient survival was 2% to 5% lower than that of whites at each of the time intervals *[Table 9.11a]*. Patient survival was similar by ethnicity and gender. Patients transplanted from the ICU had a lower posttransplant survival when compared with patients who came in from home a difference seen in both short-term and long-term survival. The difference in survival was 7% at three months, 9% at one year; 11% at three years and 9% at five years. Patients on life support before transplant had an 80% survival at three months and 63% at five years, which was 13% and 10% lower, respectively, than for those who were not on life support ($P<0.0001$) *[Table 9.11a]*.

Figure VII-13. Five Year Unadjusted Patient Survival Among Liver Transplant Recipients, by Diagnosis



Source: *2003 OPTN/SRTR Annual Report,* Table 9.11. Cohorts are for transplants performed during 1996-1997 for 5 year survival.

Patient survival also varied based on etiology of liver disease (Figure VII-13). Five-year patient survival was worst for malignancy (59%). Acute hepatic necrosis (69%) and non-cholestatic liver diseases (70%) were an intermediate group. The best survival rates were seen with metabolic liver disease (80%), biliary atresia (80%), and cholestatic liver disease (81%) *[Table*

9.11a]. These differences are related to two factors: 1) severity and recurrence of disease and 2) age differences in the recipients.

The volume of liver transplants performed per center did not influence the unadjusted patient survival at all time intervals to five years posttransplant. Donor age above 65 was associated with a lower patient survival (90% at three months, 61% at five years) *[Table 9.11a]*.

The overall annual death rate per 1,000 patient years at risk posttransplant decreased from 244 in 1993 to 163 in 2001 and 145 in 2002 *[Table 9.7]*. The rate was higher at the extremes of age. In 2002, the annual death rate per 1,000 patient years at risk in the first year posttransplant was 279 in infants under 1 year, a marked reduction from the corresponding figure in 1993 (1,060), and was 181 in patients older than 65 years *[Table 9.7]*.

The annual death rate per 1,000 patient years at risk in the first year posttransplant was moderately different by ethnicity and race; 128 for Hispanics and 145 for whites, 146 for African Americans and 164 for Asians *[Table 9.7]*. African-Americans' patient survival was 2% to 5% lower than that of whites at each of the time intervals ($P<0.05$ for each year). The risk of death posttransplant was also similar among different blood types. The risk almost tripled if the recipient had any previous solid organ transplant (337 vs. 130 after primary transplants) *[Table 9.7]*.

In 2002, for the first year following transplant, recipients who underwent transplant from the ICU had an annual death rate per 1,000 patient years that was 2.5 times higher than that of patients who came from home. In 1993, the corresponding difference in death rate between patients receiving transplant from the ICU versus from home was 3.1. The overall risk for patients in the ICU has decreased by 54%, from 485 in 1993 to 263 in 2002. Similarly, patients on life support before transplant had a threefold higher annual death rate per 1,000 patient years at risk in the first year than those who were not. Despite the improvements in care seen over the last decade, the higher risk of death experienced by patients on life support has changed little over the decade *[Table 9.7]*.

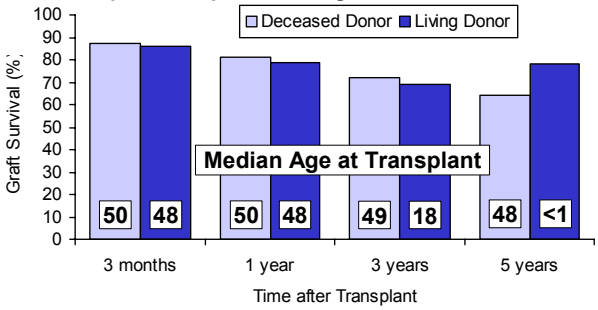
In 2002, the annual death rate per 1,000 patient years at risk in the first year posttransplant was highest for patients with acute hepatic necrosis (229) and malignancy (203), followed by those with non-cholestatic liver diseases (143), cholestatic liver diseases (96), metabolic liver diseases (77), and biliary atresia (74) *[Table 9.7]*. This raises the question as to whether most malignancies are recurring early posttransplant.

There was an overall trend of improvement in the annual death rate per 1,000 patient years at risk in the first year posttransplant for all of the former medical urgency status groups: Status 1 patients (452 in 1993 to 257 in 2002), Status 2A (387 in 1997 to 160 in 2002), Status 2B (456 in 1997 to 100 in 2002), and Status 3 (115 in 1997 to 63 in 2002) *[Table 9.7]*.

