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Liver and intestine transplantation: summary analysis, 1994–2003

Douglas W. Hanto[a,*], Thomas M. Fishbein[b], C. Wright Pinson[c], Kim M. Olthoff[d], Mitchell L. Shiffman[e], Jeffrey D. Punch[f] and Nathan P. Goodrich[g]

[a] *Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA*
[b] *Georgetown University Hospital, Washington, DC*
[c] *Vanderbilt University Medical Center, Nashville, TN*
[d] *Hospital of the University of Pennsylvania, Philadelphia, PA*
[e] *Virginia Commonwealth University Medical Center, Richmond, VA*
[f] *University of Michigan, Ann Arbor, MI*
[g] *Scientific Registry of Transplant Recipients, University Renal Research and Education Association, Ann Arbor, MI*
* *Corresponding author: Douglas W. Hanto, dhanto@bidmc.harvard.edu*

With nearly two years of data available since the inception of the MELD and PELD allocation system, this article examines national OPTN/SRTR data to describe trends in waiting list composition, waiting list mortality, transplant rates, and patient and graft outcomes for liver transplantation.

Following a 6% reduction in the size of the waiting list after MELD was implemented in 2002, the number of patients on the waiting list grew by 2% from 2002 to 2003, while the number of liver transplants increased by 6%. The overall death rate while on the liver waiting list has decreased from 225 deaths per 1,000 patient years in 1994 to 124 deaths in 2003. As with the waiting list death rates, post-transplant death rates have also decreased over the past decade. Unadjusted one-year patient survival was lower for older donor age groups (88% for donors aged 18–34, 87% for donors aged 35–49, 85% for donors aged 50-64); a similar trend was observed at three and five years following transplantation.

Intestine transplantation is performed with slowly increasing frequency and success. Early graft losses and rejection rates have changed little since 1994, but rejection is easier to control and long-term survival is improving.

Key words: Deceased donors, graft survival, intestine transplantation, liver transplantation, liver-intestine transplantation, living donors, MELD, organ donation, patient survival, PELD, SRTR, waiting list

Introduction

Liver transplantation in 2003 faced many of the same challenges as in 2002, although much progress has been made. The number and characteristics of patients waiting continue to differ greatly from those of patients transplanted each year. These differences affect nearly every policy and every decision made in the field of liver transplantation. The organ shortage has driven changes in allocation policy to de-emphasize waiting time, to transplant sicker patients and to expand regional sharing for Status 1 patients. It has led to the provision of higher-assigned model for end-stage liver disease (MELD) scores for patients with hepatocellular carcinoma, in order to increase their probability of transplantation before the disease spreads outside the liver and transplantation becomes unwise. It has forced clinicians to expand donor criteria to include older donors and those who are hepatitis C positive, hepatitis B core antibody positive, donors after cardiac death and those who have livers with steatosis. It has led to living donor transplants, split-liver transplants and domino transplants. Intestine transplantation, often performed in combination with liver transplantation, continues as a challenging but increasingly successful procedure for patients with intestinal failure.

In these rapidly changing fields, it is as important as ever to constantly reassess whether the implemented changes have had the desired effect and what other improvements need to be made in order that patient care will be improved. Analyses by the Scientific Registry of Transplant

Note on sources: The articles in this report are based on the reference tables in the *2004 OPTN/SRTR Annual Report*, which are not included in this publication. Many relevant data appear in the figures and tables included here; other tables from the *Annual Report* that serve as the basis for this article include the following: *Tables 1.5, 1.7, 1.8, 1.13, 9.1, 9.2a, 9.2b, 9.3, 9.4a, 9.4b, 9.7a, 9.7b, 9.9a, 9.9b, 9.10a, 9.10b, 9.11a, 9.11b, 9.12a, 9.12b, 9.13a, 9.14, 9.15, 10.1–10.12, 10.14 and 15.2*. All of these tables may be found online at http://www.ustransplant.org.

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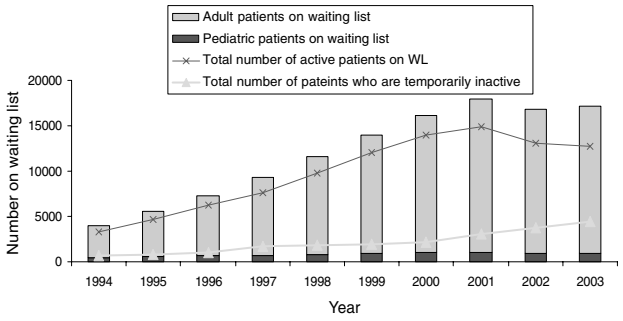

Figure 1: Pediatric and adult liver waiting list candidates, total and temporarily inactive at year-end, 1994–2003. Source: *2004 OPTN/SRTR Annual Report,* Table 9.1.

Recipients (SRTR) allow us to annually evaluate the national data supplied by transplant centers and organ procurement organizations (OPOs) across the country. The data analyzed for this report for the decade ending in 2003 are extensive and revealing. They include data for the first complete year under the MELD/pediatric end-stage live disease (PELD)-based deceased donor liver allocation system that was implemented in March 2002.

Unless otherwise noted, the statistics in this article are drawn from the reference tables in the *2004 OPTN/SRTR Annual Report*. Two companion articles in this report, 'Transplant data: sources, collection and research considerations' and 'Analytical approaches for transplant research, 2004', explain the methods of data collection, organization and analysis that serve as the basis for this article (1,2). Additional detail on the methods of analysis employed herein may be found in the reference tables themselves or in the Technical Notes of the *OPTN/SRTR Annual Report*, both available online at http://www.ustransplant.org.

Liver

Liver waiting list characteristics

The gap between the number of patients waiting for liver transplantation and the number of transplants performed has continued to widen over the past decade. The waiting list grew from 3955 candidates in 1994 to 17 171 in 2003, having reached a high of 17 953 patients in 2001 (Figure 1). There was a 6% drop in waiting list size between 2001 and 2002 following the implementation of the MELD system, but in 2003 the number of registrants on the waiting list grew by 2% to 17 171, while the number of liver transplants increased by 6%, from 5060 in 2002 to 5364 in 2003. However, the number of patients listed as temporarily inactive increased from 707 patients in 1994 to 3036 in 2001, 3727 in 2002 and 4456 in 2003—now making up 26% of the list (Figure 1). Therefore, the number of active patients on the waiting list has actually dropped over the past 2 years, from 14 917 in 2001 to 13 063 in 2002 and 12 715 in 2003—a 12% drop from 2001 to 2002 and a further 3% drop from 2002 to 2003.

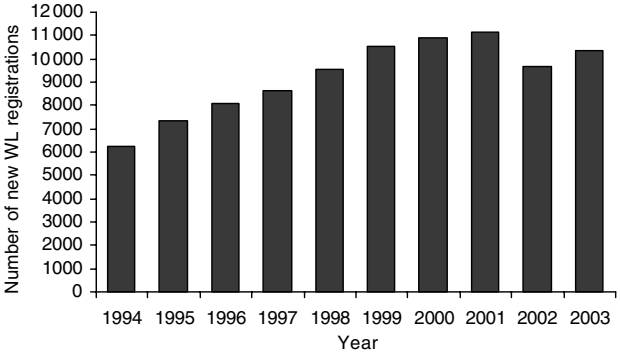

Figure 2: New liver waiting list registrations, 1994–2003. Source: *2004 OPTN/SRTR Annual Report,* Table 1.5.

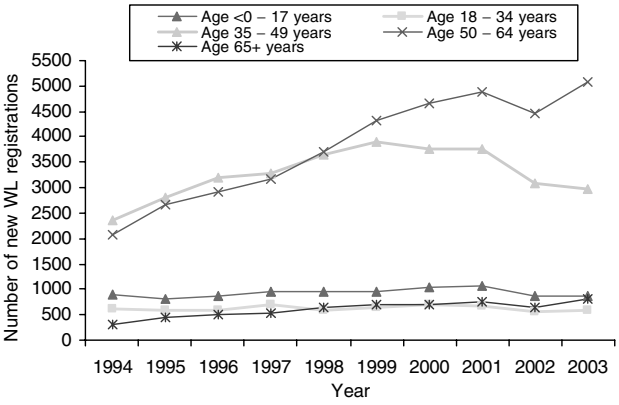

Figure 3: New liver waiting list registrations by age, 1994–2003. Source: *2004 OPTN/SRTR Annual Report,* Table 15.2.

The number of new waiting list registrations increased from 6228 in 1994 to 11 127 in 2001, then dropped to 9648 in 2002 before increasing in 2003 to 10 331. (Figure 2). The decrease in the number of registrants for the past 2 years most likely reflects implementation of the MELD/PELD system and the decrease in importance of waiting time. As shown in Figure 3, new registrations for those <18 years old, 18–34 years old, and >65 years old have remained relatively stable during the past decade. During 2001–2003, however, there was a definite increase in the number of registrants 50–64 years old and a decrease in the number of registrants in the 35–49 year age group.

Age: Over the past 10 years, the pediatric waiting list has grown more slowly than other age groups, expanding from 492 patients in 1994 to 922 patients in 2003. The greatest growth has been in the 11–17 age group, which more than doubled from 125 patients in 1994 to 293 in 2003. The adult waiting list grew more rapidly from 1994 to 2003, and therefore the waiting list percentage for pediatric patients has decreased, dropping from 13% in 1994 to 5% in 2003.

The adult waiting list has seen a progressive shift to older patients. In 1994, patients 18–34 years old made up 9% of the waiting list compared to 5% in 2003, and patients 35–49 years old dropped from 38% to 26% of the waiting list. In contrast, patients 50–64 years old and older than 65 made up 34% and 6% of the list in 1994, compared to 53% and 10% in 2003.

Race and ethnicity: Over the past decade, the racial distribution on the waiting list has remained relatively constant. In 2003, 86% of the patients were white, 7% African American and 4% Asian. The increase in the number of Hispanic/Latino registrants increased from 11% in 1994 to 15% in 2002 and remained constant at 15% in 2003.

Gender: The percentage of males on the waiting list remains greater than that of females. In 1994, 54% of patients waiting were male, a percentage that increased each year and reached 58% in 2003.

ABO type: Patients with blood type O continue to be overrepresented on the waiting list relative to their proportion in the general population. The distribution of ABO blood types on the waiting list has remained relatively constant and in 2003, 50% of the registrants had blood type O, 36% blood type A, 11% blood type B and 3% blood type AB. U.S. residents made up 99% of the waiting list in 2003, a percentage that has not changed significantly over the past decade.

Prior transplant: In 1994, 7% of the patients on the waiting list had undergone a prior liver transplant. After a decrease to 5% in 1999, the percentage remained 7% from 2001 through 2003.

