American Journal of Transplantation 2008; 8 (Part 2): 958–976
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2008.02174.x

Liver and Intestine Transplantation in the United States, 1997–2006

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Liver transplantation in 2006 generally resembled previous years, with fewer candidates waiting for deceased donor liver transplants (DDLT), continuing a trend initiated with the implementation of the model for end-stage liver disease (MELD). Candidate age distribution continued to skew toward older ages with fewer children listed in 2006 than in any prior year. Total transplants increased due to more DDLT with slightly fewer living donor liver transplants (LDLT). Waiting list deaths and time to transplant continued to improve. In 2006, there also were fewer DDLT for patients with MELD <15, fewer pediatric Status 1A/B transplants and more transplants from donation after cardiac death (DCD) donors. Adjusted patient and graft survival rates were similar for LDLT and DDLT. This article also contains in-depth analyses of transplantation for hepatocellular carcinoma (HCC). Recipients with HCC had lower adjusted 3-year posttransplant survival than recipients without HCC. HCC recipients who received pretransplant ablative treatments had superior adjusted 3-year posttransplant survival compared to HCC recipients who did not. Intestinal transplantation continued to slowly increase with the largest number of candidates on the waiting list since 1997. Survival rates have increased over time. Small children waiting for intestine grafts continue to have the highest waiting list mortality.

Key words: Deceased donors, donation after cardiac death (DCD), hepatocellular carcinoma (HCC), intestine, liver waiting list, living donors, MELD, organ donation, PELD, SRTR, waiting list

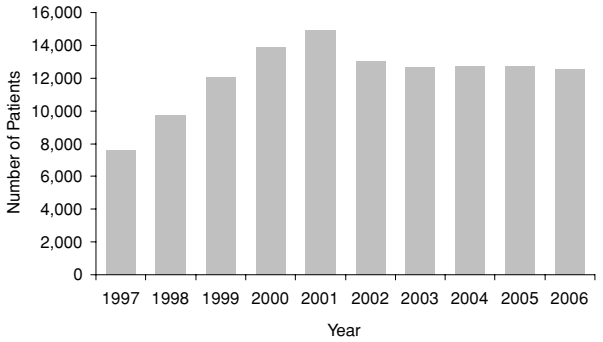
Introduction

The allocation of deceased donor livers for transplantation in the United States has undergone a major transformation since implementation of the model for end-stage liver disease (MELD) and the pediatric model for end-stage liver disease (PELD). February 27, 2007, marked the 5-year anniversary of MELD/PELD, and data collected during the past 5 years allow for assessment of the system after transplant professionals have adjusted to and accumulated experience with it. In addition to the documentation of trends in the liver waiting list, deceased and living donor transplant recipients, and posttransplant outcomes, special sections on donation after cardiac death and patients with hepatocellular carcinoma are included. Intestinal transplantation is commonly performed in combination with other organs, most often with liver or liver and pancreas, and has continued to offer options for individuals with intestine failure. Trends in intestinal transplantation are described in the article following liver transplantation.

Liver waiting list

At the end of 2006, 12 548 patients were active on the liver transplant waiting list, a slight decrease from 2005 (Figure 1). The number of patients on the liver waiting list between 2003 and 2006 was roughly constant, differing by less than 250 persons from year to year. It is likely that the implementation of the MELD/PELD system for deceased donor liver allocation in 2002 precipitated the end of steady annual increases in the size of the waiting list with a one-time decrease from 14 893 in 2001 to 13 036 in 2002. Allocation of livers based on disease severity rather than waiting time has removed the incentive to list relatively healthy patients early solely to accumulate waiting time.

Age, race/ethnicity, gender and blood type: The liver waiting list continued its aging trend in 2006. Adults aged 50 and older represented 72% of the waiting list, compared to 70% in 2005 and 48% in 1997. The proportion of pediatric candidates continued to decline and comprised only 3% of the list in 2006 compared to 4% in 2005 and 7% in 1997. A similar declining trend was observed for younger adults. The racial/ethnic distribution of the waiting list in 2006 was almost identical to 2005, with 72.4% white (71.8% in 2005), 6.4% African American (6.8% in



Source: *2007 OPTN/SRTR Annual Report*, Table 9.1a.

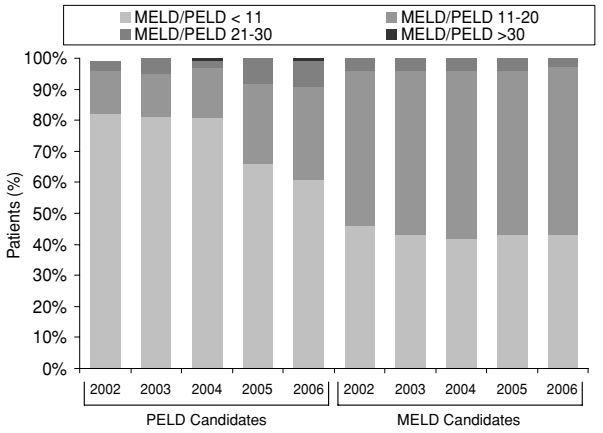
Figure 1: Number of candidates on the liver waiting list, active at year-end, 1997–2006.

2005), 15.9% Hispanic (16% in 2005), 4.7% Asian American (4.7% in 2005) and 0.7% other (0.7% in 2005). As in past years, men outnumbered women on the waiting list (males 61%, females 40%). The distribution of blood types among waiting list candidates was similar to previous years; 50% had blood group O, 38% had blood group A, 11% had blood group B and 2% had blood group AB. Compared with the late nineties, there were fewer candidates who were female, had blood type O or had previous liver transplants.

Primary diagnosis at listing and previous transplant: The distribution of liver transplant candidates across the major diagnostic categories of liver disease in 2006 was similar to previous years. Noncholestatic cirrhosis was the largest diagnostic category with 73% of candidates on the waiting list. Cholestatic cirrhosis was the second largest grouping with 10%, followed by 'other' with 9%. Acute hepatic necrosis was the primary diagnostic category for 4% of the waiting list, while biliary atresia, metabolic diseases and malignant neoplasms each accounted for less than 2% of the waiting list. The fraction of the waiting list with a previous liver transplant was 3% in 2006, which was less than in the late 1990s.

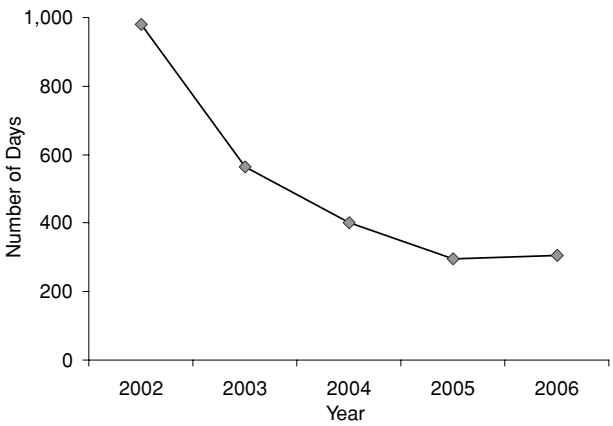
MELD/PELD scores: Distribution of MELD scores for adults on the waiting list has changed very little since the implementation of MELD/PELD in 2002 (Figure 2). At the end of 2006, 73% of all candidates had MELD scores <15, a fraction similar to previous years. Of those on the waiting list with PELD scores, slightly over 80% had PELD scores <11 from 2002 through 2004. On 12 January 2005, a change to allocation policy was implemented to use the adult MELD score for adolescents aged 12 to 17. This changed the composition of the PELD candidates group from those under age 18 (2002–2004) to those under age 12 (2005–2006). The fraction of PELD candidates with scores under 11 in 2005 was 66% and in 2006 it was even lower at 61%. Correspondingly, the fraction of children with PELD scores >11 has increased over time. In 2006, about 1% of children on the waiting list had PELD scores above 30.

Waiting time and median time to transplant: By the end of 2006, about 64% (17.5% waiting 1–<2 years and 46.6% waiting 2+ years) of the waiting list with active status had been listed for more than 1 year with almost 47% listed for more than 2 years. Figure 3 shows the median time to transplant (TT) among candidates on the waiting list that were initially listed in the given calendar year. The median time to transplant is calculated as the number of days until half of the new waiting list registrants in the calendar year have received a transplant. Median TT for liver waiting list candidates decreased substantially after the implementation of MELD/PELD in 2002 when the median TT was 981 days.



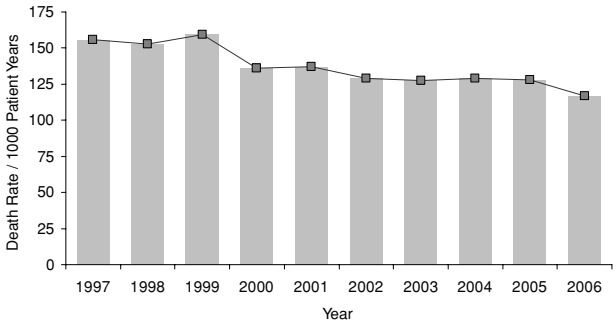
Source: *2007 OPTN/SRTR Annual Report*, Table 9.1a.

Figure 2: Distribution of MELD/PELD scores among candidates on the liver waiting list at year-end, 2002–2006.



Source: *2007 OPTN/SRTR Annual Report*, Table 1.5.

Figure 3: Median time to transplant (TT) for new liver waiting list registrations, 2002–2006.



Source: *2007 OPTN/SRTR Annual Report*, Table 9.3.

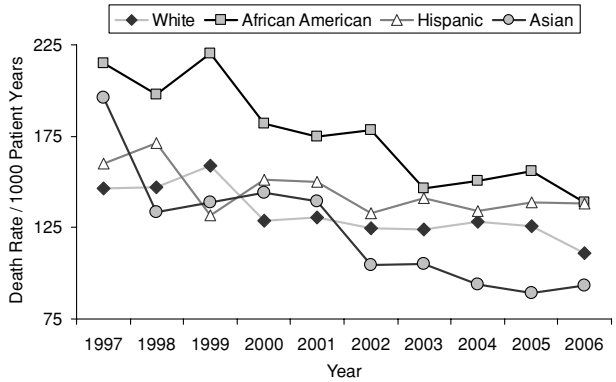
Figure 4: Unadjusted death rates per 1000 patient-years at risk, 1997–2006, liver waiting list.

In 2003, it decreased to 564 days and to 402 days in 2004. In 2005, it was a 10-year low of 296 days, and it remained roughly the same in 2006 at 306 days.

Death rates on the waiting list: The waiting list death rate (deaths per 1000 patient-years) declined in 2006 to 117 from 128 in 2005 (Figure 4) and varied according to demographic and medical factors. Patients older than 65 years carried a greater risk of death. However, children less than 5 years old carried a greater risk of death than older patients, while children less than 1-year old had the highest rate of all age groups (879 deaths per 1000 patient-years). All ethnic groups experienced declining death rates over the past 10 years (Figure 5). In 2006, Asian Americans had the lowest death rate on the waiting list at 93 (slightly higher than 2005's rate of 89), followed by whites with 111, down from 126 in 2005. Death rates for African Americans and Hispanics were similar at 139 and 138, respectively, and both were lower than 2005. In 2006, males and females had roughly the same rate with 116 for males and 118 for females, and both were lower than 2005.