Liver Transplant Graft Survival

Graft survival after deceased donor liver transplantation was 87% at three months, 81% at one year, 72% at three years, and 64% at five years posttransplant *[Table 9.9a]*. As with patient survival, unadjusted living donor recipient graft survival was slightly lower at all time points except five years posttransplant (Figure VII-14). The one-year adjusted deceased donor recipient graft survival increased from 72% in 1992 to 81% in 2001 *[Table 1.12a]*.

Figure VII-14. Unadjusted Graft Survival Among Liver Transplant Recipients, Living vs. Deceased Donor



Source: *2003 OPTN/SRTR Annual Report,* Table 9.8. Cohorts are for transplants performed during 2000-2001 for 3 month & 1 year; 1998-1999 for 3 year; and 1996-1997 for 5 year survival.

African Americans tended to have worse graft survival than the white patient population. The gap has been 2% to 6% each year and has tended to increase. There was no difference in graft survival between Hispanics and non-Hispanics or between male and female patients *[Table 9.9a]*.

Notably, patients with blood type AB had graft survival 4% to 6% higher than the patients with other blood types at the three-month interval. Patients who underwent retransplantation had 18% to 21% lower graft survival than those who underwent primary transplantation *[Table 9.9a]*.

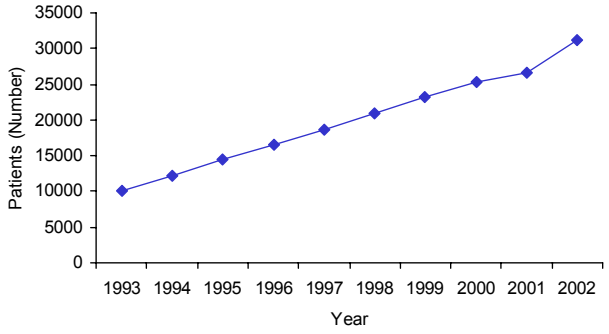
In terms of severity of illness, there was a difference in graft survival among patients who came to transplant from home, those who were in the hospital, and those who were in the ICU. Patients who were in the ICU had 12% to 14% worse graft survival than those who came from home. Three-month graft survival was 79% for

patients transplanted from the ICU and 91% for those who came from home. This difference was maintained over time; five-year graft survival rates were 56% and 69%, respectively *[Table 9.9a]*. Donor age was also associated with differing effects on graft survival, especially at the extremes of age. For donors younger than 1 year, three-month graft survival was 77% and five-year graft survival was 61%. The best graft survival was seen with donors 11-17 years old (89% and 70%, respectively). Among donors of adult age, graft survival declined as age increased. Graft survival was 82% at three months and 51% at five years posttransplant using organs from donors 65 years or older *[Table 9.9a]*. Because these graft survival statistics by donor age are not adjusted for other factors, the potential confounding effects of various recipient selection factors are not apparent. However, the separate results by donor age and recipient disease severity highlight the increased risk of placing the most marginal grafts (e.g., from donors older than 60) into ICU-bound patients on life support. Differences in unadjusted graft survival between groups of patients at each time period were significant at $P \leq 0.05$ for comparisons based on race, medical condition, blood type, retransplantation status, and donor age.

Prevalence of Liver Transplant Patients with Functioning Grafts

Given the overall success of liver transplantation, the prevalence of people living with a functioning liver graft in the United States increased gradually from 10,141 in 1993 to 31,195 in 2002 (Figure VII-15). In the most recent year, 27,138 were white, 2,532 were African American, and 981 were Asian *[Table 9.12]*. The prevalence of patients with functioning grafts allows one to study trends over time for both incidence and outcome, although the figures are more heavily weighted toward recent transplants, as a higher proportion of recent transplant recipients will be alive.

Figure VII-15. Prevalence of People Living with a Functioning Liver Transplant, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 9.12.

The proportion of patients with functioning liver transplants who were African American increased from 7.7% in 1993 to 8.1% in 2002, Asians increased from 2.1% to 3.1% and whites decreased from 88.7% to 87.0%. The Hispanic proportion increased from 9% to 11%. This likely reflects improved access to transplantation over time, rather than improved outcomes in these racial and ethnic groups. Among patients living with a liver graft, 59% were male and 41% were female. Blood type distribution was similar to the general population, which reflects the donor blood type distribution and not the distribution on the waiting list.