Waiting time and time to transplant: The overall waiting time for liver transplantation increased from 1994 to 2003. In 1994, 16% (639/3955) of the patients had been waiting more than 2 years and this has steadily increased, reaching 51% (8756/17 171) in 2003. This may be misleading because many of these patients listed for more than 2 years are inactive and, as noted above, the proportion of these patients has grown to 26% of the list in 2003. In actuality, the data in the MELD/PELD era are showing a decrease in waiting time for new registrants, and this analysis may be more reflective of what is actually happening on the waiting list. In 2003, it took 10 days for 10% of the patients on the waiting list to be transplanted and 56 days for 25% of the patients to be transplanted, down from 28 and 193 days in 2000, 29 and 168 days in 2001 and 14 and 80 days in 2002, respectively (Figure 4). This shortening of waiting time reflects the emphasis of the MELD/PELD system on transplanting sicker patients first, thereby deemphasizing waiting time and eliminating the incentive to list patients in order to accrue waiting time. Prior to the introduction of the MELD/PELD system, the median time to transplant increased from 225 days in 1994 to 1811 days in 1999, the most recent year for which the data can reliably be interpreted. Undoubtedly the median time to transplant will be shown to increase until 2002, after which it should decline dramatically. Analyses excluding inactive patients will need to be performed for a truer picture.

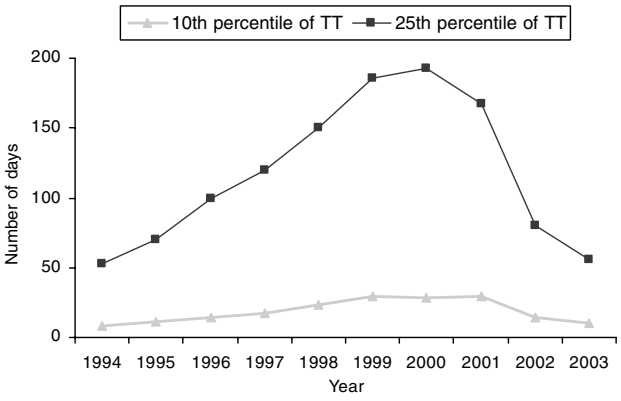

Figure 4: Time to transplant (TT) for new liver waiting list registrations, 1994–2003. Source: *2004 OPTN/SRTR Annual Report,* Table 1.5.

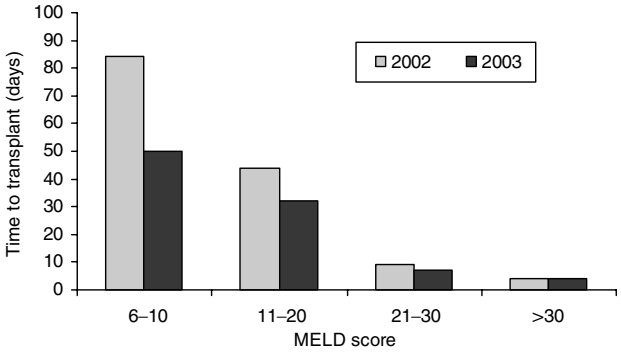

Figure 5: Tenth percentile of time to transplant by MELD score. Source: *2004 OPTN/SRTR Annual Report,* Table 15.2.

In the MELD/PELD era, it is more important to determine whether a patient receives a transplant within a certain period of time—this time being determined, hopefully, by the MELD or PELD score—than to examine the actual waiting time. The 10th and 25th percentiles' time to transplant in 2002 and 2003 varied by MELD and PELD score. The 10th percentile time to transplant in 2003 was 50 days for MELD scores 6–10, 32 days for 11–20, 7 days for 21–30 and 4 days for >30, all but the last group significantly lower than they had been in 2002 (Figure 5). The 25th percentile time to transplant in 2003 was 335 days for MELD scores 6–10, 119 days for 11–20, 20 days for 21–30 and 7 days for >30, all lower than they had been in 2002.

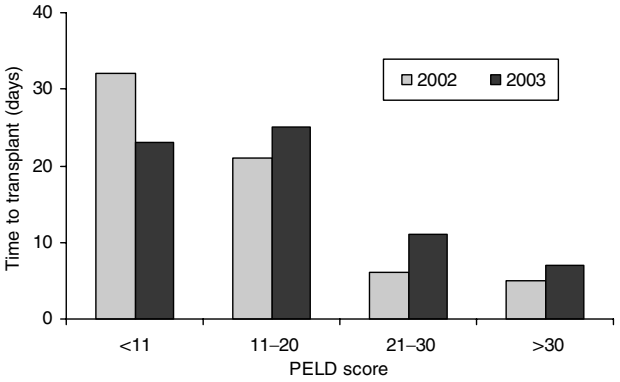

Figure 6: Tenth percentile of time to transplant by PELD score. Source: *2004 OPTN/SRTR Annual Report,* Table 15.2.

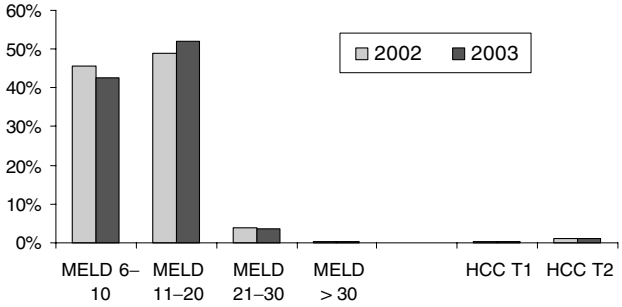

Figure 7: Distribution of active liver waiting list patients at end of year by MELD score and HCC, 2002–2003.* Adult patients only (excludes Status 1 candidates). Of all listed liver candidates, 26% were 'temporarily inactive' in 2003; 22% were inactive in 2002. Source: *2004 OPTN/SRTR Annual Report,* Table 9.1.

Time to transplant by PELD scores did not drop as consistently between 2002 and 2003. Only those with PELD < 11 experienced a drop in the 10th percentile time to transplant (32 days in 2002, 23 in 2003). Groups with PELD < 21 experienced shorter 25th percentile time to transplant in 2003 than in 2002, but those with higher PELD scores experienced longer times (Figure 6).

For registrants with T1 hepatocellular carcinoma (HCC), the 10th percentile of the time to transplant dropped from 14 days in 2002 to 12 days in 2003; the 25th percentile rose from 31 to 34 days during the same period. For registrants with T2 HCC, time to transplant rose slightly for both the 10th and 25th percentiles from 2002 to 2003. Because of the short time to transplant and the increasing percentage of candidates with HCC being transplanted relative to the rest of the waiting list, the number of MELD points assigned to HCC patients was lowered in April 2003, from 24 to 20 for T1 and from 29 to 24 for T2. Every 3 months, candidates with HCC are still assigned additional MELD points corresponding to a 10% increase in 3-month mortality risk (3).

Diagnosis: Non-cholestatic cirrhosis was the primary diagnosis of 59% and 67% of the patients on the waiting list in 1994 and 2003, respectively, compared to 15% and 10%, respectively, for cholestatic liver disease/cirrhosis, most likely reflecting the increasing proportion of patients with hepatitis C. Percentages of candidates with other disease categories, including acute hepatic necrosis (5%), biliary atresia (2%), metabolic diseases (2%) and malignant neoplasms (1%), remained constant over the decade.

Status 1: Among patients first added to the liver waiting list as Status 1 in 2002 or 2003, 7 days after wait-listing 14% were still listed as Status 1, 5% were downgraded to a MELD/PELD score, 11% were inactive, 44% had been transplanted, 11% had died, 4% were too sick to be transplanted, 11% had recovered and 1% had been removed from the list for other reasons. Fifteen days after wait-listing among the same group of patients, only 5% were still listed as Status 1, 6% were downgraded to a MELD/PELD score, 10% were inactive, 49% had been transplanted, 13% had died, 5% were too sick to transplant, 13% had recovered and 1% had been removed from the list for other reasons. Since it appears that nearly 18% of Status 1 patients die without being transplanted, wider sharing for Status 1 patients may need to be considered to further reduce the waiting time and increase the chances for a timely transplant in these critically ill patients.

MELD/PELD: The year 2003 was the first full year of the MELD/PELD system. Out of 17 171 patients on the waiting list at the end of 2003, 30 (0.2%) were listed as Status 1, 11 995 (70%) according to the MELD score, 374 (2%) according to the PELD score, 161 (0.9%) as HCC T1 or T2 and 155 (0.9%) as other exceptions. In 2003, 4456 (26%) patients were listed as temporarily inactive. Approximately 96% of the active adult patients listed with a MELD score had a score of 20 or less. These included 43% with a MELD score of 6–10 and 53% with a MELD score of 11–20. Patients with a MELD score between 21 and 30 represented 4%, and those with a MELD score > 30 represented 0.4% of the total active waiting list (Figure 7). Of the pediatric patients who were actively listed with a PELD score, 80% had a PELD score of <11, 14% had a PELD score between 11 and 20, 5% had a PELD score between 21 and 30 and 1% had a PELD score > 30 (Figure 8).

Patient events on the waiting list: Events 30 days after a snapshot of the waiting list on January 1, 2003, showed that among patients listed with MELD/PELD <10, 93% were still on the list with MELD/PELD <10, 4% had a MELD/PELD score between 11 and 20 and 0.1% had

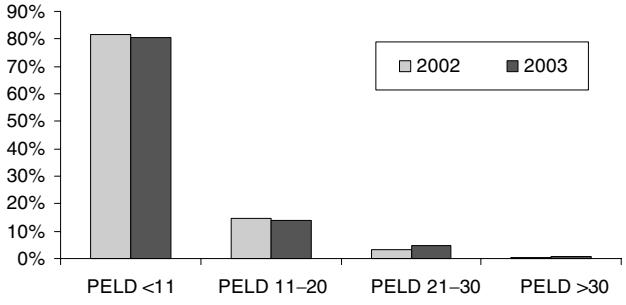

Figure 8: Distribution of active liver waiting list patients at end of year by PELD score, 2002–2003. PELD waiting list patients only (excludes Status 1 candidates). Of all listed liver candidates, 26% were 'temporarily inactive' in 2003; 22% were inactive in 2002. Source: *2004 OPTN/SRTR Annual Report,* Table 9.1.

scores between 21 and 30. At this time, 0.7% of the candidates were removed for transplant, 0.3% for death and 1.1% went to inactive status. At 60 and 90 days, the data were not significantly different and only 1.9% of the candidates had been transplanted at 90 days. Recent SRTR analyses suggest that, on average, survival of adults on the waiting list with a MELD score below 15 is significantly better than with transplantation (3,4). It is possible that such risk-benefit results might be used in developing minimal listing criteria in the future, although it will be useful to see the effects of more follow-up on the results. Such data are not currently available for the pediatric population.