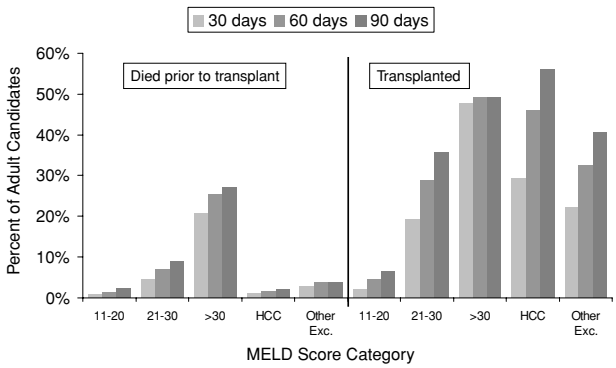
When stratified by diagnostic group, all disease etiologies had decreasing death rate trends over the past 10 years. In 2006, not surprisingly, acute hepatic necrosis had the highest death rate at 187, up slightly from 2005 when it was 171 but down 3-fold since 1997, likely a result of regional sharing (introduced in 1997 and 1998) and improved patient selection for placement on the waiting list. 'Other' diagnoses had the second highest death rate on the waiting list at 169, which was unchanged from the year before. The remaining categories were: 143 for metabolic disorders; 123 for malignant neoplasms; 109 for noncholestatic cirrhosis; 77 for cholestatic cirrhosis and 61 for biliary atresia. Waiting list death rates were extremely high for candidates listed as Status 1 A at 1299, even though this number is lower than 2005 (4833). As expected, death rates increased as MELD and PELD increased, from 34 for MELD scores 6–10 to 654 for MELD scores 21–30 and 3673 for MELD over 30. Likewise, waiting list death rates increased with increasing PELD scores from 18 for PELD <11, to 602 for PELD scores 21–30 and 2470 for PELD greater than 30. Patients with exceptions for hepatocellular carcinoma (HCC T2) had a death rate of 110, down from 152 in 2005, and those with exceptions for other diagnoses had a death rate of 150, compared to 119 in 2005.

Patient events on the waiting list: Figure 6 shows the incidence of transplant or death over the ensuing 3 months for adults on the waiting list on 1 January 2006, by MELD score category. Patients removed from the list as too sick to transplant are not included in the figure. By 30 days after 1 January less than 1% of candidates with MELD scores less than or equal to 11 at that time had either died (0.3%) or received transplants (0.7%). Similarly, very few patients with MELD scores in the 11–14 range died or received transplants (0.4% for death and 0.7% for transplant). Of those with MELD 15–20 on 1 January, 2% died and 5% received a transplant within 30 days. For candidates with MELD scores



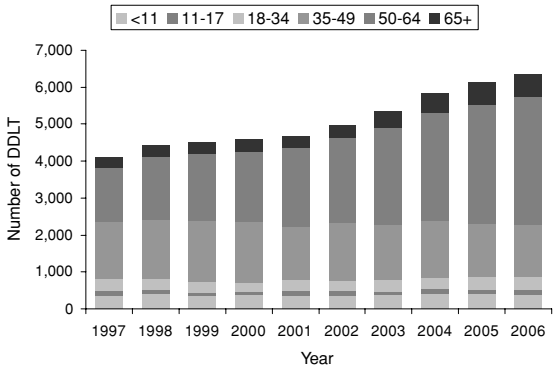
Source: *2007 OPTN/SRTR Annual Report*, Tables 9.3.

Figure 5: Unadjusted death rates per 1000 patient-years at risk, 1997–2006, liver waiting list by race/ethnicity.



Source: *2007 OPTN/SRTR Annual Report*, Table 9.2b. Uses laboratory MELD score.

Figure 6: Waiting list candidates with events within 30, 60 and 90 days after snapshot (1 January 2006) by MELD.



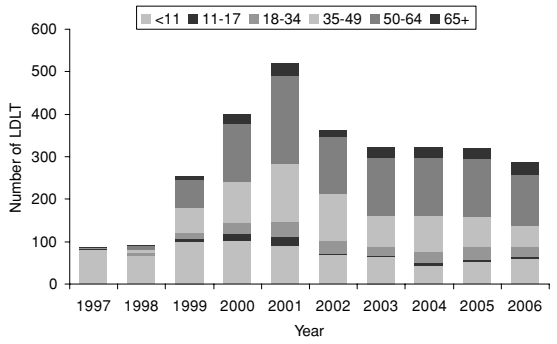
Source: *2007 OPTN/SRTR Annual Report*, Table 9.4a.

Figure 7: Number of deceased donor liver transplants by age, 1997–2006.

21–30, these fractions increased to 4% and 19% respectively. For patients in the highest MELD score group (MELD >30), approximately one fifth died, while almost half (48%) received transplants within 30 days. One percent of patients listed with HCC exceptions had died 30 days later and 29% received a transplant.

Liver transplant recipients: The total number of liver transplants performed in the United States continued to increase in 2006 to 6649, compared to 6441 in 2005. Of these, 96% were from deceased donors and 4% were from living donors. Compared with 2005, there were 242 more deceased donor transplants (DDLT) but 34 fewer living donor transplants (LDLT) performed.

Age: Figure 7 shows the age distribution for recipients of DDLT across the past decade. The number of pediatric (less than 18 years of age) deceased donor recipients has not changed much and was only 8% of all DDLT in 2006 (6% for children under 11 and 2% for children age 11–17).



Source: *2007 OPTN/SRTR Annual Report*, Table 9.4b.

Figure 8: Number of living donor liver transplants by age, 1997–2006.

The largest increase in adult DDLT since 1997 has been in the '50–64' and '65+' age groups, with DDLT declining slightly in the younger adult categories over the years.

Living donor liver transplant (LDLT) recipients have decreased in numbers since a peak of 520 transplants in 2001 (Figure 8). LDLT recipients' age distribution is considerably different from the DDLT recipient population. The majority of LDLT cases was performed for pediatric candidates in 1997 (97%), but by 2006 pediatric recipients were only 22% of the total. Adult-to-adult LDLT has increased from 3% of LDLT in 1997 to 78% of LDLT in 2006.

Gender, race/ethnicity, blood type and residence: Not surprisingly, the distribution of demographic factors such as gender, race/ethnicity and blood type among DDLT recipients in 2006 was very similar to the waiting list. More men received DDLT in 2006 than women, although, women comprised a higher proportion of LDLT (46%) than DDLT (34%). Proportionately, more African Americans (11%) and Hispanics (14%) and fewer whites (70%) received DDLT in 2006 compared to 2005 (white: 72%; African American: 10%; and Hispanic: 13%). Blood group distribution among DDLT and LDLT recipients did not change from 2005 to 2006. Over the previous decade, fewer DDLT were performed for nonresident aliens, 2.4% in 1997 and less than 1% in 2006.

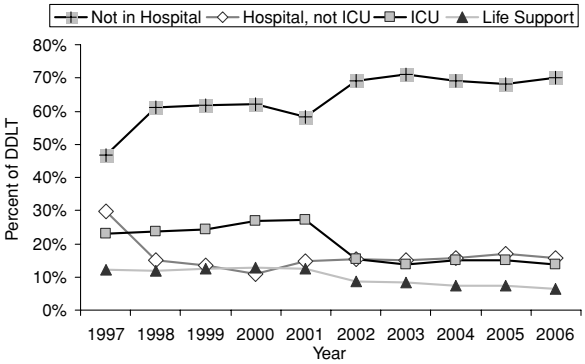
Insurance: The primary source of payment among DDLT recipients changed very little from 2005 to 2006. Most DDLT recipients had private insurance (59%), while Medicare paid for 19% and Medicaid paid for 17%. Other methods of payment were used by 5% of DDLT recipients. Compared with DDLT recipients, more LDLT recipients had private insurance at 69%, with fewer having Medicare (13%) or Medicaid (14%) coverage.

Previous transplant: The number of DDLT recipients transplanted in 2006 who had a previous liver transplant decreased slightly to 8.6% from 9% in 2005. The percentage of recipients in 2006 with a previous transplant was lower than any other year except 2004 (8.3%). Only five (2%) LDLT recipients in 2006 had a previous transplant, down from a high of 18 in 1999.

Diagnosis: Noncholestatic cirrhosis was the most frequent diagnosis in 2006 for both DDLT and LDLT. Among DDLT recipients, 60% had noncholestatic liver disease as their primary diagnosis in 2006, a slight decrease from 62% in 2005. The second most common diagnosis among DDLT recipients was malignant neoplasms, which increased to 10% in 2006 from 9% in 2005. This was the highest fraction of DDLT to candidates with malignant neoplasms in the past 10 years likely due to the

priority given to HCC candidates. The remaining diagnostic categories were: 'other' diagnoses (9%); cholestatic liver disease (9%); acute hepatic necrosis (6%); metabolic disorders (3%); and biliary atresia (2%). Acute hepatic necrosis and biliary atresia decreased from 2005, but the other categories increased. Distribution of diagnoses for LDLT recipients differed greatly from that of DDLT recipients. Noncholestatic cirrhosis was the most common diagnosis, as was the case for DDLT, but accounted for only 40% of LDLT recipients down from 46% in 2005. The second most common diagnosis was cholestatic liver disease at 23% in 2006, an increase from 21% in 2005. Reflecting the greater proportion of LDLT going to children under age 12, biliary atresia was the third most common diagnosis at 12%, an increase from 2005 (8%). The remaining diagnoses were: 9% for malignant neoplasms; 8% for 'other' diagnoses; 6% for acute hepatic necrosis; and 2% for metabolic disorders.

Medical condition: In 2006, a lower proportion of patients were in the intensive care unit (ICU) at the time of their DDLT (14%) compared with 2005 (15%). Over the last decade there has been a general trend toward decreased frequency for hospitalized and ICU-bound candidates at the time of transplant (Figure 9). The fraction of candidates emergently transplanted with deceased donor livers in the Status 1/1A category decreased from 19% in 1997 to 7% in 2006. Only 44 cases (0.7% of all DDLT) were transplanted as Status 1B (the relatively new medical urgency category for pediatric candidates with chronic disease implemented in late August 2005). Consistent with the recently implemented policies designed to direct more organs to higher MELD patients, such as Share 15, there has been a trend toward higher proportions of DDLT going to candidates with higher MELD scores and fewer transplants performed for candidates with MELD <15. The distribution of DDLT for pediatric patients remained relatively unchanged and evenly distributed across PELD strata with the highest proportion consistently in the PELD <11 category. Despite concerns of over-prioritizing patients with HCC, there was only a slight increase in 2006 in the proportion of transplants performed for patients with HCC exceptions from 14% in 2005 to 15%.