At the end of 2002, a total of 29,859 recipients of deceased donor grafts were living, as were 1,336 recipients of living donor grafts. Among patients with a functioning graft, 57% had been transplanted for non-cholestatic liver disease, 15% for cholestatic liver disease, 8% for acute hepatic necrosis, 6% for biliary atresia, 5% for metabolic disease, and 3% for malignancy. Living retransplant recipients accounted for 8% of the total.

Distribution by medical urgency status at transplant was as expected, given the relative rates of these transplants and their relative survival; 63% came to transplant from home, 18% were in hospital, and another 19% were in the ICU. For these patients, 9% had been on life support before transplant; 3,934 patients (13%) had been transplanted as status 1 *[Table 9.12]*.

INTESTINE

Intestinal failure, due either to loss or non-function of the gastrointestinal tract, can be a pernicious disorder often resulting in disability or death of the patient. Intestinal transplantation was proposed as treatment for those patients who had life-threatening complications of total parenteral nutrition (TPN), particularly TPN-related liver disease. During the past 15 years, organ replacement therapy in the form of liver, liver/small bowel, and isolated small bowel transplantation has been used as a lifesaving tool for patients who have failed TPN therapy.

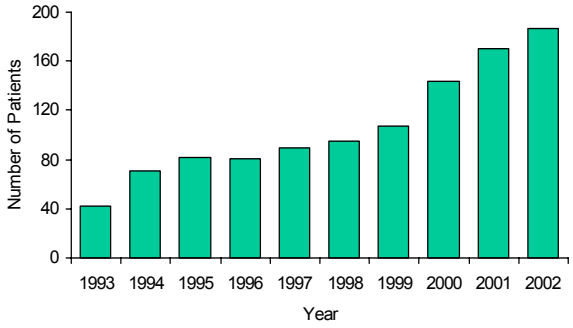
Approval by the Centers for Medicare and Medicaid Services (CMS) for reimbursement of intestinal transplantation was the most important governmental change in the field of intestinal transplantation in 2002. CMS approval is often the yardstick that third party payers use to determine if a new procedure is investigational or experimental. One of the major obstacles to access to intestinal transplantation has been financial. While some commercial carriers were providing this service to their policyholders, many

carriers and state Medicaid agencies were not. As a consequence of the CMS findings, more patients were provided an opportunity to be considered for intestinal transplantation. There were no major OPTN policy changes in 2002 regarding this procedure, but the stage had been set for changes to occur in 2003. Specifically, efforts were being made to provide extra MELD/PELD points to patients with intestinal failure. In 2003, the OPTN approved a policy change that encouraged regional review boards to allow patients on the waiting list for combined liver/small bowel transplant to receive an extra 12 MELD/PELD points. 2004 will probably see further developments in this area.

Intestine Waiting List Characteristics

The number of patients listed for intestinal transplantation has gradually increased since 1993, with the exception of a 9% reduction in patient registrations in 2002. At the end of 2002, however, there were more patients listed for intestinal transplant compared with 2001 (Figure VII-16). The age of the patients awaiting intestinal transplants was weighted heavily toward children (73%). Children less than 6 years of age represented 51% of the list. Race and ethnicity were characterized predominately as white and non-Hispanic/non-Latino, respectively. There were many more males than females listed, and the predominant blood type was O. Prior transplant had been performed in 9% of patients, with the majority having undergone prior intestinal transplantation (7%) *[Table 10.1]*.

Figure VII-16. Patients on the Intestine Waiting List, 1993-2002

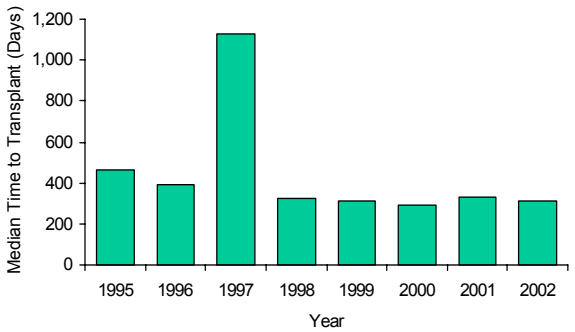


Source: *2003 OPTN/SRTR Annual Report,* Table 10.1.

Intestine Time to Transplant

Nearly one-third of patients awaiting intestinal transplants have waited longer than two years, and two-thirds have waited at least six months. The median time to transplant was 310 days in 2002 and was slightly less than in 2001 (Figure VII-17) *[Table 10.2]*. Children tended to have longer waiting times than adults. The median time to transplant based on race did not differ among white, Asian and other/multi-race candidates. Follow-up was insufficient to evaluate the African American and Hispanic/Latino groups. Neither prior transplant nor blood type appeared to have a major effect on waiting time. The only exception to this was blood type AB, which had a median time to transplant of only 44 days.