At 30 days for patients with MELD/PELD scores 11–20, 89% were still on the list within the same range, and 3% had dropped to MELD/PELD <10. Approximately 2% had increased to MELD/PELD of 21–30 and only 0.1% now had a score over 30. At 30 days, 2% had been transplanted and 0.7% had died. Again, data at 60 and 90 days were not different, except that 6% of candidates had been transplanted by 90 days. For MELD/PELD 21–30, 52% remained with the same score whereas 0.4% dropped to less than 10, 15% to 11–20 and 3% increased to MELD/PELD greater than 30. At 30, 60 and 90 days, the transplant and death rates were 16% and 5%, 26% and 9%, and 30% and 11%, respectively. Finally, for the MELD/PELD score > 30, 11% remained in this MELD/PELD category while 6% dropped to 21–30. At 30 days, 37% of the candidates had been transplanted, 32% had died and 13% had been removed for other reasons. At 60 and 90 days, only 6% and 3% remained at this same MELD score and 41% and 44%, respectively, had been transplanted. The mortality rates at 60 and 90 days were 33% and 35%, respectively. This breakout illustrates the high risk of death in patients on the waiting list with a MELD/PELD score > 30 (Figure 9).

Hepatocellular carcinoma: Patients with HCC Stage T1 were transplanted within 30, 60 or 90 days in 22%, 41% and 47%, of cases, respectively. At the same time points, 4%, 10% and 12%, respectively, were removed for death, other causes or inactivation. Patients with HCC Stage T2 were transplanted within 30, 60 or 90 days in 39%, 57% and 64%, of cases, respectively. At the same time points, 9%, 15% and 17% were removed for death, other causes or inactivation.

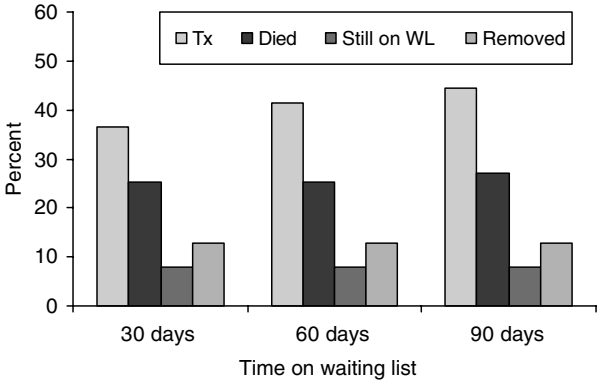

Figure 9: Events after snapshot of waiting list for liver candidates with MELD/PELD > 30 points. As of January 1, 2003. Source: *2004 OPTN/SRTR Annual Report,* Table 9.2b.

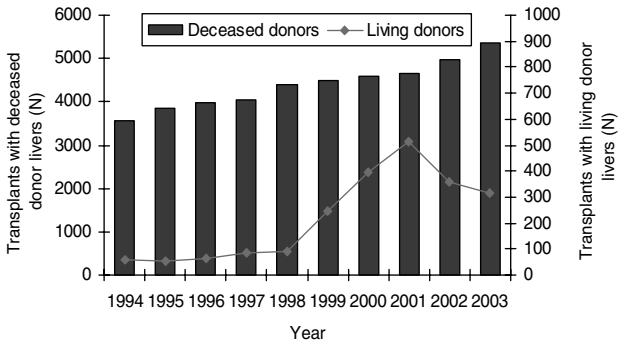

Figure 10: Liver transplant recipients of deceased and living donors, 19940–2003. Source: *2004 OPTN/SRTR Annual Report,* Tables 9.4a and 9.4b.

Liver transplant recipient characteristics

Number of transplants: During the past 10 years, there has been a steady increase in the number of patients who have undergone liver transplantation with a deceased donor organ, from 3574 in 1994 to 5344 in 2003. Although the yearly percent increase in the number of patients undergoing transplantation varied widely (from 2% to 9%), this increase stayed around 2% between 1999 and 2001. In contrast, during the calendar years 2002 and 2003, the number of transplants performed with a deceased donor liver increased by 6% and 8%, respectively (Figure 10). This dramatic increase in the past 2 years has resulted from an expansion of donor criteria to include the use of older donors, the use of donors after cardiac death and the splitting of deceased donor livers.

Age: The single largest and continuously expanding group of liver transplant recipients is the 50–64 year age group. During the last year, 2599 (49%) recipients were in this age range, an increase of 13% between 2002 and 2003. The percentage of pediatric patients (younger than 18 years old) undergoing liver transplantation remained relatively constant over the decade and accounted for 9% of the liver transplant recipients in 2003.

Gender, race, ethnicity and blood type: Approximately 64% of liver transplant recipients were male, 84% were white and 10% were African American; nearly 13% were Hispanic/Latino. These percentages were similar to the population on the waiting list. The most common blood type of liver transplant recipients was O, which represents 44% of all patients transplanted, followed by blood type A (37%), B (14%) and AB (5%). No significant shift in sex, race, ethnicity or blood group has occurred in liver transplant recipients over the past decade.

Prior transplant: Five hundred and six patients who underwent liver transplantation with a deceased donor liver (10%) had received a previous organ transplant, 465 (92%) of whom had received a previous liver transplant.

Diagnosis: The primary indication for undergoing deceased donor liver transplantation was non-cholestatic cirrhosis. This category included chronic hepatitis C virus, chronic hepatitis B virus and cirrhosis secondary to alcohol; it accounted for 59% of all patients who underwent transplantation with a deceased donor liver in 2003. Cirrhosis secondary to cholestatic liver disease was the indication for liver transplantation in 9% of the patients. The percentage of patients who underwent liver transplantation with malignant neoplasms increased nearly threefold between 2001 and 2003. Prior to 2002, only 2–3% of patients who underwent liver transplantation had malignant neoplasms. In 2003, malignant neoplasm was the primary indication for 6% of the patients who underwent liver transplantation with a deceased donor liver. This increase was a direct result of the elevated priority assigned to patients with Stage T1 and T2 HCC by the MELD scoring system, as described above.

MELD score: The MELD scoring system was implemented by the OPTN in March 2002 as a way to prioritize patients on the waiting list (5). Since then, the percentage of patients who were hospitalized at the time of transplantation declined from 42% to 29%. This was almost exclusively the result of a decline in the number of patients who were in an intensive care unit or on life support at the time they underwent liver transplantation. This decline suggests that MELD has been successful in identifying those patients at greatest risk for hepatic decompensation and liver-related death and selected the majority of these patients for transplantation prior to their need to enter an intensive care unit. During 2003, 33% of the patients who underwent liver transplantation with a deceased donor liver had a MELD score above 20, while 32% had a MELD score of 20 or less (Figure 11).

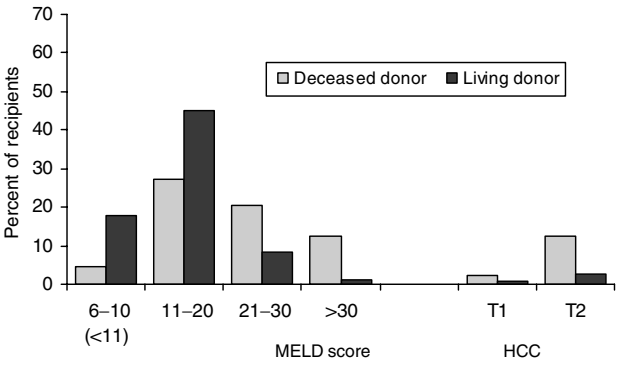

Figure 11: Percent of liver recipients by MELD score and HCC at time of transplant, deceased versus living donor, 2003. Percentage of adult MELD and HCC recipients only. Source: *2004 OPTN/SRTR Annual Report,* Tables 9.4a and 9.4b.

Living donor liver transplantation: As opposed to the stepwise increase in liver transplantation utilizing deceased donor organs, the number of living donor liver transplants performed on an annual basis has declined from a high of 511 in 2001 to 360 in 2002 and 318 in 2003. This represents a decline of 38% in the number of liver transplants performed with living donors over the past 2 years. In the preceding years, the number of living donor liver transplants had increased by more than 450% between 1998 and 2001. The marked rise and fall in living donor liver transplantation since 1998 was almost exclusively the result of changes in the number of adults who have undergone this procedure. In contrast, the number of patients younger than 18 who underwent living donor liver transplantation between 1994 and 2003 ranged between 52 and 117 children each year.

The marked changes in the number of adults undergoing living donor liver transplantation between 1998 and 2003 have a number of causes. The sizeable increase in living donor liver transplantation between 1998 and 2001 was primarily driven by the urgency of adult patients with HCC and relatively preserved hepatic function to undergo transplantation before they developed metastatic disease. Such patients did not receive additional priority while on the waiting list at that time, and in the absence of a living donor these patients were at risk of developing advanced or metastatic HCC, which would exclude them as liver transplant candidates. The adoption of the MELD scoring system in 2002

allowed these patients to undergo transplantation with a deceased donor liver, which has reduced the urgency for living donor liver transplantation.

A second factor that has probably contributed to the rise and fall in living donor liver transplantation since 1998 is the waiting list effect. As many programs began to offer living donor liver transplantation between 1998 and 2001, approximately 25% of patients who had been on the waiting list and interested in undergoing this procedure were both acceptable candidates themselves and able to identify an appropriate living donor. As a result, a large number of patients already on the waiting list underwent this procedure within a short period of time. Following this, only about 25% of new patients placed on the waiting list were both acceptable candidates to undergo living donor liver transplantation and able to identify an appropriate living donor. As a result, the number of patients who underwent living donor liver transplantation declined.

A final factor that may have contributed to the decline in the number of patients electing living donor liver transplantation during the past 2 years was the nationwide publicity associated with the death of a living donor in 2001 and the increased recognition by the public of the potential for morbidity and mortality associated with this operation (6,7).

The majority of patients who underwent living donor liver transplantation in 2003 were between the ages of 50 and 64 years (43%); 53% were male, 88% white and 5% African American; 14% were Hispanic/Latino. Approximately 21% of these patients had cirrhosis secondary to cholestatic liver disease. Except for the higher percentage of females and those with cholestatic liver disease, the demographic features, blood type and percentages of being hospitalized, in an intensive care unit, or on life support were all similar to those observed for recipients of deceased donor livers. Of the 2181 patients who underwent living donor liver transplantation since 1994, 66 (3%) had previously undergone a liver transplant. As noted above, implementation of the MELD scoring system has enabled more patients with HCC to undergo liver transplantation from a deceased donor. Despite this, the percentage of patients who underwent living donor liver transplantation for stage T1 or T2 HCC increased over 22% within the past year, rising to 3% in 2003. However, for the calendar year 2003, this percentage was still less than half that observed for patients with HCC undergoing transplantation with a deceased donor graft (Figure 11). In the absence of stage T1 or T2 HCC, the MELD score of patients who underwent living donor liver transplantation was in general lower than that observed for patients who underwent transplantation from a deceased donor; 63% of patients who underwent living donor liver transplantation had a MELD score of 6–20 and only 10% had a MELD score >20. Donors for living donor liver transplantation were generally members of the recipients' families; 15% were parents, 28% offspring, 17% siblings and 7% spouses. The absolute number of parents has remained relatively constant since 1994, suggesting that parents are rarely accepted as donors for adult recipients. Approximately 20% of the living liver donors were unrelated to the recipient.