Source: *2007 OPTN/SRTR Annual Report*, Tables 9.4a.

Figure 9: Deceased donor transplant recipients by hospitalization status, 1997–2006.

Only 3% (8 cases) of LDLT were performed for patients on mechanical support, paralleling the trends for DDLT. Almost half (45%) of LDLT were performed for candidates with MELD scores <15 in 2006 representing a slight increase over past years. This likely represents the increasing proportion of LDLT done for adults compared with 5 to 10 years ago when the majority of LDLT was done for children.

Partial liver grafts and ischemia time for DDLT: The number of partial or split liver transplants among DDLT recipients declined to its lowest level in the past 10 years in 2006, when 178 patients received partial or split livers. This represented 3% of DDLT performed in 2006, down from 4% in 2004 and 2005 and 5% in 1997. There was a trend toward shorter cold ischemia time throughout the 1997–2006 period with more DDLT done with less than 10-h cold ischemia time (79%) in 2006 compared with previous years. This likely reflects improved placement and transportation of organs and improved surgical techniques.

Posttransplant death rates: The unadjusted death rate 1 year after transplant for patients receiving DDLT in 2005 was 165 deaths per 1000 patient-years, up somewhat from 153 deaths per 1000 patient-years in 2004 but similar to 167 deaths per 1000 patient-years in 2003. The 1-year death rates for patients transplanted in 2005 increased for most DDLT age categories, although two categories declined (ages 1–5 and 18–34). All age groups have had significant reductions in death rates compared with 1997. Child recipients under 1 year of age had the lowest death rate 1-year posttransplant at 88, which was higher than in 2004 when it was 59. DDLT recipients less than 50 years old had death rates lower than the overall rate, while those aged 50–64 had a death rate of 176 (up from 151 in 2004). The oldest recipients (65 and older) had the highest death rate during the first year following DDLT at 244. Among racial and ethnic groups, Hispanics had the lowest death rate at 148, which declined from 156 in 2004. Whites had a death rate of 162 in 2005, which was an increase from 150 in 2004. Asians and African Americans also saw increases in their death rates, with 195 for Asians and 195 for African Americans. Those identified as 'other' or multi-racial had the highest death rate in 2005 at 206. Women had a higher death rate than men at 180 compared to 158 for men, although both were higher than in 2004 (men: 150; women: 160).

Posttransplant death rates also varied by medical factors. In 2005 DDLT recipients with previous transplants (any organ) had a 1-year death rate of 384 deaths per 1000 patient-years, compared to 147 deaths per 1000

patient-years for those who had their first transplant in 2005. Recipients not hospitalized prior to their transplant in 2005 had a lower death rate at 123, compared to those in the hospital (not intensive care) at 200 and those in intensive care at 356. Those on mechanical support at the time of transplant in 2005 had a death rate of 457. The category 'other' had the highest death rate among primary diagnostic groups for DDLT in 2005 at 286, up from 177 in 2004.

Acute hepatic necrosis had the next highest death rate at 214, which increased from 191 in 2004. Death rates for the other categories were: 172 for malignant neoplasms, 157 for noncholestatic liver disease; 145 for metabolic disorders; 124 for cholestatic liver disease and 73 for biliary atresia. These rates are all lower than in previous years, with the exception of noncholestatic liver disease, which increased (148 in 2004 to 157 in 2005). Over the past decade, patients with biliary atresia have had the most dramatic reduction in death rate from 257 for DDLT done in 1997 to 73 for DDLT done in 2005. Acute hepatic necrosis, malignancies and noncholestatic cirrhosis death rates also decreased since 1997; however, metabolic diseases have increased.

In 2005, patients receiving transplants at MELD scores of 15–20 had the lowest 1-year death rates for adults (90 deaths per 1000 patient-years). Patients transplanted at MELD 6–10 (159) and 11–14 (120) had higher death rates than MELD 15–20. The increased death rates for the lowest MELD categories may be due to the higher proportion of these patients receiving higher risk grafts. Generally, PELD patients had lower death rates than MELD patients. However, rates were similar at the high ranges of MELD/PELD scores (PELD>30: 249 and MELD>30: 272). Recipients with exceptions for HCC Stage 2 (T2) had death rates slightly lower than the MELD 21–30 range nonexception patients (145 compared to 169) and have increased from 2002 through 2005. Patients receiving transplants with other exceptions in 2005 had death rates similar to HCC T2.

Since 1997, all DDLT donor age ranges have been associated with decreasing recipient death rates each year with the youngest donors conferring the lowest death rates for their recipient. For DDLT transplants performed in 2005, there was an increase in recipient death rates for longer cold ischemia times with almost a 2-fold higher death rate for DDLT with 16–20 h of cold ischemia time (229) compared with organs with 0–5-h cold ischemia time (129). There were too few organs transplanted with more than 21 h of cold ischemia time to reach meaningful results.

The unadjusted death rate for LDLT recipients overall also increased in 2005 to 126 deaths per 1000 patient-years from 85 deaths per 1000 patient-years in 2004. This may reflect the fact that a higher proportion of LDLT recipients were adults in the more recent years. Similar to DDLT, recipients of LDLT not hospitalized before their transplant had a lower death rate at 117 compared with hospitalized LDLT recipients (133). Those in intensive care had the highest LDLT rate (192) in 2005.

Liver transplant recipient survival: Among the most recent transplant cohorts for whom follow-up data were available, adjusted patient survival following DDLT was 94% at 3 months, 88% at 1 year and 79% at 3 years. Survival rates were adjusted for recipient age, gender, race, diagnosis and laboratory MELD/PELD score at transplant. Since the cohort for 5-year survival includes pre-MELD era transplant recipients, only survival for 3 months, 1 year and 3 years could be calculated with MELD as a covariate. The adjusted patient survival for LDLT was not statistically different from DDLT at 95% for 3 months ($p = 0.24$), 90% for 1 year ($p = 0.18$) and 82% for 3 years ($p = 0.08$). Adjusted graft survival was somewhat lower than the adjusted patient survival. For DDLT, graft survival was 90% at 3 months, 83% at 1 year and 74% at 3 years. These rates were not statistically different for LDLT with 89% at 3 months ($p = 0.65$), 83% at 1 year ($p = 0.92$) and 75% at 3 years ($p = 0.56$).

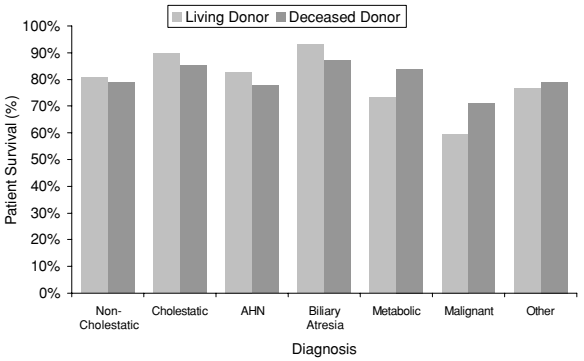
Age: Adjusted patient survival varies with the age of the recipient. Patient survival for recipients of DDLT at 3 months was highest for adolescents (age 11–17) at 97%, followed by those less than 1-year old (96%). The lowest survival was for the oldest age group (adults aged 65 and older) at 90%. For LDLT, those aged 65 and older had the lowest 3-month survival at 86%, followed by adults aged 50–64 at 94%. At 1 year, patient survival among DDLT recipients was lowest for those aged 65 and older at 80%, followed by adults aged 50–64 at 87% and highest for children under age 1 at 94% and adolescents aged 11–17 at 94%. LDLT recipients aged 65 and older also had the lowest survival rate at 1 year at 84%, followed by adults aged 50–64 at 86%. It was highest for adults aged 18–34 at 96%. At 3 years, the highest survival rate for DDLT was 90% for children less than 1 year old and for LDLT was 92% for adolescents aged 11–17. The lowest survival was for adults aged 65 and older for both types of transplants (DDLT: 70%, LDLT: 73%).

Race/ethnicity and gender: Adjusted patient survival varied with race. For DDLT, survival was similar across races at 3 months (between 91% and 94% for all groups) and 1 year (between 86% and 88% for all groups). Differences appeared at 3 years, with African American DDLT recipients having the lowest survival rate (74%) and Asians having the highest (82%). Among LDLT, African Americans had better survival than whites at 3 months (100% vs. 95%) and at 1 year (96% vs. 90%), but lower survival at 3 years (78% vs. 81%). Hispanic LDLT had the lowest

survival rate at 3 months (92%) and 1 year (86%), but the highest survival rate at 3 years (86%). Men and women who received DDLT had similar survival rates at 3 months (93% vs. 94%), 1 year (87% vs. 88%) and 3 years (79% for both). The results were similar for LDLT with 95% for both at 3 months, 89% for men and 91% for women at 1 year, and 81% for men and 84% for women at 3 years.

Medical factors: At 3 months, adjusted patient survival for DDLT among primary diagnosis categories at transplant was between 90% (acute hepatic necrosis) and 95% (cholestatic liver disease). For LDLT recipients, adjusted patient survival ranged from 100% for acute hepatic necrosis to 88% for metabolic disorders. At 1 year, the adjusted patient survival rates for DDLT were: biliary atresia (91%), cholestatic liver disease (90%), metabolic diseases (88%), noncholestatic cirrhosis (88%), acute hepatic necrosis (87%), 'other' disorders (86%) and malignant neoplasms (83%). For LDLT, adjusted patient survival at 1 year was slightly higher and a different pattern emerged: acute hepatic necrosis (96%), cholestatic liver disease (92%), 'other' diagnoses (92%), noncholestatic cirrhosis (89%), metabolic diseases (82%) and malignant neoplasms (76%). There were not enough data to estimate a 1-year rate for biliary atresia among LDLT.

Figure 10 shows 3-year adjusted survival rates by diagnostic categories for DDLT and LDLT. The distribution of adjusted survival rates for DDLT is similar at 3 years to 1 year: biliary atresia (87%), cholestatic liver disease (85%), metabolic disorders (84%), 'other' diagnoses (79%) and noncholestatic cirrhosis (79%), acute hepatic necrosis (78%) and malignant neoplasms (71%). Three-year patient survival for malignant neoplasms is significantly lower than all of the other diagnoses at $p < 0.001$. Patterns differed somewhat for LDLT. At 3 years, adjusted survival for LDLT from highest to lowest was: biliary atresia (93%), cholestatic liver disease (90%), acute hepatic necrosis (83%), noncholestatic cirrhosis (81%), 'other' diagnoses (77%), metabolic diseases (73%) and malignant neoplasms (60%). For LDLT, 3-year patient survival for malignant neoplasms is statistically significantly different from acute hepatic necrosis ($p = 0.02$), biliary atresia ($p < 0.001$), cholestatic liver disease ($p < 0.001$) and noncholestatic cirrhosis ($p = 0.01$). It is not statistically different from metabolic disorders ($p = 0.24$) or other diagnoses ($p = 0.10$).