Figure VII-17. Median Time to Intestine Transplant, 1995-2002

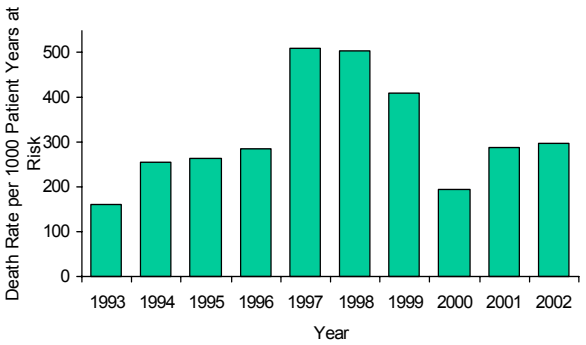


Source: *2003 OPTN/SRTR Annual Report,* Table 10.2.

Intestine Waiting List Deaths

Reported deaths and annual death rates per 1,000 patient years at risk have fluctuated over the past 10 years (Figure VII-18). In 2002, there were 363 patients at risk for death on the waiting list; this was a modest increase from 342 in 2001 and a sixfold increase from the 58 patients at risk in 1993. *[Table 10.3]*.

Figure VII-18. Death Rate per 1,000 Patient Years at Risk on the Intestine Waiting List, 1993-2002



Source: *2003 OPTN/SRTR Annual Report,* Table 10.3.

The death rate for all patients waiting for intestinal transplants in 2002 was 298 . This rate is much higher than that of any other transplant group (e.g., heart-lung is 185) *[Tables 1.7 , 10.3]*. Despite considerable variability over the years, the age group at greatest risk consisted of those patients younger than one year. Factors that contribute to this high number include the

need for size compatible donor organs (typically 25% smaller) and donor cytomegalovirus serologic status. A review of other demographic factors, such as race, ethnicity, and gender, failed to demonstrate any differences. Blood type B did have an apparent effect, with a reported death rate of over 500 compared with 251 and 267 for blood types O and A, respectively *[Table 10.3]*. Currently efforts are being made to change organ allocation policy to improve candidates' opportunity to receive intestine transplants.

Intestine Transplant Recipient Characteristics

The number of intestinal transplant recipients did not change considerably from 2001 to 2002. Children continue to make up the majority of the recipients, particularly those younger than 5 years. Recipient demographics including race, ethnicity, and gender did not differ from the general population. In contrast, a far greater proportion of blood type A patients received an organ transplant than is reflected in the general population. In 2002 twice as many patients underwent an intestinal retransplant as did in the previous year *[Table 10.4]*. This rise probably reflects the growing number of recipients whose allografts failed and returned to the waiting list. The degree of medical acuity has changed since 2001 but remained similar to years prior to that. In 1999, 2000, and 2002 approximately half of the recipients were not hospitalized when called for transplant. In 2001 more than two-thirds of patients were called in from home. Reflecting the tenuous condition of these patients, 14% were in the ICU at time of transplant. The most common cause of intestinal failure requiring transplant in the United States is short bowel syndrome followed by functional bowel disorders, such as chronic idiopathic intestinal pseudo-obstruction (9) The prevalence of these causes of intestinal failure is reflected in the pretransplant diagnoses of the recipients.

Intestine Transplantation — Posttransplant Death Rates

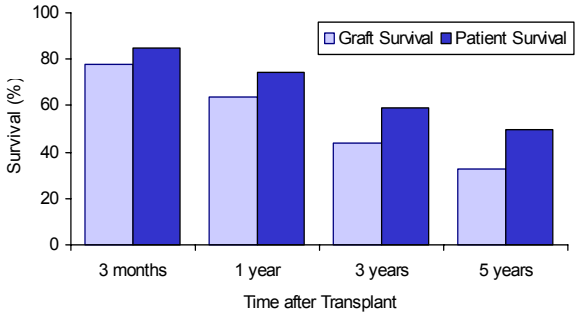
In 2002, the annual death rate per 1,000 patients years at risk during the first posttransplant year was 318, which was lower than reported in 2001 (482) *[Table 10.7]*. In 2001, children ages 1-5 years were at greatest risk (791); fortunately, this group demonstrated considerable improvement (384) in 2002. The small number of patients probably accounts for much of the variability. Many of the age groups had such small numbers of patients that interpretation was not possible. Race, gender, and ethnicity did not seem to play a large role in death rates. Analysis of blood groups suggests a higher survival for blood type B, but, again, this involved very small numbers of patients. The most profound effect on annual death rates was in the group who had a prior transplant. Nearly one-half of the patients in this group died in the first year. The prior transplant was typically either an isolated small bowel transplant or a liver transplant.