Center volume: In 2003, 118 different hospitals performed at least one liver transplant. Of these, 71 (60%) performed 25 or more transplants; these centers accounted for 95% of all liver transplants performed nationwide. Sixteen centers performed between 50 and 74 transplants, 12 centers performed between 75 and 99 transplants and 13 centers performed 100 or more transplants during 2003.

Liver transplant patient survival

Deceased and living donor transplants: The adjusted patient survival rates for deceased donor liver transplant recipients were 93% at 3 months, 88% at 1 year, 80% at 3 years and 74% at 5 years. For a discussion of the methodology used to determine adjusted survival rates, see 'Analytical Approaches for Transplant Research', an accompanying article in this report (2). Overall survival for living donor recipients was nearly identical at the same time points. Adjusted patient survival varied by age for both deceased and living donor recipients. Survival for younger and older age groups generally became progressively worse, with the exception of living donor recipients less than a year of age who exhibited an 87% 3-year survival rate. Adjusted patient survival for deceased donor recipients did not vary by recipient race or gender, but cholestatic and metabolic diseases were associated with improved survival rates. Living donor recipient survival at 3 years was lower for older recipients (50 and older); at 5 years it was lower for males and recipients with malignancy.

Unadjusted patient survival in deceased donor liver transplants was similar to the adjusted survival rates: 92% at 3 months, 87% at 1 year, 79% at 3 years and 73% at 5 years. The rates were virtually identical for living donor recipients, except at 5 years where there was a 5% survival advantage for the living donor group (78%) (Figure 12). From 1994 to 2003, there have been very small incremental improvements in patient survival in deceased donor liver transplants. The most remarkable improvement, however, has been in the 3-month patient survival rates in living donor recipients, which increased from 89% in 1994 to 97% in 2003.

Hospitalization: One-year patient survival for deceased donor recipients was 89% for patients who were at home prior to their transplant, 83% for patients who were hospitalized at the time of transplant and 79% for patients who were in an intensive care unit at the time of transplant. The differences in survival were stable at 3 and 5 years, indicating that being hospitalized or in an intensive care unit primarily affects survival in the first post-transplant year.

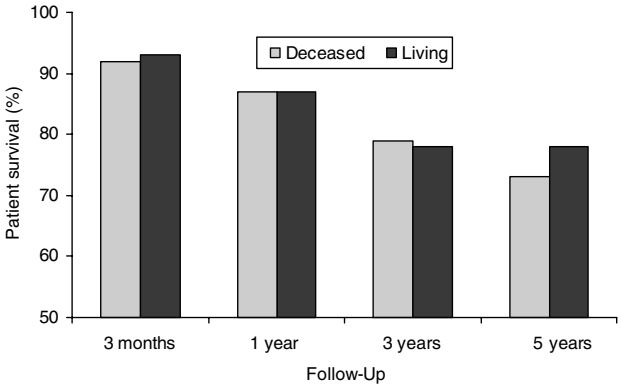

Figure 12: Unadjusted patient survival, living versus deceased donor liver transplants. Source: *2004 OPTN/SRTR Annual Report,* Tables 9.12a and 9.12b.

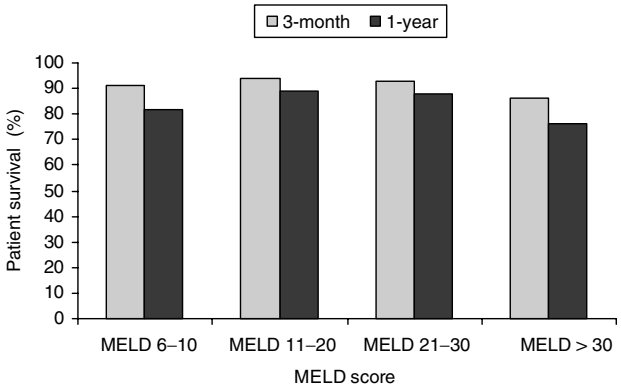

Figure 13: Three-month and 1-year unadjusted survival of deceased donor liver recipients, by MELD score. Source: *2004 OPTN/SRTR Annual Report,* Table 9.12a.

Age: Patient survival in deceased donor recipients also varied significantly with recipient age. Five-year survival was 86% for the 6–10 age group and only 65% for recipients older than 65. Five-year patient survival for living donor recipients was 85% in the 6–10 age group and 67% in recipients over 65 years of age. Five-year survival for female living donor recipients was 84%, compared to 71% for males. Other comparisons could not be made for living donor recipients because of small numbers of the procedure.

MELD score: Deceased donor recipients with MELD score >30 at transplantation exhibited unadjusted patient survival of 86% at 3 months and 76% at 1 year (Figure 13). Interestingly, unadjusted 1-year patient survival for patients with a MELD of 6–10 was also low (82%), compared to patients with a MELD score of 11–30 (approximately 89%). This may relate to the use of expanded criteria livers for these patients. The 1-year survival for patients listed as MELD exceptions (91%) was higher than that of all MELD groups. There was no apparent effect of the PELD score on pediatric recipient survival and there were not sufficient numbers for comparisons in the living donor recipients. Future analyses will need to differentiate the survival-based MELD scores solely related to laboratory abnormalities from patients granted additional MELD/PELD points for exceptions—for example, HCC.

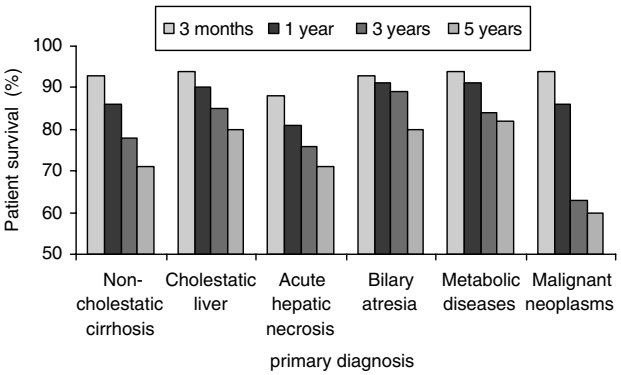

Figure 14: Unadjusted survival of deceased donor liver recipients, by primary diagnosis. Source: *2004 OPTN/SRTR Annual Report,* Table 9.12a.

Diagnosis: The etiology of liver disease also affected patient survival of deceased donor livers (Figure 14). The highest 1-year unadjusted survival rates were seen for patients with metabolic diseases (91%), biliary atresia (91%), and cholestatic liver disease (90%). This trend continued at 3 and 5 years. Patients with acute hepatic necrosis had the lowest 1-year patient survival rate (81%). Patients transplanted for malignancy had 1-year survival of 86%. However, by 5 years following transplantation, this survival rate had dropped to 60%, presumably due to recurrent malignancy.

Survival rates for living donor recipients also varied by disease. The 1-year patient survival for cholestatic liver disease was the highest: 96%, compared to 86% for biliary atresia and 79% for metabolic diseases. Survival for acute hepatic necrosis was 69% at 1 year, much lower than that for deceased donor liver transplants. Patients transplanted for malignancy exhibited 1-year survival of 73% but 5-year survival of only 50%.

Donor age: Unadjusted 1-year patient survival was 90% when the deceased donor age was 11–17 years. Survival rates were slightly lower for recipients of organs from deceased donors aged 18–34, 35–49 and 50–64. A more substantial decrease in the 1-year survival (79%) was seen for recipients of livers from donors, aged 65 years or older. These trends continued at 3 and 5 years. Living donors

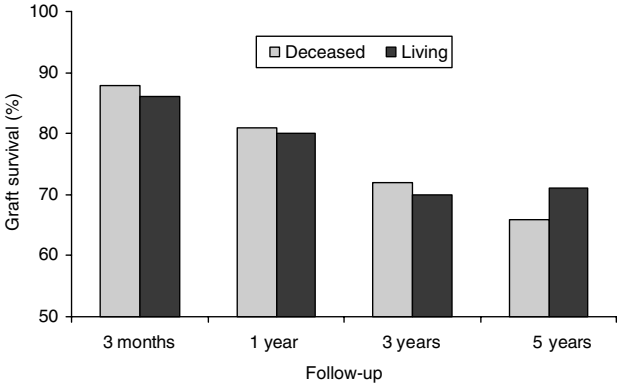

Figure 15: Unadjusted graft survival, living versus deceased donor liver transplants. Source: *2004 OPTN/SRTR Annual Report,* Tables 9.9a and 9.9b.

were generally (89%) between the ages of 18 and 49 and no differences in recipient survival by donor age were noted.

Cold ischemia time and center volume: The vast majority (71%) of liver transplants are performed with less than 10 h of cold ischemia time. Short- and long-term patient survival did not appear to be affected by the duration of cold ischemia, however. Center volume did not have a large effect on patient outcomes at any time point.

Liver transplant graft survival

Deceased and living donor transplants: Unadjusted graft survival for deceased donor liver transplant recipients was 88% at 3 months, 81% at 1 year, 72% at 3 years, and 66% at 5 years. Overall unadjusted graft survival for living donor recipients at these same time points were 86%, 80%, 70% and 71%, respectively (Figure 15). (Note that the 5-year survival analysis uses a different cohort than the 3-year survival analysis, allowing it to be higher.) The 1-year unadjusted graft survival in deceased donor liver transplants increased from 76% in 1994 to 82% in 2002. The 3- and 5-year survival rates improved only slightly. For living donor recipients, the 1-year graft survival rates increased from 64% to 80%, with little change in the 3- and 5-year survival rates. African American and white recipients of deceased donor livers had equivalent graft survival rates at 3 months and 1 year, but African Americans exhibited 9% lower rates at 3 years and 5% lower rates at 5 years. Recipient ethnicity and gender did not affect graft survival. AB blood type continues to show a 4–7% survival advantage over other blood types. Prior liver transplantation had a major effect on graft survival in deceased donor and living donor recipients. The 1-year graft survival rates were 18% and 16% lower, respectively, among patients who had undergone prior deceased or living donor transplantation.