Source: SRTR Analysis. Data as of May 2007. Rates adjusted to the means of the 3 month/1 year cohort of all liver transplants. Model includes MELD at transplant.

Figure 10: Adjusted 3-year patient survival of LDLT and DDLT recipients by diagnosis.

Over the previous decade, there has been a trend toward improving adjusted patient survival for each year of DDLT, although, more recently (in 2004 and 2005), there is a suggestion that this trend is leveling off. A similar trend in improving patient survival was observed in LDLT recipients over the previous year with no apparent plateau, perhaps indicative of the ongoing learning curve for the LDLT procedure. The prevalence of people living with a functioning liver transplant at the end of each calendar year continues to increase indicating the increasing impact of successful liver transplantation.

Donation after cardiac death (DCD) liver transplants

In 2006, the number of livers transplanted from DCD continued to increase numerically and proportionately, although the increase from 2005 to 2006 was less than in years past (Table 1). Since 2000, livers from DCD have come more frequently from donors who were: aged 18–49 years ($p < 0.001$); more often male ($p < 0.001$); more often white and less often African American or Hispanic ($p < 0.001$); and more likely to have anoxia and less likely to have stroke as a cause of death ($p < 0.001$) compared with donation after brain death (DBD) (Table 2). Over this same time frame, recipients of DCD livers were less often children ($p < 0.001$), more likely male ($p = 0.01$), and slightly more likely to be white than any other race/ethnic group ($p < 0.001$). They had slightly greater body mass index ($p < 0.001$), were less likely to be in the ICU or hospitalized

Table 1: Liver transplants using DCD donors and number of liver transplant programs that performed DCD liver transplants by year (1 January 2000 to 31 December 2006)*

Year of transplant	Total donors N	DCD donors N	DCD donors % of total	DCD liver TX programs N
2000	4407	39	0.9%	11
2001	4465	68	1.5%	20
2002	4697	76	1.6%	28
2003	5043	110	2.2%	38
2004	5458	178	3.3%	42
2005	5679	259	4.6%	54
2006	5849	277	4.7%	60
Total	35 598	1007	2.8%	78

*Excludes multi-organ transplants.
Source: SRTR Analysis, May 2007.

Table 2: Donor characteristics by deceased donor type (DCD vs. DBD) (1 January 2000 to 31 December 2006)*

	DBD		DCD		P-value DBD vs. DCD
	N	Percent	N	Percent	
Total	34 591	100.0%	1007	100.0%	
Age					<.001
Under 2	575	1.7%	4	0.4%	
2 to 5	619	1.8%	9	0.9%	
6 to 11	869	2.5%	23	2.3%	
12 to 17	2978	8.6%	96	9.5%	
18 to 39	12 335	35.7%	405	40.2%	
40 to 49	6355	18.4%	238	23.6%	
50 to 59	5801	16.8%	171	17.0%	
60 to 69	3367	9.7%	52	5.2%	
70 and older	1692	4.9%	9	0.9%	
Gender					<.001
Female	14 190	41.0%	350	34.8%	
Male	20 401	59.0%	657	65.2%	
Race					<.001
White	24 292	70.2%	859	85.3%	
Black	4964	14.4%	82	8.1%	
Other	1028	3.0%	19	1.9%	
Hispanic	4305	12.4%	47	4.7%	
Missing	2	0.0%	0	0.0%	
Cause of Death					<.001
Anoxia	4027	11.6%	294	29.2%	
Stroke	14 705	42.5%	223	22.1%	
Trauma	14 858	43.0%	427	42.4%	
Other	990	2.9%	63	6.3%	
Missing	11	0.0%	0	0.0%	

*Excludes multi-organ transplants.
Source: SRTR Analysis, May 2007.

($p < 0.001$), and more likely to have noncholestatic cirrhosis ($p < 0.001$) as their primary diagnosis than recipients of livers from DBD (Table 3). A higher percentage of DCD livers were shared compared with DBD grafts, and they were more likely to be used in transplants with identical blood type. Interestingly, the cold ischemia time did not differ between DCD and DBD livers ($p = 0.65$). A smaller proportion of DCD grafts were used for candidates with higher MELD/PELD scores compared with DBD livers, although these differences were modest (Table 4).

Previous reports have documented inferior liver graft survival for grafts procured from DCD donors compared with DBD organs (1,2). This updated analysis also found significantly inferior graft survival at 3-month, 1-year and 3-year time points (Figure 11). Covariates in these models included: all donor characteristics in Table 2; all recipient characteristics in Table 3 (plus diabetes); preexisting candidate malignancies; Status 1/1A/1B at transplant; recipient previous abdominal surgery; recipient pretransplant dialysis; MELD/PELD at transplant; recipient inotropic blood pressure support; history of portal vein thrombosis; hepatitis B positive; hepatitis C positive; partial or split liver graft; donor location; ABO compatibility and cold ischemia time. Thus, even with this extensive risk adjustment, the current data suggest that DCD liver grafts have inferior graft survival results.

We performed two different analyses to assess whether there is a learning curve effect for DCD liver transplantation. When examining eras (1 January 2000–31 January 2003 vs. 2 February 2003–31 March 2006) we found no significant difference in DCD outcome, and when examining center experience with DCD liver transplantation there was no difference among centers with varying levels of DCD graft use in adjusted analyses (data not shown).

Liver transplantation for candidates with HCC

The first liver transplants were performed for patients with extensive primary hepatocellular carcinoma (HCC) (3). Initial results were complicated by technical problems and early recurrences that dampened enthusiasm for treating malignancies with liver transplantation. In the mid 1990s, teams from France (4) and Italy (5) published excellent results for liver transplantation applied to patients with well-defined, early-stage HCC. The group from Milan found a low risk for HCC recurrence after liver transplantation for single tumors less than 5 cm in size, and up to three tumors with the largest being no larger than 3 cm (3). These 'Milan criteria' formed the basis of the HCC policy contained within the MELD-based priority system (6). In this policy, candidates with HCC meeting Milan criteria were

Table 3: Recipient characteristics by deceased donor type (DCD vs. DBD) (1 January 2000 to 31 December 2006)*

	DBD		DCD		P-value DBD vs. DCD
	N	Percent	N	Percent	
Total	34 591	100.0%	1007	100.0%	
Age					<.001
Under 1	798	2.3%	4	0.4%	
1 to 5	994	2.9%	6	0.6%	
6 to 11	525	1.5%	3	0.3%	
12 to 17	702	2.0%	8	0.8%	
18 to 24	723	2.1%	14	1.4%	
25 to 34	1280	3.7%	22	2.2%	
35 to 44	4069	11.8%	101	10.0%	
45 to 54	13 005	37.6%	406	40.3%	
54 to 64	9592	27.7%	325	32.3%	
65 and older	2903	8.4%	118	11.7%	
Gender					.01
Female	12 134	35.1%	313	31.1%	
Male	22 457	64.9%	694	68.9%	
Race					<.001
White	25 056	72.4%	784	77.9%	
Black	3298	9.5%	82	8.1%	
Other	1806	5.2%	25	2.5%	
Hispanic	4431	12.8%	116	11.5%	
Body mass index					<.001
Under 20	3300	9.5%	65	6.5%	
20 to 24	8294	24.0%	262	26.0%	
25 to 29	11 009	31.8%	341	33.9%	
30 plus	9501	27.5%	316	31.4%	
Missing	2487	7.2%	23	2.3%	
Medical condition					<.001
In ICU	6077	17.6%	119	11.8%	
Hospitalized	5062	14.6%	137	13.6%	
Not hospitalized	23 427	67.7%	751	74.6%	
Missing	25	0.1%	0	0.0%	
Mechanical support					.03
Not on mechanical support	31 491	91.0%	940	93.3%	
On mechanical support	3076	8.9%	67	6.7%	
Missing	24	0.1%	0	0.0%	
Previous liver-transplant					.02
No	31 516	91.1%	938	93.1%	
Yes	3075	8.9%	69	6.9%	
Diagnosis					<.001
Acute hepatic necrosis	2605	7.5%	52	5.2%	
Noncholestatic cirrhosis	21 429	61.9%	695	69.0%	
Cholestatic cirrhosis	3210	9.3%	85	8.4%	
Metabolic disorders	1155	3.3%	31	3.1%	
Malignant neoplasm	2436	7.0%	78	7.7%	
Other	3756	10.9%	66	6.6%	
Missing	0	0.0%	0	0.0%	

*Excludes multi-organ transplants.
Source: SRTR Analysis, May 2007.

allowed extra priority on the waiting list because their risk of cancer progression was estimated to be much higher than the mortality risk predicted by their laboratory-based MELD score. Initially, policymakers estimated that the cancer progression risk for patients with Stage 2 HCC was 30% at 3 months, which equated to a MELD mortality risk score of 29, and that the risk for Stage 1 HCC was 15%, equating to a MELD score of 24. Subsequent studies suggested that these progression risk estimates were too high and therefore policy was revised downward to remove extra priority for Stage 1 disease and reduce the HCC Stage 2 priority to a MELD score of 22, equivalent to a 15% risk of waiting list death. To our knowledge, this is the first comprehensive analysis of the effects of the HCC allocation policies within the MELD/PELD system to be published.

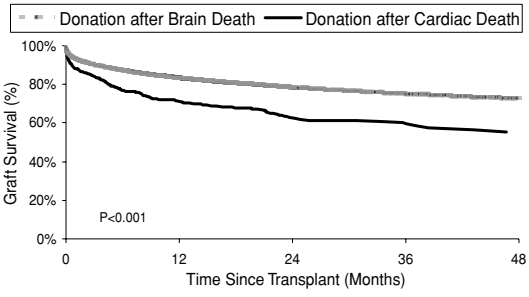
Table 4: Distribution of MELD/PELD score at transplant* by deceased donor type (DCD vs. DBD) (1 September 2001 to 31 December 2006)**

MELD/PELD at transplant	DBD		DCD	
	N	Percent	N	Percent
Under 10	3308	12.2%	102	11.0%
10 to 14	5189	19.1%	212	22.9%
15 to 19	6306	23.3%	249	26.9%
20 to 24	4521	16.7%	166	17.9%
25 to 34	4753	17.5%	124	13.4%
35 and higher	3044	11.2%	73	7.9%
Total	27 121	100.0%	926	100.0%

*Excludes multiorgan transplants.
**MELD/PELD data collection began 1 September 2001.
Source: SRTR Analysis, May 2007.