A number of other variables can affect the posttransplant death rates, including condition of the patient, underlying diagnosis, and donor age. The condition of the patient was categorized into one of three groups: on life support, in the ICU, or hospitalized/at home. The numbers of patients on life support were too small to calculate an annual death rate. However, in 2000, patients transplanted from the intensive care unit had a threefold higher death rate compared with patients on a general ward in the hospital and an almost twelvefold higher rate when compared with patients coming from home *[Table 10.7]*. The primary diagnosis had a modest effect on survival, with short gut syndrome patients associated with about a 40% lower death rate when compared with patients with functional bowel problems. Donor age demonstrated wide variability within the various age groups examined.

Intestine Transplantation — Graft Survival and Function

Adjusted graft survival was determined at four time points following transplantation: three months, one year, three years, and five years. Sixty-four percent of patients had a functioning allograft at one year, but this number was only 33% at five years *[Table 10.8]* (Figure VII-19). No obvious trends could be seen by age group, race, gender or primary diagnosis. This reflects the small number of patients in the various groups. Patients who underwent retransplantation had by far the worst outcome. Neither center volume nor donor age had a major effect on graft survival.

Figure VII-19. Adjusted Graft vs. Patient Survival Among Intestine Transplant Recipients



Source: *2003 OPTN/SRTR Annual Report,* Tables 10.8. 10.9. Cohorts are for transplants performed during 2000-2001 for 3 month & 1 year; 1998-1999 for 3 year; and 1996-1997 for 5 year survival.

All organ replacement therapies seek first to save patient lives but also to provide the organs that function adequately. For intestinal transplantation, adequate function would be represented by freedom from TPN. As of 2002 there were 299 patients with functioning intestinal allograft. Children ages 1 to 5 years represented the largest group (31%) with a functioning allograft. No long-term effect on graft function could be seen based on pretransplant diagnosis *[Table 10.12]*.

Intestine Transplant Patient Survival

Patient survival rates at three months, one year, three years, and five years following intestine transplantation were 85%, 74%, 59%, and 50%, respectively *[Table 10.10]* (Figure VII-19). The very young and very old appeared to fair worse in both short- and long-term follow-up. The greatest success was achieved in the 18 to 34 year age range in the adjusted survival, a difference not found in the unadjusted analysis. Where adequate data were available, no major differences could be seen based gender or ethnicity. Racial differences were evident between whites and African Americans at all time points. Recipient blood type did not influence survival in the short term, but some differences did appear at the five-year mark. Blood type B had the best survival, while the AB fared the worst, though the limited number of patients makes this finding difficult to interpret. Primary diagnosis had no effect on patient survival, while the retransplant group was poorly represented and no data were available. A negative center effect could only be seen in programs that performed only one transplant per year.

SUMMARY

The most significant development in liver transplantation in the United States over the past year was the full implementation of MELD- and PELD-based allocation, which has shifted emphasis from waiting time within broad medical urgency status to one based on prioritization by risk of waiting list death. The implementation of this system has led to a decrease in pretransplant mortality without increasing post-transplant mortality, despite a higher severity of illness at the time of transplant. Over the next years, the focus will shift to refining and improving the model to limit the need for exception and regional review boards, as well as addressing disparities in organ distribution and incorporating posttransplant outcomes. The trend over the last several years of rapidly increasing numbers of living donor transplants has stabilized or declined, with a reduction in these procedures in adults in 2002. Living donor transplants account for less than 10% of all liver transplants, in contrast to kidney transplantation, in which the number of living donor and deceased donor grafts are nearly matched. Concerns about living donor safety, early graft survival, and, at present, limited applicability to critically ill patients has decreased the use of this procedure. It is hoped that new data showing the benefit of living donor liver transplantation on waiting list mortality, along with further refinement in donor and recipient selection, will allow ongoing growth of this procedure and added benefit for all patients awaiting liver transplantation. (10) Intestinal transplantation remains a low-volume procedure limited to a few transplant centers, and like liver transplantation in its early days, it is still fraught with both pre- and posttransplant risks. As this procedure matures, its application will likely increase to include recipients at an earlier stage of disease and with better likelihood of success.

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