Hospitalization: Graft survival rates were notably associated with severity of illness. The 3-month and 1-year graft survival rates for those patients not hospitalized were 91% and 85%, respectively, compared to 87% and 79% for hospitalized patients, 80% and 72% for patients in an intensive care unit and 72% and 63% for patients on life support at the time of transplant. These differences persisted out to 5 years. The effect of severity of illness was even more pronounced for living donor recipients. The 3-month and 1-year graft survival rates for those patients not hospitalized were 88% and 83%, respectively, compared to 86% and 75% for hospitalized patients, 68% and 56% for patients in an intensive care unit and 63% and 47% for patients on life support at the time of transplant.

Age: For recipients of deceased donor organs, graft survival was poorer for recipients at the extremes of the age range: 1-year survival for children <1 year was 76% and for those over age 65 graft survival was 77%. The best graft survival rate was in the 11–17 age group (86%). These differences were less pronounced at 5 years. In contrast, the best results for living donor liver transplant recipients were in those <1 year old (84% 1-year graft survival).

MELD score: The MELD score at the time of transplant affected graft survival in deceased donor recipients. The 3-month and 1-year graft survival rates for MELD >30 were 83% and 73%, respectively, compared to 91% and 85%, respectively, for MELD 21–30 (Figure 16). As seen with patient survival, patients with MELD 6–10 had poorer graft survival at 3 months (88%) and 1 year (77%)—likely reflecting the use of expanded donors in these patients. Graft survival rates for HCC T1 and T2 were 83% and 86% at 1 year, respectively. Graft survival rates for exceptions were 90% at 3 months and 85% at 1 year. No apparent

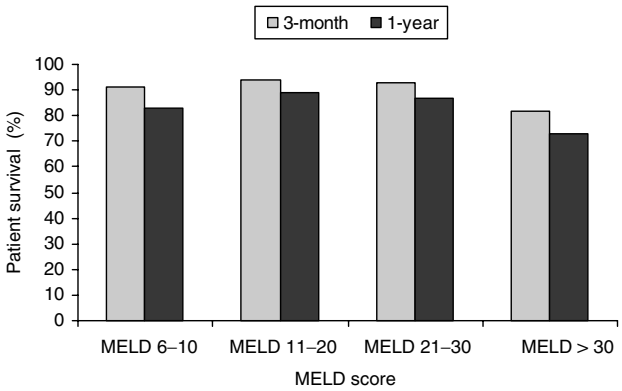

Figure 16: Three-month and 1-year unadjusted graft survival of deceased donor liver recipients, by MELD score. Source: *2004 OPTN/SRTR Annual Report,* Tables 9.9a.

differences in graft survival according to the PELD score were noted except with PELD >30 but the numbers were too small to draw any firm conclusions.

Diagnosis: The 3-month and 1-year graft survival rates for deceased donors were poorest in patients with a diagnosis of acute hepatic necrosis (83% and 75%), compared to cholestatic liver disease (90% and 85%). Patients transplanted for malignancy had a 5-year graft survival rate of only 53%, which paralleled the patient survival rates.

Donor age: Donor age <1 year of age was associated with a marked decrease in graft survival (71% at 1 year), as was donor age 50–64 (79%) and over 65 years of age (70%), compared to other age groups, all of whose 1-year survival rates were in the neighborhood of 84%. Living donors were generally (89%) between the ages of 18 and 49 and no differences in graft survival by donor age were noted.

Cold ischemia and center volume: No obvious differences in unadjusted graft survival were seen based on center volume. However, cold ischemia times of 0–5 and 6–10 h were associated with a 5–6% improvement in the 3-month graft survival compared to 11–15 h. These differences diminished with time. Longer cold ischemia times were not associated with greater rates of graft loss, although the numbers are small and may reflect donor and recipient selection factors in addition to cold ischemia time.

Pre-transplant death rates

The overall death rate while on the liver transplant waiting list has decreased considerably over the last 10 years, dropping from 225 deaths per 1000 patient years in 1994 to 124 in 2003 (Figure 17).

Age: Candidates under 1 year of age had the highest death rate in 2003 with 818 deaths per 1000 patient years, although the patient numbers are small (18 deaths among 137 patients). The second highest death rate was 170 deaths per 1000 patient years, which was observed for candidates 65 years or older.

Race and ethnicity: In 2003, African Americans had the highest death rate on the liver waiting list, at 144 per 1000 patient years, followed by whites at 123 and Asians at 100. The increased risk of death for African Americans could be related to several possible factors that need to be examined by the transplant community—such as less access to health care leading to listing at a later stage of disease and consequent higher risk of waiting list death, or reduced quality of care while on the waiting list. The death rate for Hispanics/Latinos was higher than that for non-Hispanics/non-Latinos (136 and 122 deaths per 1000 patient years, respectively). The death rates per 1000 patient years for males and females were 129 and 116, respectively. There was very little variation in death rates by blood type.

MELD/PELD score and Status 1: As expected, the waiting list death rates increased with increasing MELD scores at the time of listing. In 2003, candidates with MELD scores from 6 to 10 had a death rate of 51 per 1000 patient years, candidates from 11 to 20 had a rate of 132, candidates from 21 to 30 had a rate of 689 and candidates with MELD scores >30 had a death rate of 3390 deaths per 1000 patient years (Figure 18). The death rates also tended to increase with increasing PELD scores, but the smaller number of patients and observed deaths make the estimates less certain than the estimates by MELD scores. The death rate per 1000 patient years was 50 for candidates with PELD scores of 10 or under, 171 for candidates from 11 to 20, 462 for candidates from 21 to 30 and 214 for candidates with a PELD >30. The death rate for candidates

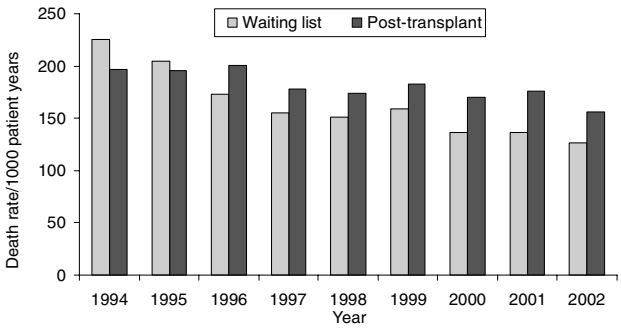

Figure 17: Unadjusted death rates per 1000 patient years at risk, 1994–2002, liver waiting list versus post-transplant. Source: *2004 OPTN/SRTR Annual Report,* Tables 9.3 and 9.7a.

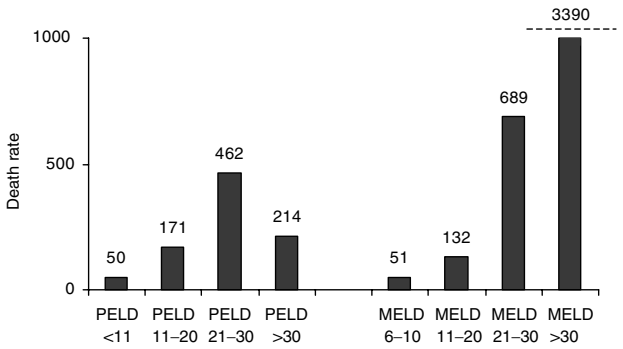

Figure 18: Waiting list death rates by PELD and MELD, 2003. Source: *2004 OPTN/SRTR Annual Report,* Table 9.3.

listed as Status 1 was 518 deaths per 1000 patient years in 2003.

Post-transplant death rates

Deceased and living donor transplants: As with the waiting list death rates, post-transplant death rates also displayed a decreasing trend over the past 10 years (Figure 17). (Because of the follow-up time required, the most recent data for the 1-year death rates are for those who received a transplant in 2002.) The death rate in the first year following deceased donor liver transplant was 156 deaths per 1000 patient years in 2002 compared to 197 in 1994. The corresponding rates for living donor recipients remained relatively stable with 161 deaths per 1000 patient years in 1994 to 158 in 2002. (Note: The number of living donor transplants is not large enough to make reliable comparisons among various subgroups; therefore all subsequent post-transplant death rate comparisons refer to deceased donor liver transplants.)

Age: The death rates in 2002 following deceased donor liver transplant were highest among patients 1–5 and 50–64 years old: 177 and 176 deaths per 1000 patient years during the first year after transplant, respectively.

Race and ethnicity: The post-transplant death rate per 1000 patient years was highest among Asians (156), followed by whites (155), then African Americans (146). Hispanics/Latinos had a post-transplant death rate of 171 deaths per 1000 patient years in 2002, while non-Hispanics/non-Latinos had a death rate of 154.

Previous transplant and diagnosis: In 2002, the post-transplant death rate among recipients who had received a previous organ transplant was substantially higher than the rate for first-time transplant recipients (334 deaths per 1000 patient years during the first year after transplant, compared to 140). There was a high degree of variability in post-transplant death rates by primary diagnosis category. For 2002, the death rate per 1000 patient years was 154 for non-cholestatic liver disease, 100 for cholestatic liver disease, 270 for acute hepatic necrosis, 115 for biliary atresia, 98 for metabolic diseases, 160 for malignancy and 184 for other diagnoses.

MELD/PELD score: While there does seem to be a trend toward higher post-transplant death rates with increasing MELD scores, it is not as pronounced as the trend for waiting list death rates. As shown in Table 1, in 2002 the post-transplant death rate in the first year after transplant was 201 per 1000 patient years for recipients with a MELD at transplant from 6 to 10, 122 for MELD 11–20, 140 for MELD 21–30 and 290 for MELD >30. The death rates by PELD at transplant followed the same pattern. The death rate was 25 deaths per 1000 patient years for recipients with a PELD of 10 or under at transplant, 66 for PELD from 11 to 20 and 165 for PELD 21 to 30. There were not enough transplants to patients with a PELD >30 to compute a death rate. The death rate for recipients transplanted as Status 1 was 313 deaths per 1000 patient years in 2002.

Table 1: Adult and pediatric death rates by MELD/PELD score, waiting list versus 1-year post-transplant, 2002

MELD/PELD score or status	Adult		Pediatric	
	Pre-Tx	Post-Tx	Pre-Tx	Post-Tx
6–10 (MELD) or >11 (PELD)	68	201	37	25
11–20	137	122	359	66
21–30	723	140	757	165
>30	3567	290	1153	*
Status 1 (all patients)	476	313	–	–

* Not enough patients or deaths to calculate a death rate.
Death rates are measured as deaths per 1000 patient years at risk. Post-transplant (post-Tx) rates are based on the number of deaths within 1 year following transplantation.
Source: *2004 OPTN/SRTR Annual Report,* Tables 9.3 and 9.7a.