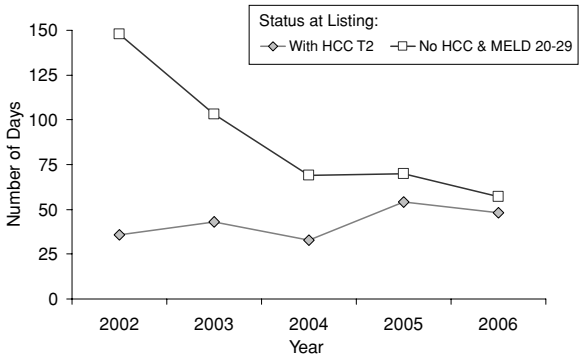
Waiting list and exception applications: With the implementation of the MELD-based liver allocation policy in 2002, 1421 candidates had applications for increased priority due to HCC, compared with 1644 HCC applications in 2006. Whites, blacks and Hispanics have similar fractions of candidates with HCC exclusion applications, and these proportions have stayed fairly steady across the 5 years. A higher percentage of Asian candidates applied for HCC exclusions than the other racial groups at 15% in 2002, falling to 12% in 2004 and at 13% in 2005 and 2006. Whites consistently represent the majority of HCC applications at 62% to 66% of all HCC applications in each year of the MELD era. The fraction of candidates within a region who had applied for an exclusion for HCC varied slightly, with all regions between 3% and 6% in 2002 and between 4% and 7% in 2006.

Figure 12 shows the median time to transplant (TT) for candidates with Stage 2 (T2) HCC exceptions and candidates with MELD scores 20–29 (M20–29) at listing. Since TT decreases with increasing MELD score, it is important to compare candidates with HCC T2 to non-HCC candidates with MELD scores in the range assigned by the HCC



*Adjusted for donor age, donor cause of death, donor race, donor sex, donor height, recipient age, recipient sex, recipient diabetes, recipient race, recipient diagnosis, recipient medical condition at tx, recipient status 1 at tx, pre-tx dialysis, need for pre-tx life support, recipient history of malignancy, recipient previous abdominal surgery, recipient body mass index, previous liver transplant, recipient MELD/PELD at tx, recipient inotropic blood pressure support, recipient history of portal vein thrombosis, recipient hepatitis B positive, recipient hepatitis C positive, blood type compatibility, regional/national tx, cold ischemia time, and partial/split liver tx.
Source: SRTR Analysis. Data as of May 2007.

Figure 11: Adjusted graft survival for DCD and DBD liver transplants, 1 September 2001 to 31 March 2006.

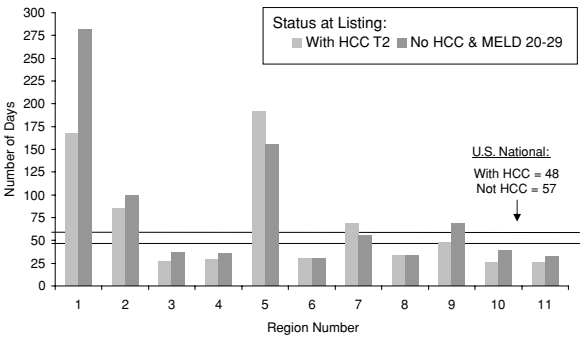


Source: SRTR Analysis. Data as of August 2007.

Figure 12: Median time to transplant (TT) for new liver waiting list registrations, HCC T2 exception and MELD 20–29 with no HCC exception, 2002–2006.

priority policy. Median TT for HCC T2 exception holders at listing has been fairly constant across time, ranging from a low of 33 days in 2004 to a high of 54 days in 2005, a difference of 3 weeks. In contrast, the median TT for M20–29 candidates has decreased dramatically since 2002, from almost 5 months (148 days) in 2002 to less than 2 months (57 days) in 2006. In 2006, the median TT of HCC T2 exception holders was 9 days shorter than the median TT of non-HCC, M20–29 candidates. Thus, at least by this measure of waiting list equity, the HCC T2 and M20–29 candidates seem to be gaining similar access to deceased donor liver transplantation in 2006.

Figure 13 shows the wide variation in median TT for HCC T2 candidates and for M20–29 candidates across the OPTN regions in 2006. The horizontal lines show the overall US median TT for each group. HCC T2 candidates' median TT ranged from a low of 26 days in Regions 10 and 11 to a high of 168 days in Region 1, while M20–29 candidates' median TT ranged from 30 days in Region 6 to 155 days in Region 5. In most regions, 50% of HCC T2 candidates received



Source: SRTR Analysis. Data as of August 2007.

Figure 13: Median time to transplant for new liver waiting list registrations, HCC T2 exception and MELD 20–29 with no HCC, by OPTN region, 2006.

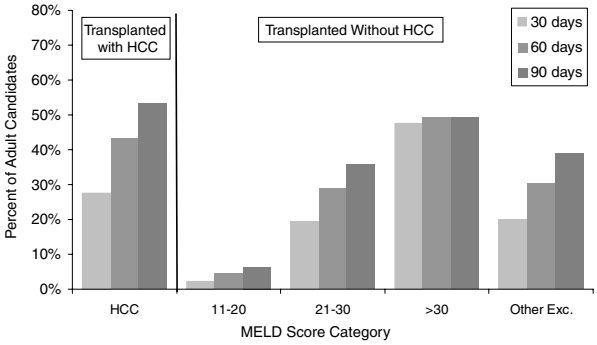


Figure 14: Waiting list candidates with and without HCC exceptions receiving liver transplants within 30, 60 and 90 days of snapshot (1 January 2006) by MELD.

transplants sooner than M20–29 candidates (7 regions), although the difference is small for several of these regions. Regions 6 and 8 have the same median TT for HCC T2 candidates and M20–29 candidates, while HCC T2 candidates wait longer than M20–29 candidates in Regions 5 and 7. These results (looking at M20–29 only, not HCC patients) indicate that there are considerable regional differences in the prioritization of candidates, likely due to different levels of organ availability, center listing and acceptance practices and regional review board policies and operations.

Analyzed another way, candidates listed as of 1 January 2006, with HCC exceptions (any HCC, not just T2) received transplants more frequently 30, 60 and 90 days later than candidates without exceptions who had MELD scores between 11 and 30, but had a similar fraction transplanted as candidates with MELD >30 (Figure 14). Unlike Figure 6, which looked only at death, Figure 15 looks at removal rates for death or being too sick for a transplant (which in the case of HCC, means cancer progression or so-called

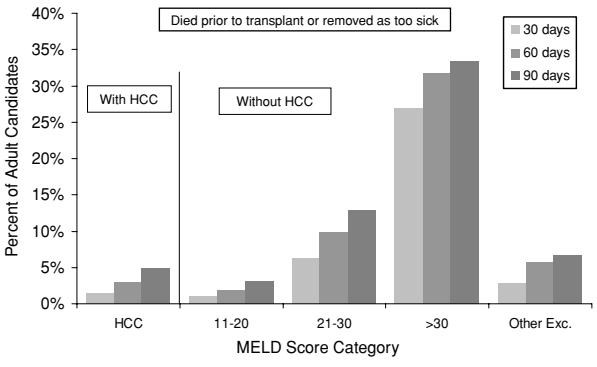


Figure 15: Waiting list candidates with and without HCC exceptions who died or were removed as too sick within 30, 60 and 90 days of snapshot (1 January 2006) by MELD.

waiting list 'drop out'). These 'drop out' rates were much lower for HCC candidates than for those non-HCC candidates prioritized by MELD without exceptions.

Table 5 contains unadjusted death rates per 1000 patient-years on the waiting list, overall and by race and region, for candidates with an HCC Stage 2 (T2) exception at listing and for a similar group without HCC exceptions, who had MELD scores between 20 and 29 (M20–29), inclusive. In this table, death includes death and removal from the waiting list for being too sick to transplant (but not removal for other reasons). Compared to M20–29 candidates, those with an HCC T2 exception at listing had somewhat lower death/removal rates, with a high of 360 in 2005 and a low of 174 in 2002, when the HCC exception was 29 rather than the current 22. M20–29 candidates had the highest death/removal rate on the waiting list in 2003 at 520, although it was similar in 2005 at 511. The lowest rate was in 2002 at 424. In 2006, those with an HCC T2 exception had a waiting list death/removal rate of 272 while M20–29 candidates had a death/removal rate of 431. Waiting list death/removal rates by race/ethnicity were lower for HCC T2 candidates than M20–29 candidates, except for Hispanics in 2006 where the death/removal rate for HCC T2 candidates was 444 and the rate for M20–29 candidates was lower at 426. HCC T2 and M20–29 rates were closer to each other among African Americans, especially before 2006 (African American waiting list death/removal rates, HCC T2 vs. M20–29: 2002: 346 vs. 380; 2003: no deaths among HCC T2 candidates; 2004: 552 vs. 587; 2005: 491 vs. 517 and 2006: 280 vs. 341). Waiting list death/removal rates vary by region, ranging from 88 to 642 in 2006 for those with HCC T2 exceptions at listing and from 312 to 659 for M20–29 candidates. Three regions actually had higher waiting list death/removal rates for HCC T2 candidates than for M20–29 in 2006 (Region 6: 615 vs. 379; Region 7: 437 vs. 374 and Region 8: 642 vs. 337).

Treatment of HCC while waiting: Loco-regional treatment for HCC remains controversial. To date, no randomized control trials have been performed so there is no strong evidence indicating the benefit of these ablative treatments (AT) for reducing drop out rates, down-staging HCC lesions, or improving survival. Despite lack of convincing evidence, transplant programs have increasingly reported performing AT for waiting candidates (among those with HCC exceptions for any stage) over the last 5 years. Approximately 255 HCC candidates reported having AT in 2003 and more than 50% reported having AT in 2006. Trans-arterial chemo-ablation (TACE) is gradually gaining favor and there was a slight trend toward fewer cases of radiofrequency ablation (RFA) reported in 2006 (Figure 16).

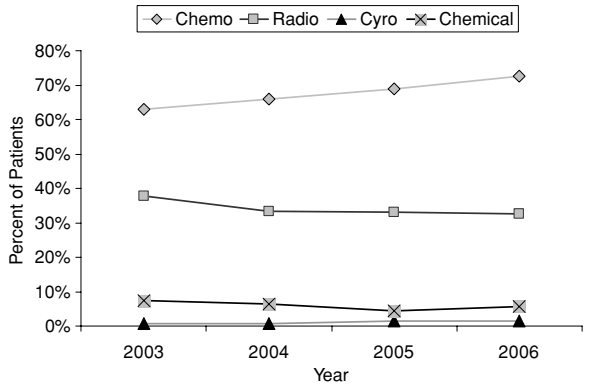
The reporting of ablation did not vary greatly across demographic groups (Table 6). Older individuals had more ablation reported than average (65% for age 65+ vs. 55%

Table 5: Unadjusted annual death rates† per 1000 patient-years at risk for candidates with HCC exceptions and with MELD 20–29 on the waiting list, 2002 to 2006

	With HCC T2 exception					Without HCC & with MELD 20–29				
	2002	2003	2004	2005	2006	2002	2003	2004	2005	2006
Total	174	261	292	360	272	424	520	494	511	431
Race/Ethnicity										
White	173	299	257	393	257	383	517	484	508	440
African American	346	–	552	491	280	380	421	587	517	341
Hispanic/Latino	104	319	631	341	444	695	550	530	636	426
Asian	202	192	62	181	152	392	663	360	185	371
Other/multi-race	–	–	–	–	–	929	1085	374	606	1673
Region										
1	439	139	240	329	111	452	409	466	384	485
2	119	103	276	431	323	438	452	532	409	345
3	202	512	300	267	175	419	661	796	812	650
4	141	–	382	349	223	457	571	455	637	312
5	157	233	186	230	311	365	485	435	522	425
6	437	–	–	–	615	332	830	429	280	379
7	–	270	207	719	437	268	543	430	389	374
8	–	519	877	327	642	491	614	429	515	337
9	179	583	525	250	88	652	601	631	622	528
10	1012	627	826	1415	320	633	704	344	573	659
11	837	712	218	497	181	343	313	467	396	354

Source: SRTR Analysis, May 2007.
†Death rates include death and removal as medically unsuitable or condition declined, too sick for transplant.
With HCC T2 exception = had an exception at listing for Stage 2 (T2) HCC.
Without HCC & with MELD 20–29 = never had an HCC exception and had MELD at listing of 20–29.
(–) = No deaths in category.

overall in 2006). Men had slightly more ablation than women, in 2006, 57% of men and 51% of women had ablation reported on their HCC exclusion application. Ablation appears to vary by race, with African Americans and Asians reporting more ablation than whites (in 2006: African American 63%, Asian 62% and white 55%), and Hispanics reporting less (47% in 2006). Those of other race had ablation reported for 80%, although there are very few candidates in that category. Most candidates had HCC in combination with another liver diagnosis. Of those with noncholestatic cirrhosis, 52% reported having ablation in 2006. The fraction receiving ablation was greatest for those with a primary diagnosis of malignant neoplasms. Reporting of ablation also varied across geographic (OPTN) region in 2006 from a low of 31% in Region 4 to a high of 65% in Region 5.