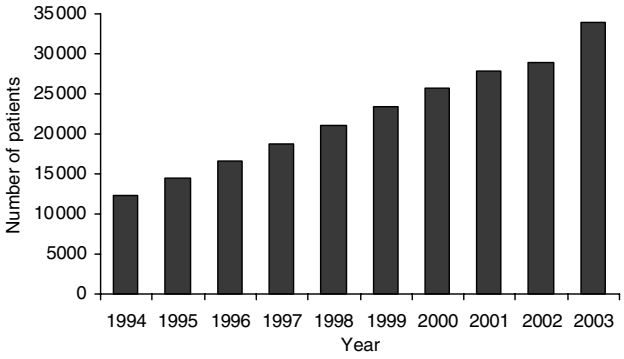

Figure 19: People living with a functioning graft at year-end, 1994–2003. Source: *2004 OPTN/SRTR Annual Report,* Table 9.14.

Prevalence of liver transplant recipients with functioning grafts

The prevalence of people living with a functioning liver graft in the United States has increased steadily from 12 237 in 1994 to 33 854 in 2003 (Figure 19). Of these, 32 293 were recipients of deceased donor livers and 1561 were recipients of living donor livers. As can be seen from Figure 20, the proportion of people living with a functioning graft who had received living donor livers increased steeply from 0.9% in 1994 to 1.3% in 1998 and 4.4% in 2002; however, this increasing trend seems to have leveled off in 2003 with only a slight increase to 4.6%. The proportion of pediatric recipients living with a functioning graft (<18 years of age) decreased from 17% in 1994 to 13% in 2003.

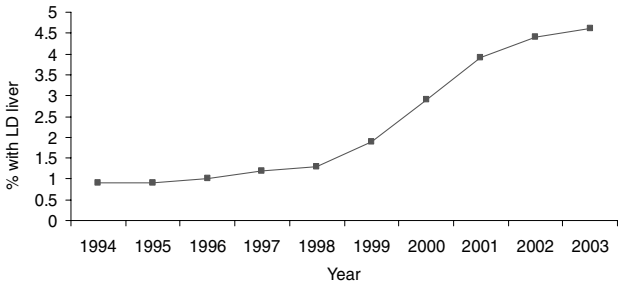

Figure 20: Proportion of people alive with living donor liver transplants as percentage of all liver transplants by year, 1994–2003. Source: *2004 OPTN/SRTR Annual Report,* Table 9.14.

Race, ethnicity, ABO type and gender: The percentage of recipients with functioning liver grafts who were African American increased from 7.7% in 1994 to 8.2% in 2003, Asians increased from 2% to 3% and whites decreased from 89% to 87%. The Hispanic/Latino proportion increased from 9% to 12%. The distribution, among blood types, of people living with a liver graft has remained relatively constant over the past 10 years. In 2003 42% were blood type O, 40% A, 12% B and 5% AB. The proportion of males with a functioning graft increased from 54% in 1994 to 59% in 2003 while the proportion of females decreased from 46% to 41%.

Diagnosis: Of people living with a functioning graft at the end of 2003, 58% had been transplanted due to non-cholestatic liver disease, 15% for cholestatic liver disease, 7% for acute hepatic necrosis, 6% for biliary atresia, 5% for metabolic disease and 3% for malignancy. Retransplants accounted for about 7% of the total.

Status 1 and hospitalization: The proportion of people with a functioning graft who were transplanted at Status 1 decreased from 17% in 1994 to 12% in 2003. For recipients with a functioning graft at the end of 2003, the proportion of recipients who had been on life support prior to transplant was 8%. The proportion of recipients who were in an intensive care unit prior to transplant was 18% and the proportion who were hospitalized prior to transplant was 17%, compared to 64% who were not hospitalized.

Liver allocation policy update for 2003

MELD/PELD: Studies showing that the waiting list mortality has increased directly in proportion to the listing MELD score (8) have brought much attention to the implications of the MELD/PELD scoring system. Based on more points of discrimination compared to the Child–Turcotte–Pugh (CTP) scoring system, the receiver operating characteristic (ROC) for the MELD score was 0.83 compared to 0.76 for the CTP score ($p < 0.001$) and it was concluded that the MELD score was better able to accurately predict the 3-month mortality among patients with chronic liver disease on the waiting list (8).

Freeman et al. evaluated the results of the first year of the new liver allocation plan using the MELD/PELD scoring system (9). A 'before and after' study was designed to evaluate the impact of MELD on the number of waiting list registrations, removals, transplants, and deaths during the year prior to and after the allocation policy change. After MELD, there was a 12% reduction in new liver registrants, with the largest reductions in those with low MELD/PELD scores. After MELD, there was a 4% reduction in the waiting list death rate ($p = 0.076$) and a 10% increase in deceased donor transplants that was evenly distributed across all demographic and medical strata, with some variation in geographic variables. Early patient and graft survival was unchanged (9).

At the conference 'Evolving Concepts in Liver Allocation in The MELD/PELD Era' in December 2003, there was consensus that the MELD/PELD system was suceeding and was working better than the prior allocation system (3). Data presented during the conference demonstrated the following points: (1) the rate of death on the waiting list, adjusted for the size of the waiting list, declined over the 18-month period with the new system, but not significantly; (2) the transplant rate increased for adults; (3) the MELD score at transplant was decreasing significantly over time, in part due to the reduction in the score assigned to candidates with HCC; (4) overall 6-month survival rates were excellent, at 90% for adult MELD patients and 80% for Status 1 patients and (5) the ability of the MELD score to predict waiting list mortality was confirmed again. Since hyponatremia appears to be a good marker for ascites, adding this parameter might improve the MELD score's predictive ability. For adults, 21% of liver transplants were for patients with MELD scores of 14 or less. In some OPOs, more than 10% of transplants were for candidates with MELD scores <10, while in other OPOs this percentage was zero. The hazard ratio (HR) for death is greater than 1 for patients with MELD scores of less than 10 and for patients with MELD scores in the 10–14 range (statistically significant), meaning that there is no demonstrable survival benefit to transplanting patients with low scores. As the MELD/PELD score increases, the hazard ratio decreases, indicating an increasing benefit to transplantation, with statistically significant results (10). A more recent SRTR analysis confirmed and elaborated on the survival benefit of liver transplantation presented at this conference, finding a 38% lower 1-year mortality risk for recipients than candidates at MELD 18–20 and increasing benefit at higher MELD scores. This analysis found significantly higher mortality risk for recipients at MELD 6–14 (4).

The conference ended with several recommendations that drove certain allocation policy discussions in the months that followed: (1) regional sharing for MELD scores 15 or higher before local allocation to patients with MELD score

<15; (2) a required minimum MELD score of 10 for placement on the waiting list; (3) continued exception scores for hepatocellular T2 lesions, but a decrease in T1 exception points; (4) allowing exception points for larger single T3 lesions that are treated prior to transplant and finally, (5) collect prospective data on serum sodium.

Change in MELD/PELD: The concept of change in MELD/PELD was introduced by the SRTR during 2003. The change in each patient's MELD score (ΔMELD) or PELD score (ΔPELD) was studied to determine its impact on pre-transplant mortality. The baseline for comparison consisted of modest changes (0 to +5) in MELD or PELD scores over a 30-day period. Changes in the MELD score of >5 points over a 30-day period were associated with a statistically significant threefold increase in the relative risk of death compared to the baseline group ($p < 0.00001$). ΔMELD might be used to break ties between patients with the same mortality risk as expressed by the MELD score. The SRTR also concluded that, as seen with ΔMELD, a rapidly increasing ΔPELD is associated with higher mortality risk than a stable or decreasing ΔPELD. However, after liver-simulated allocation modeling (LSAM), the SRTR showed that the use of ΔMELD/PELD as a tiebreaker would not have a large effect on the distribution of transplants or on waiting list mortality (11,12).

HCC: For patients with HCC in 2003, presentation to review boards was no longer required to obtain increased MELD/PELD score equivalent to an 8% probability of pre-transplant death within 3 months for a T1 lesion and 15% probability for a T2 lesion. The special circumstance for T1 lesions was later removed. Further, candidates received additional MELD/PELD points equivalent to a 10% increase in pre-transplant mortality every 3 months until a transplant was received.

Regional differences: In 2003, despite the improvement in allocation with MELD/PELD, there remained concerns about discrepancies in allocation from region to region and donation service area to donation service area. Many factors affect the probability of a patient getting a transplant, some related to geography and some not (e.g. local competition and OPO efficiency). An analysis of the MELD system revealed little variation in terms of MELD score at listing among regions and OPOs. There are variations in donors per million population by OPO as well as listings per million population and donors per listed patient by center and within OPOs. An analysis of variance (ANOVA) analysis revealed that the region contributed to 5% of the variation in mean MELD score at transplant, versus 17% contributed by the OPO. For mean MELD at death, the region contributed 2%, versus 7% contributed by the OPO. This indicates that the variation among OPOs within a region is greater than the variation between regions. As a response to these concerns, there is more interest in exploring minimum listing criteria and forced intraregional shares above certain MELD scores.

Regional review boards: Voigt et al. (13) explored the regional review board (RRB) process to determine its functionality and fairness by retrospectively analyzing 1965 non-Status 1 requests made to the RRBs between February 2002 and November 2002 and comparing Kaplan–Meier survival and time to transplant between those approved and those denied. A Cox proportional hazards model was used to determine whether referring physicians predicted mortality better than the score. More requests were denied for patients with non-sanctioned conditions ($p < 0.0001$) and fewer patients denied had a transplant at all ($p < 0.0001$). However, the time to transplant was not different between the groups ($p = 0.2$). Non-sanctioned denied patients had a lower mortality than approved cases ($p < 0.04$). Referring physicians predicted mortality poorly ($p = 0.23$) while MELD/PELD was highly predictive of waiting list mortality ($p = 0.0003$). They concluded that the RRBs were fair and could adequately distinguish between high- and low-risk patients, while the referring physicians did not predict patient mortality well (13).

However, variation, consistency and timeliness of RRB decisions remain a concern. This was partly addressed in two ways: (1) by ruling that if an RRB does not act in the sanctioned time period the transplant center's request on behalf of its patient becomes essentially uncontestable; and (2) by exploring the idea of a national review board—which could provide a more standardized process, a potentially faster response time, and reviewers better educated about the guidelines and review process for an estimated 700 cases per year. This latter plan could limit the ability for areas to be innovated; however, a national review board could provide for regional experiments. The MELD/PELD data for each local area would be provided to such a board.

Living liver donation: Policy surrounding living liver donation was revised in 2003. There were guidelines discussed for living donor transplant program that included a minimum of 25 major hepatic resection operations over a 3-year period, of which 10 must be living donor surgeries. There was interest in collecting data on living liver donors. It was suggested that transplant centers would follow donors for the first year, after which time a central registry would follow the donors for years 2–10. Guidelines were established for living liver donor evaluation that included a minimum recipient MELD/PELD score of 10. It was felt that avoiding conflicts of interest is desirable, so that whenever possible the donor and recipient procedures should be performed by different surgeons having primary responsibility for either the donor or recipient.

HLA typing: While laboratories must HLA type all transplant recipient and donors when requested to by a physician or other authorized individuals, and be able to perform a prospective crossmatch when requested, it was confirmed in 2003 that routine HLA typing or crossmatching for liver transplantation is not required.

Intestine

Intestine transplantation continues to be performed with modest but increasing frequency, with 112 transplants (including multiorgan procedures) performed in 2003. While total registrations have increased annually nearly every year since 1994, the increase in deceased donor organs has been minimal. In contrast to prior trends with liver and kidney transplantation, live donor intestine transplantation has not become a viable option for the vast majority of cases, with only four living donors registered for the calendar year 2003. This is likely related to the majority of registrants being very small children, for whom living donation has not been offered for technical reasons.

The intestine, perhaps more than other organs, is frequently transplanted in combination with other solid organ transplants. This is consistent with historical trends (14). In 2003, 52 isolated intestine transplants were registered with 48 deceased donors and four living donors. In the same period, 64 intestine transplants were performed with at least one other organ. Among these multiorgan grafts, there has also been a trend toward slightly decreasing numbers of combined liver–intestine transplants performed since 2000 with a commensurate increase in the number of liver–intestine–pancreas allografts performed (multivisceral transplants). Thus, while in 1995 there were 21 liver–intestine transplants and a single liver–pancreas–intestine allograft, in 2003, only 22 liver–intestine transplants were performed in comparison to 29 liver–pancreas–intestine transplants. This may reflect center-specific comfort with one anatomical variation of transplantation of the intestine as a multivisceral graft as compared with combined liver–intestine transplantation without pancreatic inclusion.

Patient and graft survival rates continue to improve with maturation of intestine transplantation. Patient and graft survival for isolated intestine transplants exceed those for combined transplants with the liver out to 1 year from transplantation. This is consonant with single-center reports of survival with this transplant rivaling other more common solid organ transplants (15). At 5 years of follow-up, both patient and graft survival advantages are lost, suggesting chronic graft loss late as a persistent factor in grafts not containing livers. Although improvements have been modest, a steady trend toward improving patient survival has occurred with intestine transplant recipients such that the overall group currently exhibits a 74% 1-year survival rate. These data confirm what has been reported from other registries (16).

Intestine waiting list characteristics

The number of patients listed for intestine transplantation has continued to grow annually since 1994, with the exception of a slight decrease in the total number waiting at the end of 2003 to 172 patients. Of the 172 patients on the list in 2003, 26% were listed as inactive, similar to the liver waiting list. There were 205 new patients added to the list

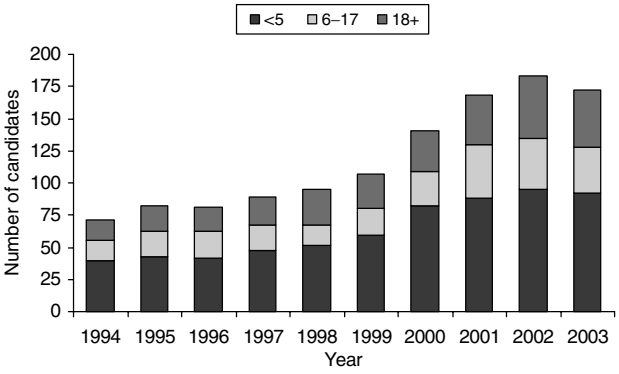

Figure 21: Intestine waiting list by age, end of year 1994–2003.
Source: *2004 OPTN/SRTR Annual Report,* Table 10.1.

in 2003, up from 84 in 1994 and 171 in 2000. The patient population continues to be largely pediatric, with 74% of patients under 18 years old and 54% of patients <5 years old (Figure 21). This is in sharp contrast to the liver waiting list, for which only 3% of the population listed is less than 5 years old. Furthermore, a larger proportion of patients on the intestine waiting list are African American, constituting 19% of the waiting list at the end of 2003, compared to 7% of the liver waiting list. No large differences were noted between the intestine and liver waiting list according to gender (44% female), blood type (49% O, 33% A, 14% B and 4% AB) or national residency (98% U.S. residents). A prior transplant had been performed in 5% of candidates, down from 9% the prior 2 years, with the majority having undergone a failed intestine transplant (4%, down from 7% the prior 2 years). As discussed below, this may relate to improved primary graft survival rates with isolated small bowel transplantation leading to fewer early graft failures requiring retransplantation.

In 2003, 41% of patients on the waiting list had been waiting <6 months, 29% 6 months–2 years, and 30% had been waiting more than 2 years. The percentage of patients waiting <6 months for a transplant had been declining steadily since 1998 until this year when an increase was noted for the first time in 5 years.

For patients awaiting intestine transplantation, the short gut syndrome is the primary diagnosis in 64%, unchanged from prior years. Patients with functional bowel problem constitute 14% of patients. The proportion of patients listed for intestine transplant in the 'other' category has steadily increased from 9% in 1997 to 22% in 2003, suggesting the need for future analyses to incorporate new primary diagnosis categories that may be increasing in frequency.

Intestine time to transplant

Complete data for median time to transplant is not available over the past 10 years for intestine candidates for two reasons: insufficient follow-up time and the fact that for some years fewer than 50% of listed candidates have

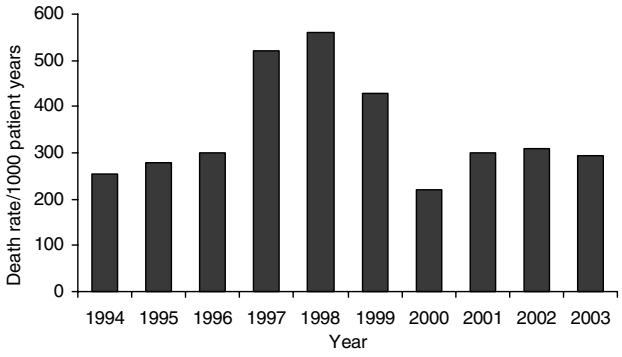

Figure 22: Intestine waiting list death rates, 1994–2003. Source: *2004 OPTN/SRTR Annual Report,* Table 10.3.

yet received a transplant. The 10th and 25th percentiles of the time to transplant were 34 and 89 days in 2003, respectively, compared to 30 and 98 days, in 2002. The 25th percentile time to transplant has remained relatively stable between 91 and 102 days from 1996 to 2002. Historically, time to transplant has been longer for children than for adult registrants listed for intestine transplantation. Again, complete data allowing analysis of median time to transplant is not currently available; however, the 25th percentile of time to transplant for children younger than 1 remains high—154 days in 2003, compared to 44 days for adults 18–34 years old. In 2003, median time to transplant for children 1–5 years old remained stable at 292 days and increased substantially from 60 days in 2002 to 196 days in 2003 for children 6–10 years old. The biggest decrease in waiting time occurred in adolescents 11–17 years old. In this group, the 25th percentile of time to transplant decreased from 226 days in 2001 to 51 days in 2003; the median time to transplant declined from 467 days in 2001 to 333 days in 2003. Time to transplant for older adult registrants in the 35–49 and 50–64 age groups varied over the past several years due to the small numbers of registrants available for analysis.

The 25th percentile of time to transplant in 2003 was 184 days for Asians, 140 days for African Americans, 120 days for other/multirace, and 73 days for whites. In 2002, the 25th percentile of the time to transplant for the Hispanic/Latino group was 60 days, but this increased to 368 days in 2003, compared to the non-Hispanic/non-Latino group, which experienced waits of 98 days in 2002 and 76 days in 2003. Males continue to wait longer (25th percentile waited 110 days in 2003) than females (25th percentile waited 59 days in 2003). Continuing a trend from prior years, blood group AB patients have the shortest 25th percentile time to transplant compared to all other blood groups. Prior transplant and national residence did not affect time to transplant.

Intestine waiting list deaths

Overall, the number of patients at risk for death on the waiting list has increased annually since 1994, with 367 patients at risk in 2003. The reported deaths and annual death rates of patients on the intestine waiting list have varied over the past decade, although there has been a general downward trend—from a high of 522 per 1000 patient years in 1997 to 295 in 2003 (Figure 22). All patients 1–18 years old demonstrated a decreased death rate on the waiting list in 2003 as compared to an increase for adults 18–34 and 35–49 years old, for whom there was an increase in the death rate over the prior year. Thus, the decrease in the overall death rates on the waiting list appears largely to reflect decreases among children receiving intestine transplants, the population making up the majority of those at risk. Possible explanations include greater experience, increased safety of and willingness to use expanded criteria donor organs and the application of reduced size allografts. This population requires size-matched grafts, and the lack of small pediatric allografts has previously contributed to the higher rate of waiting list deaths than adult patients.

While no significant trends in annual death rates by race had been noted for several years, there was a modest decrease in the 2003 death rate in white patients while the rate remained unchanged for African Americans. The numbers were too small for comparison in the Asian and other/multirace groups. Overall, there was a decline in the death rate for the Hispanic/Latino ethnic group from 579 in 2002 to 359 in 2003, compared to 280 and 290 in the non-Hispanic/non-Latino group. Female patients saw a slight decline in death rates, blood type O and AB patients saw modest declines, type B patients saw a major decline in death rates (528 to 379 days), and blood type A patients saw a modest increase over 2002.

Intestine transplant recipient characteristics

The number of patients receiving intestine transplants increased slightly from 106 in 2002 to 112 in 2003, compared to 23 intestine transplants performed in 1994 and 78 in 2000. As one would expect, there has also been an increase in the incidence of intestine transplantation per million population, from 0.09 in 1994 to 0.29 in 2000 and 0.4 in 2003. The majority of recipients (71, or 63%) were children under 18 years old; 43 (38%) were 1–5 years old and 10 (9%) were younger than 1 year old. Few intestine transplants were performed in the elderly—last year only five were performed in patients 50–64 years old. Recipients were 88% white, 8% African American, 2% Asian and 2% other/multirace; there has been some fluctuation in racial percentages over the past 10 years. Recipient ethnicity included 88% non-Hispanic/non-Latino, 11% Hispanic/Latino and 1% other/multirace. As in prior years, there was a slight predominance of males (57%) over females. Blood type distribution did not appear to have a significant effect on intestine transplant recipients. Approximately 54% of recipients were blood type O, 34% type A, 9% type B and only 4% type AB.

In the last year's report it was noted that twice as many patients underwent intestine retransplantation in 2002

compared to 2001; the percentage did not change between 2002 and 2003, staying at 11% of the recipients. This reflects the patient population failing primary transplantation and returning to the transplant list. All but one of the recipients were U.S. residents.