Source: SRTR Analysis. Data as of May 2007. Collection of ablation data began 4/2003.

Figure 16: Reported type of ablation among waiting list candidates with hepatocellular carcinoma exceptions, active at end of year.

HCC recipient characteristics: The proportion of deceased donor transplants to HCC candidates (any stage granted an exception, not just T2) has remained stable over the MELD era years (16–18%, see Figure 17). Only a small fraction of the transplants performed for HCC have been done with living donor grafts, in keeping with similar trends for nonmalignant liver transplant indications (Figure 18). Deceased donor transplant rates per 1000 patient-years for candidates receiving HCC exceptions are approximately three to four times higher than the rates for non-HCC patients (full range of MELD scores) (Table 7). Across racial groups in 2006, African Americans had the highest transplant rates per 1000 patient-years for both HCC candidates (1572) and non-HCC candidates (530), while Asians had the lowest (851 for HCC and 239 for non-HCC). For non-HCC candidates, 'other' race had the second-highest rate at 349, followed by whites (312) and Hispanics (279). For HCC candidates the order was: whites (1424), Hispanics (1124) and 'other' (1048). Transplant rates in 2006 for HCC candidates varied greatly across OPTN regions from a high of 3165 in

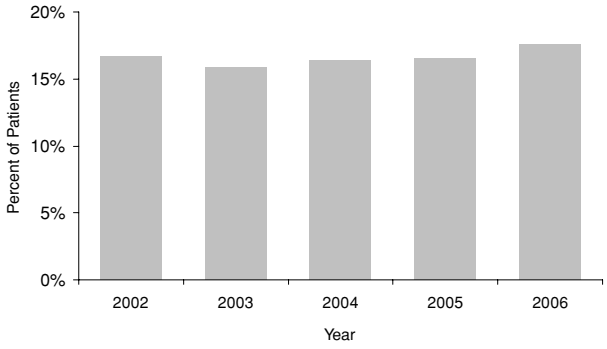
Table 6: Fraction of HCC exception waiting list candidates with reported ablation within demographic and clinical group

	2002	2003	2004	2005	2006
Total	958	977	872	781	614
Total with ablation	243	412	384	354	339
Percentage with ablation	25%	42%	44%	45%	55%
Age					
18–34 years	11%	30%	20%	13%	56%
35–49 years	24%	40%	37%	37%	50%
50–64 years	27%	44%	47%	47%	54%
65+ years	23%	40%	43%	48%	65%
Sex					
Female	27%	39%	40%	39%	51%
Male	25%	43%	46%	48%	57%
Race/ethnicity					
White	25%	40%	43%	43%	55%
African American	25%	45%	48%	51%	63%
Hispanic/Latino	26%	40%	44%	43%	47%
Asian	29%	53%	50%	56%	62%
Other/multi-race	20%	67%	60%	40%	80%
Primary diagnosis					
Noncholestatic cirrhosis	27%	42%	44%	45%	52%
Cholestatic liver disease	21%	25%	22%	20%	21%
Acute hepatic necrosis	13%	0%	0%	0%	0%
Biliary atresia	0%	90%	89%	100%	100%
Metabolic diseases	14%	50%	60%	50%	40%
Malignant neoplasms	21%	71%	62%	63%	72%
Other	18%	34%	49%	47%	63%
Unknown	25%	33%	45%	32%	59%
Region					
1	35%	48%	59%	50%	51%
2	17%	30%	34%	37%	63%
3	13%	21%	32%	29%	50%
4	24%	38%	40%	37%	31%
5	29%	52%	53%	56%	65%
6	25%	24%	46%	28%	40%
7	20%	37%	39%	41%	50%
8	31%	45%	43%	49%	59%
9	27%	36%	37%	46%	45%
10	7%	10%	15%	25%	42%
11	35%	56%	45%	47%	64%

Source: SRTR Analysis, May 2007.

Region 3 to a low of 683 in Region 1, as did transplant rates for non-HCC candidates from a high of 829 in Region 3 to a low of 139 in Region 1.

Graft and patient survival: Figure 19 and Figure 20 show adjusted graft and patient survival for HCC and non-HCC recipients when MELD at transplant and other covariates are included in the survival models. The cohort used to calculate 5-year survival includes pre-MELD era transplants. Therefore, 5-year survival cannot be calculated at this time. Graft survival is higher for recipients with HCC than those without HCC at 3 months (92% vs. 90%, $p < 0.001$), the same for HCC and non-HCC recipients at 1 year (83% for both, $p = 0.71$) and lower for HCC recipients than non-HCC recipients at 3 years (70% vs. 75%, $p < 0.001$). Patient survival is the same

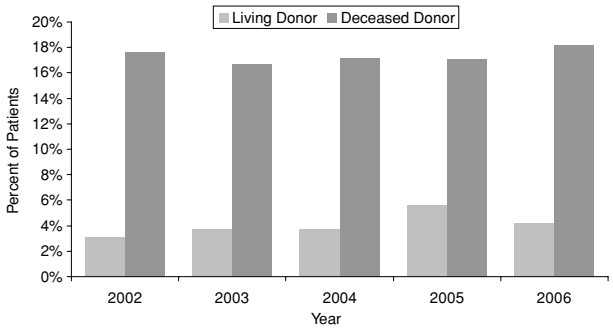


Source: SRTR Analysis. Data as of May 2007.

Figure 17: Percentage of all liver transplants to candidates with HCC exceptions.

at 3 months (94% for both, $p = 0.65$) but significantly higher for non-HCC recipients at 1 year (88% vs. 85%, $p = 0.003$) and 3 years (81% vs. 74%, $p < 0.001$). It is also informative to compare survival of HCC T2 recipients to that of non-HCC recipients with MELD scores similar to the HCC exception level. HCC T2 recipients had greater survival at 3 months than MELD = 29 recipients, but was not statistically different than MELD = 22 or MELD = 24 recipients (at 3 months, 1 year or 3 years, data not shown) or MELD = 29 recipients at 1 year or 3 years.

Consistent with an increasing proportion of HCC candidates being treated with AT before transplant, there is an increasing fraction of transplant recipients with any ablation treatment reported, and Figure 21 shows the type of AT among those reporting any AT. Recipients with HCC exceptions for whom an AT was reported have similar patient and graft survival at 3 months ($p = 0.33$ graft and $p = 0.48$ patient) and 1 year after transplantation ($p = 0.33$ and $p = 0.65$). However, at 3 years after transplant, recipients given AT have superior graft (76% vs. 71%, $p = 0.03$) and patient (79% vs. 75%, $p = 0.03$) survival, compared with HCC recipients for whom no AT was reported (Figure 22



Source: SRTR Analysis. Data as of May 2007.

Figure 18: Percentage of deceased and living donor transplants to candidates with HCC exceptions.

Table 7: Reported annual deceased donor transplant rates per 1000 patient-years at risk for candidates with and without HCC exceptions on the waiting list, 2002 to 2006

	With HCC exception					Without HCC exception				
	2002	2003	2004	2005	2006	2002	2003	2004	2005	2006
Total	769	819	936	1031	1296	253	282	300	312	319
Race/ethnicity										
White	803	848	996	1114	1424	250	282	296	311	312
African American	865	1027	1083	1318	1572	349	397	441	437	530
Hispanic/Latino	555	666	649	843	1124	238	241	261	266	279
Asian	861	741	930	720	851	204	198	252	260	239
Other/multi-race	1257	1617	1258	1740	1048	274	455	388	460	349
Region										
1	655	605	683	915	683	124	142	127	114	139
2	855	961	1048	1190	1416	247	259	266	271	256
3	1703	2095	2790	2485	3165	584	747	829	867	829
4	1250	938	1213	1482	2049	331	394	383	324	282
5	534	511	517	574	717	156	157	167	187	180
6	972	1555	2322	2038	3111	404	506	506	427	408
7	793	959	1030	1052	1329	188	255	258	300	311
8	764	808	1036	1594	1438	332	331	351	395	451
9	420	555	495	570	753	173	149	201	221	291
10	1184	2191	2858	2671	3083	445	652	809	781	635
11	765	854	1045	1318	2813	297	281	275	306	407

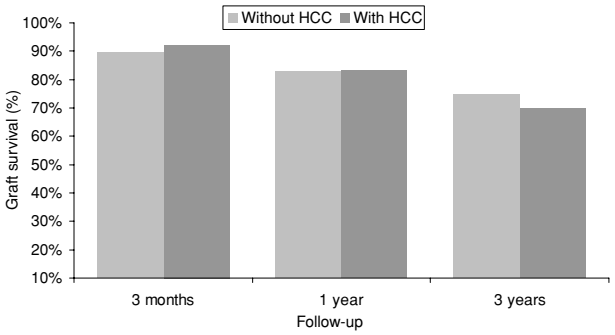
Source: SRTR Analysis, May 2007.
With HCC exception = granted an exception for HCC (any stage) at any time while on the waiting list.

and Figure 23). The reported type of ablation does not appear to have any association with improved or diminished patient or graft survival, although small sample sizes limit the precision of these estimates.

Continuing to use a portion of the deceased donor pool for liver transplantation for HCC remains controversial. Data presented above suggest, at least by some measures, that candidates receiving HCC exceptions have increased access to the deceased donor pool relative to their non-HCC counterparts and that there is considerable variation among the OPTN regions in this area (Table 7). For HCC candidates, a more evidence-based system should be developed to assess their need for liver transplant that better equates their risk of removal from the waiting list as too sick to transplant (i.e. the cancer is too widespread for transplant) with the risk of death for nonmalignant candidates. One such proposal, the HCC MELD score could meet this requirement. However, this will not equalize other geographic disparities among the regions. A move toward better standardization of regional review board processes might be required.