In 2003, there was an 11% increase in the proportion of patients receiving intestine transplants from home (69%) compared to 2002 (58%), largely due to a concomitant 9% decrease in the proportion of patients hospitalized at the time of transplant in 2003 (20%) compared to 2002 (29%). The proportion of patients in an intensive care unit at time of transplantation (12%) has not changed significantly since 2001, but has markedly decreased since its peak of 28% in 1999. Similarly, the proportion of patients on life support at time of transplantation in 2003 was only 4% compared to a high of 17% in 1999, though similar to the proportion seen in 2000, 2001 and 2002. It is likely that this trend toward transplantation of less ill patients is contributing to improved outcomes.

The most common cause of intestine failure requiring transplantation remains short gut syndrome, the diagnosis for 72% of recipients. Functional intestinal problems accounted for 21% of recipients, and 7% of recipients had other unspecified conditions. Surgeons are increasingly concerned with the duration of cold ischemia, and 95% of intestinal allografts were transplanted with a cold ischemia time of 10 h or less (14% 0–5 h and 80% 5–10 h). This is rather remarkable given the small number of centers nationally performing these transplants and the necessity of long travel times to facilitate procurement and import organs to those centers offering the procedure. The shorter cold ischemic time continues a trend dropping since 1995 when only 62% of organs were reperfused in less than 10 h.

Annual death rates after intestine transplantation

The annual death rate after intestine transplantation declined over the last year for which data are available, dropping from 404 in 2001 to 310 in 2002. This decrease was most dramatically seen among recipients 1–5 years old, for whom it dropped from 558 per 1000 patient years at risk in 2000 to 456 in 2002. Changes in the other age groups are hard to interpret because of small numbers. The death rates in the second-largest age group, recipients 35–49 years old, remained stable at 152 per 1000 years at risk in 2002. Thus, improved outcomes among pediatric recipients continued to influence the overall results. Although the number of patients for analysis is small, it appears there was a decrease in annual death rates among white and African American recipients at risk, while Asian and other/multirace groups were too small for comparison. The decreases in the annual death rates were consistent across ethnic groups, gender, all blood type groups and nationality. Annual death rates also declined over the past 2 years among patients not on life support at the time of transplantation. There was also a markedly reduced death rate in 2002 for patients not hospitalized compared to patients in hospitals or intensive care units at the time of transplantation. The primary diagnosis of intestinal failure had no impact on death rates and patients with short gut syndrome demonstrated decreased death rates in 2002. Analysis of donor age and its impact on death rate after transplant revealed that recipients of organs from donors between 11 and 17 years old and between 18 and 34 years old were associated with the lowest recipient death rates after intestine transplantation, 90 and 207 deaths per 1000 patient years, respectively. Recipients of organs from donors <1 year old had the highest annual death rate—447 in 2002.

Intestine transplant graft survival

Intestine graft survival rates, excluding multiorgan transplants other than liver–intestine, were calculated at 3 months and at 1, 3 and 5 years after transplantation. Cohorts are transplants performed during 2001–2002 for 3-month and 1-year survival; 1999–2000 for the 3-year and 1997–1998 for 5-year survival. The adjusted graft survival rates (adjusted to the characteristics of the 3-month and 1-year cohort) were 81% at 3 months, 66% at 1 year, 48% at 3 years and 34% at 5 years (Figure 23). As was true last year, no definite trends by age or gender could be identified, but African American recipients had poorer graft survival rates at all time points. The underlying primary diagnosis did not appear to affect outcome; however, the category listed as 'other' demonstrated the highest survival rates at all time points. This may reflect the fact that a majority of these patients having underlying benign abdominal tumors requiring transplantation, a population rarely demonstrating liver failure at the time of transplantation.

Unadjusted graft survival rates in 2003 were 84%, 69%, 47% and 30%, at 3 months and at 1, 3, and 5 years, similar to the adjusted survival rates. There has been some variability in unadjusted early 3-month allograft survival from 73% in 1994 to a nadir of 67% in 1998 and then to 86%

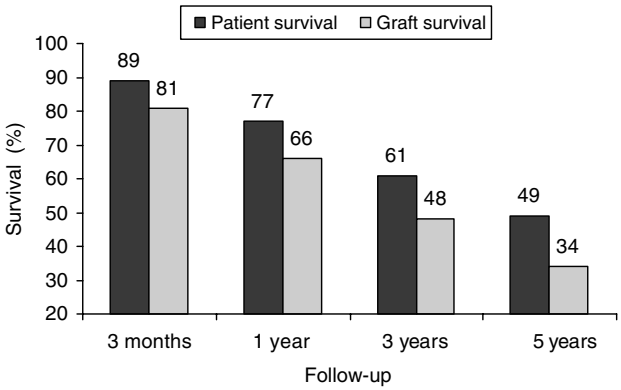

Figure 23: Adjusted patient and graft survival, intestine transplants. Adjusted for recipient age. Source: *2004 OPTN/SRTR Annual Report,* Tables 10.8 and 10.11.

in 2003. The 1-year graft survival increased from 60% in 1994 to 69% in 2002; 3-year survival improved from 41% in 1994 to 52% in 2000; and 5-year survival improved from 27% in 1994 to 36% in 1998. While improved graft survival with longer-term follow-up is evident, this was not specific to recipient gender, age or blood type. African American recipients at all time points tended to fare worse than white or other/multirace recipients, as did patients undergoing retransplantation. The 3-month graft survival rates among sicker patients were inferior: 89% if not hospitalized; 73% if hospitalized; 48% if in an intensive care unit and 0% if on life support at the time of transplant. No major effects of donor age or center volume could be identified.

Intestine transplant patient survival

Adjusted patient survival rates after intestine transplantation were 89% at 3 months, 77% at 1 year, 61% at 3 years and 49% at 5 years. (Figure 23) The younger pediatric patients <1 year and 1–5 years old, as well as the older adult patients 35–49 and 50–64 years old, had poorer survival rates than other groups. The best survival rate was seen for the 6–10 year old group. No differences were seen by gender. As with graft survival, patient survival was highest among those with a diagnosis other than short gut syndrome or functional bowel disorders and African Americans demonstrated slightly lower survival rates at all time points after transplantation than white recipients. Unadjusted analyses demonstrated similar differences in survival by age at transplant, but no differences according to gender, blood type, ethnicity or residency were seen where adequate data were available for analysis. African American patients were again shown to have inferior survival rates at all time points. Patient survival at 3 months was not affected as was graft survival by severity of recipient illness at the time of transplant. Patients with a primary diagnosis of 'other' had improved short- and long-term survival compared to patients with short gut or functional bowel problems. Centers performing between two and seven transplants per year had better outcomes than those performing eight or more. This suggests that intermediate-size centers can achieve comparable patient and graft survival rates, and that the volume criteria currently required for Medicare approval might need to be re-evaluated. Adult donors between 18 and 34 years old were associated with the best survival rates while the age of pediatric donors had no influence on outcome.

Prevalence of intestine transplant recipients with functioning allografts

The prevalence of people living with functioning intestine allografts continued to rise in 2003 to 361. Children 1–5 years old made up the largest group (33%) and recipients younger than 18 made up 63% of the total. Those with functioning grafts were far more likely to be blood type O or A and only 7% had a prior intestine transplant. Most (65%) had not been hospitalized at the time of transplantation, only 11% had been in an intensive care unit and 3% were on life support at the time of transplant. Short gut syndrome was by far the most common diagnosis (75%), compared to 18% for functional bowel problems and 7% for other.

Intestine allocation policy update

In 2003, no significant intestine allocation policies or governmental regulatory steps were implemented. However, the OPTN Liver and Intestinal Committee recommended to liver regional review boards that all patients listed for intestine transplants who also required liver transplant be accorded 12 extra MELD/PELD points. For the approved policy that is still awaiting implementation pending computer programming, this recommendation was revised to instead give points corresponding to a 10% increase in the 3-month mortality risk. It is expected that this new system of augmented points will be implemented in the coming year and its ability to accurately predict waiting list deaths will then need to be prospectively validated. In the meantime, allocation for combined liver–intestine transplantation continues to occur with livers allocated by the liver list in the majority of circumstances.

Summary

The liver transplant community continues to struggle with not having enough livers to transplant everyone who needs one. We all continue to be frustrated as we watch our patients deteriorate and die waiting. The MELD/PELD allocation system, however, has resulted in significant improvements, even though challenges remain. The continued rise in liver transplant registrants has slowed and the time to transplant has decreased markedly, reflecting the emphasis of the MELD/PELD system on transplanting sicker patients first, which has de-emphasized waiting time (while, interestingly, decreasing it overall) and eliminated the incentive to list patients in order to accrue waiting time. The continued growth in the proportion of inactive patients on the list is of concern and warrants further analysis and discussion. The proportion of patients dying on the list or being removed from the list illustrates the continued need for more livers to transplant. The ability of MELD/PELD to predict waiting list mortality was again confirmed. The trends toward the listing and transplanting of older patients mirrors those for renal transplantation. Adult living donor liver transplants continued to decrease in frequency in 2003, reflecting concern over the risk of donor morbidity and mortality. Since the implementation of MELD/PELD, the percentage of patients in the intensive care unit or on life support at the time of transplantation has declined markedly. This suggests that MELD/PELD has been successful in identifying those patients at greatest risk for hepatic decompensation and liver-related death and selected the majority of these patients for transplantation prior to their need for intensive care unit care.

Patient and graft survival rates remain excellent even among patients with higher MELD scores. Future analyses

will need to differentiate survival based 'lab' versus 'exception' MELD scores. The lower patient and graft survival rates for patients with low MELD scores may reflect the use of expanded criteria donors for this population; based on data showing less risk of death on the list than with a transplant in patients with MELD <15, this practice needs to be reconsidered by all centers even while minimal listing criteria are being decided upon. Continued review of the MELD/PELD system, including the granting of exceptions by regional review boards, has shown that the system appears to be working well, but further refinements including a national review board are being considered. Hyponatremia is being examined as a way of identifying patients with intractable ascites who may have a waiting list mortality that is higher than would be predicted by their MELD score. Finally, it is gratifying that there are now nearly 34 000 patients alive with functioning livers in the United States.

Intestine transplantation is performed with slowly increasing frequency and success. Surgeons increasingly perform this procedure with short cold ischemia times, which appears to correlate with improved long-term allograft survival. The population of patients receiving and being listed for these transplants remains largely young, and younger organs tend to correlate with better outcomes. Early graft losses and rejection rates have changed little since 1994, but rejection is easier to control, and long-term survivals are improving. Newer immunosuppressive agents such as daclizumab and sirolimus are being used frequently, for both induction and delayed maintenance therapy. Diagnoses other than short bowel syndrome and functional bowel disorders are associated with the highest survivals, and more attention should be paid to defining these disease categories in the future.

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