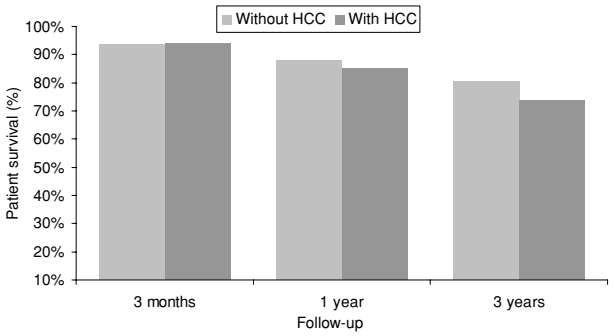
Summary

In terms of number of patients being treated and success rates, progress continues in all aspects of liver transplantation. Over the previous decade, patient and graft survival



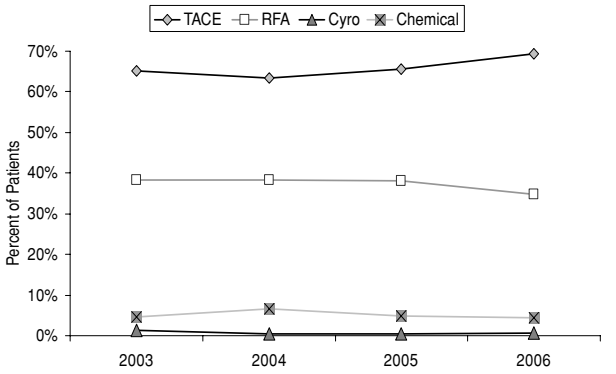
Source: SRTR Analysis. Data as of May 2007. Rates adjusted to the means of the 3 month/1 year cohort of all liver transplants. Model includes MELD at transplant.

Figure 19: Adjusted graft survival of liver transplant recipients with and without HCC exceptions.



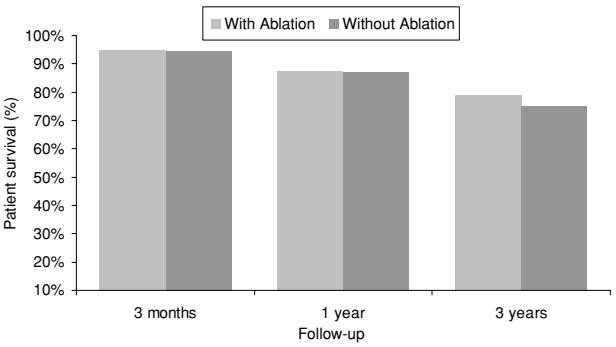
Source: SRTR Analysis. Data as of May 2007. Rates adjusted to the means of the 3 month/1 year cohort of all liver transplants. Model includes MELD at transplant.

Figure 20: Adjusted patient survival of liver transplant recipients with and without HCC exceptions.



Source: SRTR Analysis. Data as of May 2007. Collection of ablation data began 4/2003.

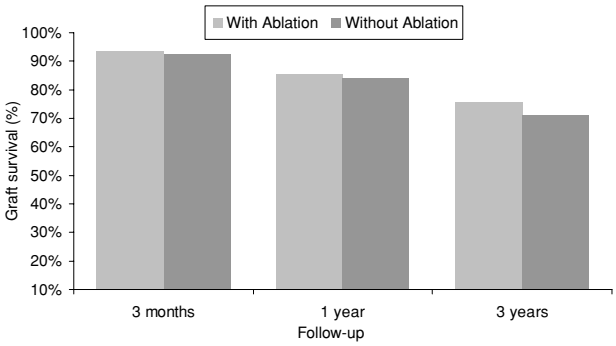
Figure 21: Reported type of ablation among transplant recipients with HCC exceptions.



Source: SRTR Analysis. Data as of May 2007. Rates adjusted to the means of the 3 month/1 year cohort of all liver transplants. Model includes MELD at transplant.

Figure 23: Adjusted patient survival of liver transplant recipients with HCC exceptions, with and without ablation reported.

rates remained unchanged, despite increasingly more ill and older candidates having received DDLT. Introduction of the MELD/PELD system has reduced waiting list deaths and waiting list numbers have also decreased due to the removal of waiting time as a driving force for priority. As a result, median times to transplant for patients prioritized by MELD/PELD have been significantly reduced. The current data suggest that LDLT outcomes are equal to DDLT when severity of candidate disease is accounted for in survival models. Wider application of DCD liver transplantation has increased access to transplantation, but the clearly inferior results with DCD liver grafts will need further monitoring. Given the very high waiting list mortality risk for patients with high MELD scores, continued application of DCD is justified for these candidates. But given the clear increased risk of graft failure for DCD livers, use of these grafts has to be weighed against the risk of dying on the waiting list without receiving a liver graft for each individual patient. Emerging evidence suggests that despite remaining geographic differences, previous adjustments in HCC priority policy have reduced some disparities in DDLT access among HCC and non-HCC candidates, but HCC candidates still enjoy much higher transplant rates compared with non-HCC patients.



Source: SRTR Analysis. Data as of May 2007. Rates adjusted to the means of the 3 month/1 year cohort of all liver transplants. Model includes MELD at transplant.

Figure 22: Adjusted graft survival of liver transplant recipients with HCC exceptions, with and without ablation reported.

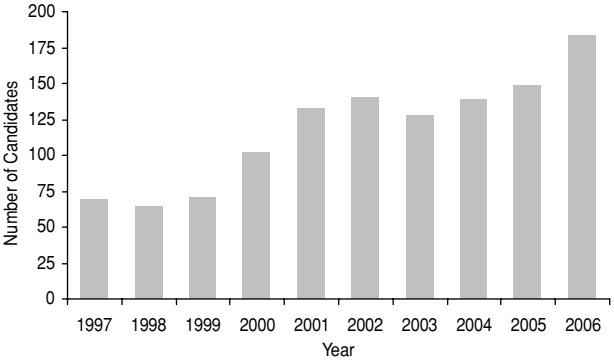
Intestine transplantation

Intestine transplantation has shown remarkable advancement over the past decade in not only volume of transplants performed but also in outcomes. There are many areas in which intestine transplant still lags behind other solid organ transplants. The OPTN and the Scientific Registry of Transplant Recipients (SRTR) Annual Report data analysis can be helpful in assessing results and areas of improvement. This is particularly true in regards to candidate listing, donor characteristics, recipient outcomes and immunotherapy. These topics, as highlighted by the data tables, will be discussed in this section.

Intestine waiting list

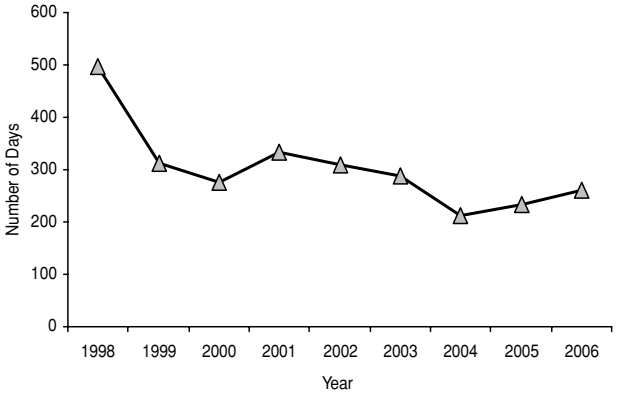
Candidates for intestine transplantation typically meet a defined set of criteria first published in 2002 (7). They must have irreversible intestinal failure with one or more complications associated with parenteral nutrition such as loss of central venous access, a history of severe and frequent catheter infections and parenteral nutrition associated liver disease either in a reversible or end-stage form. Other less common indications include severe pain/motility issues, complicated fluid and electrolyte management and panportosplenomesenteric venous thrombosis not amenable to standard surgical or medical management.

The OPTN/SRTR data set indicates that the number of candidates listed for the various forms of intestine transplantation has steadily increased from 87 candidates (70 active and 17 inactive) in 1997 to 236 candidates (183 active and 53 inactive) in 2006 (Figure 24). Overall, most of the characteristics of the intestine candidates active on the waiting list have changed little. Most candidates were under



Source: *2007 OPTN/SRTR Annual Report,* Table 10.1a.

Figure 24: Number of candidates on the intestine waiting list, active at year-end, 1997–2006.



Source: *2007 OPTN/SRTR Annual Report,* Table 1.5.

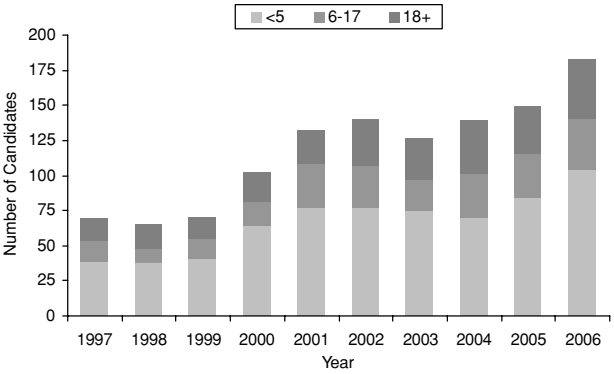
Figure 26: Median time to transplant (TT) for new intestine waiting list registrations, 1998–2006.

the age of 6 years (57%), white (66%) and male (60%) (Figure 25). The most substantial change in the waiting list characteristics over the past decade has been the percentage of candidates with a prior organ transplant—including intestine. This group has nearly tripled from 3% in 1997 to 14% in 2006. Although candidates diagnosed with short gut syndrome still represent the majority of waiting list primary diagnoses, the absolute percentage decreased from 77% in 1997 to 54% in 2006. There was no change in the percentage of candidates with the diagnosis of 'functional bowel problems' but percentages of candidates with 'other' diagnosis has increased from 9% to 32%.

The median time to transplant (TT) for new list registrations is one of the longest of any solid organ transplant (Figure 26), with the longest TT having been 496 days (1998) and the shortest TT was 212 days (2004). Currently, TT is 261 days (2006). While the TT does not appear to be dramatically influenced by ethnicity/race, gender and blood group, there are some differences. The median TT tends to be longer for males than females ranging between 306 to 411 days for men (2004 and 2005) and 179 to 199 for women.

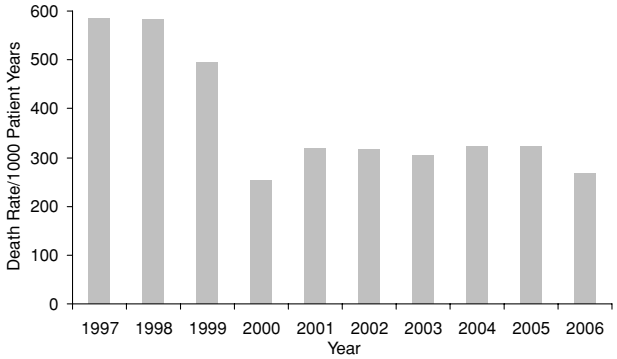
Despite the seemingly small numbers of intestine candidates on the waiting list, mortality remains high (Figure 27). This mortality rate, expressed as the death rate per 1000 patient-years at risk, is the highest among all solid organ transplants including the liver (Figure 4) (8). Overall, the death rate for intestine candidates has improved from its peak in 1997 at 586 to its current level of 265. The lowest death rate for intestine candidates was 253 in 2000. These rates are still more than double that for candidates of other solid organ transplants including kidney (70), pancreas alone (47), pancreas after kidney (31), kidney-pancreas (96), liver (115), heart (151), lung (97) and heart-lung (142).

For intestine candidates, the age groups with the highest waiting list mortality are: '1–5 year' (357), '35–49 year' (432) and '50–64 year' (373). Traditionally, the 'less than 1-year'



Source: *2007 OPTN/SRTR Annual Report,* Table 10.1a.

Figure 25: Number of candidates on the intestine waiting list by age, at year-end, 1997–2006.



Source: *2007 OPTN/SRTR Annual Report*, Table 10.3.

Figure 27: Unadjusted death rates per 1000 patient-years at risk for patients on the intestine waiting list, 1997–2006.

age group has had the worst problem with mortality rates ranging from 878 to 914 between 1997 and 2005. The data from 2006 indicate a mortality rate of only 99 (death rate per 1000 patient-years listed). However, given the small sample size in this age range, this statistic was based on 1 death among 39 candidates. Only time will tell if this is a sustainable improvement in survival or just a 1-year phenomenon due to random chance. Ongoing substantiation of these data is critical.

Race/ethnicity may also play a role in waiting list mortality. Whites and African Americans had mortality rates roughly similar to the total group, whereas Asians had a rate of 145 and Hispanics had the highest rate (399). Blood groups differed in mortality, with groups O and A having mortality rates roughly equal to the mean. Groups B and AB were higher than the mean at 319 and 338, respectively. The primary diagnosis also affected waiting list mortality rates with short gut syndrome and functional bowel problems having lower death rates (220 and 113, respectively) compared to 'other' and unknown with higher death rates (308 and 358, respectively).

These results have not gone unnoticed. In March 2003, the OPTN implemented several policy changes that a) gave combined liver-intestine candidates additional MELD/PELD points equivalent to 10% waiting list mortality risk at 3 months (Policy 3.6.4.7), b) allowed the liver to be allocated off the intestine list after regional Status 1 liver candidates are offered the organ (Policy 3.11.4) and c) allocated pediatric donor organs to pediatric recipients after Status 1 liver candidates are offered the organ (Policy 3.6). Since these policy changes have not led to a decrease in the intestine waiting list mortality, additional policy amendments were implemented in June 2007 including the addition of 23 extra MELD/PELD points to combined liver intestine candidates (Policy 3.6.4.7) (9).

Intestine procurement

Because waiting list mortality rates for intestine candidates are extremely high, it is important to focus on the intestine donor and increase the donor pool. It should be noted that based on these data sets there were 8024 deceased donors (of any organ) in the USA in 2006; this represents a 46% increase since 1997. During the same interval, there was a 156% increase in the number of deceased intestine donors up to an all time high of 184. There were also a few living-donor intestine transplants performed in 2006 (n = 3).

Intestine recipients

Overall, the number of intestine recipients has increased over the past decade. Intestine recipients include those that receive an isolated intestine graft as well as those that receive the intestine as part of a multi-organ graft complex. In 2006, there were 57 intestine alone transplants from deceased donors, representing a 171% increase since 1997 and 114 multi-organ transplants involving intestines. During the same interval, there was a 187% increase in the number of multi-organ transplants performed (n = 566). While the majority of these were kidney-liver (71%), organ combinations that include the intestine were the second most common. These included: kidney-liver-intestine (n = 1), kidney-pancreas-intestine (n = 1), kidney-pancreas-liver-intestine (n = 7), kidney-intestine (n = 1), liver-intestine (n = 35), pancreas-intestine (n = 9) and pancreas-liver-intestine (n = 60).

There have been few shifts in the demographic and medical characteristics of recipients over the past decade, although the percentage of recipients aged 1 year or less and 50–64 years increased, whereas the percentage of recipients between 1 and 10 years of age decreased. Females accounted for 40% of the waiting list candidates, and made up 52% of transplant recipients. The percentage of recipients with a prior intestine transplant decreased from 11% in 2005 to 9% in 2006. Private insurance providers covered 45% of recipients and public providers such as Medicare and Medicaid accounted for 8% and 39%, respectively. Remarkably, 64% of recipients were not hospitalized at transplant and the vast majority was not on mechanical support. Most recipients (70%) had a primary diagnosis of short gut syndrome with little change over the past decade. Ischemia times demonstrated an important trend, notably a decrease from 16% in 1997 to 3% in 2006 in cold ischemia time over 10 h. There has been a concomitant rise in the '0–5-h' group from 3% in 1997 to 18% in 2006. This represents a very positive trend, either indicating a more aggressive initiative of organ procurement organizations to identify and place intestine grafts or the emergence of intestine transplant programs.

Immunosuppressive practices have changed significantly since 1997. Use of any induction therapy was uncommon in 1997, with only 8% of transplant recipients reporting any induction therapy. By 2000, 69% of transplant recipients reported using induction therapy, with daclizumab (Zenapax, Roche, Nutley, NJ) being the most common induction agent, used in 55% of cases. In 2003 it shifted with 46% using rabbit antithymocyte globulin (ATG) (Thymoglobulin, Genzyme Corp., Cambridge, MA). By 2006, induction therapy was evenly distributed among muromonab-CD3 (OKT3, Orthobiotech, Bridgewater, NJ) (14%), rabbit ATG (18%), daclizumab (17%) and alemtuzumab (Campath-1H, Genzyme Corp., Cambridge, MA) (21%). Maintenance immunosuppression at discharge for intestinal recipients was mostly tacrolimus (Prograf, Astellas, Tokyo, Japan) and corticosteroids (53%). Recipients discharged after transplant on a steroid-free regimen were more likely to have received induction rabbit ATG or alemtuzumab. At 1-year posttransplant, intestine recipients were maintained with either tacrolimus alone (37%) or tacrolimus plus steroids (36%) indicating a wean of the maintenance immunosuppression regimen. For rejection therapy in the first year after transplant, intestine recipients received steroids in

86% of cases with antibody therapy added in 40%. The most common antibody therapy used for rejection was muromonab-CD3.

Intestinal transplantation results appear to be improving, particularly in the short term as demonstrated by these outcome measures—the death rate per 1000 patient-years at risk as well as the more commonly quoted patient and graft survival rates. Using the death rate per 1000 patient-years at risk in the first year after transplant, the overall rate for intestine recipients was 245 in 2006 (for transplants done in 2005). Based on this same measure, the groups of intestine recipients at higher risk for death are the: 'less than 1 year' age group (rate 447) and '35–49 year' age group (rate 315); whites (277); females (279); recipients of blood group O (293); those with a prior transplant of any organ (335); and those hospitalized prior to transplant (303 for hospitalized but not in the ICU and 360 for ICU). Recipients of donors less than 1 year of age had a much higher death rate (364).

Survival after intestinal transplantation has shown steady improvement since 1997. The 1-year adjusted graft survival has increased from 52 ± 6.3% in 1997 to 75 ± 3.4% in 2005. Similarly, the 1-year adjusted patient survival has improved from 57 ± 6.5% in 1997 to 80 ± 3.3% in 2005. To accurately analyze survival, it is important to separate intestine alone and liver-intestine transplants. For recipients of intestine alone, unadjusted patient survival was 81% for 1 year, 67% for 3 years, 54% for 5 years and 43% for 10 years. Graft survival during the same intervals was 73%, 54%, 37% and 23%. For comparison, patient survival for recipients of liver-intestine transplants was 76% for 1 year, 70% for 3 years, 58% for 5 years and 38% for 10 years, while intestine graft survival for the same intervals was 75%, 69%, 56% and 36%. There does not appear to be a significant difference between patient or graft survival when comparing intestine alone to liver-intestine. The lowest adjusted 1-year graft survival rates are seen in the groups aged '65+ years' and 'less than 1 year'; and the race/ethnicity group 'other/multi-race'. Despite these numbers, the number of recipients living with a functional intestine transplant is at its highest level (n = 514) since 1997.

Summary

As a field, intestinal transplantation has made great strides over the past decade. Still, there are major issues to address. Improving waiting list mortality risks for candidates on the intestine list is imperative. The current data are unacceptably high. Implementation of national organ allocation policies are underway to improve this situation, however, careful data analysis is needed to verify that these policy changes are an improvement. It is not all together clear as to why mortality rates are so high. Certainly, specific donor and recipient factors are involved, some of which have been identified through these data sets. Additionally, these data indicate the number of intestine transplants performed is at an all time high and would be expected to continue to increase. The optimal immunotherapeutic regimen is evolving and currently includes the use of induction agents. Although survival is lower than that typically seen after other solid organ transplants, survival after intestine transplantation is improving.

Conclusion

Overall, 2006 represented further progress in the field of liver and intestinal transplantation. More patients are receiving transplants in large part due to the success of the organ donation breakthrough collaborative. In addition, there is evidence that patients most in need of these life saving organs are more frequently getting access to these transplants since death rates on the waiting list are decreasing. These improved waiting list results have not been compromised by reduced survival rates. Geographic and demographic differences remain problematic, however, and should draw increasing scientific inquiry. Many challenges remain in the effort to continue improving the liver and intestine transplantation field.

Acknowledgments

The Scientific Registry of Transplant Recipients is funded by contract number 234–2005–37009C from the Health Resources and Services Administration (HRSA), US Department of Health and Human Services. The views expressed herein are those of the authors and not necessarily those of the US Government. This is a US Government–sponsored work. There are no restrictions on its use.

This study was approved by HRSA's SRTR project officer. HRSA has determined that this study satisfies the criteria for the IRB exemption described in the 'Public Benefit and Service Program' provisions of 45 CFR 46.101(b)(5) and HRSA Circular 03.

This article was produced as part of the 2007 OPTN/SRTR Annual Report. The Annual Report gathers information on many aspects of solid organ transplantation in one publication. More information can be found at www.ustransplant.org.

Note on sources: The articles in this report are based on the reference tables in the *2007 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: 1.1, 1.3, 1.13, 1.5-1.8, 9.1a, 9.2b, 9.3, 9.4a, 9.4b, 9.7a, 9.7b, 9.13a, 9.13b, 9.16, 10.1a, 10.3, 10.4, 10.6a, 10.6c, 10.6d, 10.6f, 10.6i, 10.7, 10.8, 10.9, 10.13 and 10.16. All of these tables may be found online at: www.ustransplant.org.

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