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Special Feature

Liver Transplantation in the United States, 1999–2008

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Changes in organ allocation policy in 2002 reduced the number of adult patients on the liver transplant waiting list, changed the characteristics of transplant recipients and increased the number of patients receiving simultaneous liver–kidney transplantation (SLK). The number of liver transplants peaked in 2006 and declined marginally in 2007 and 2008. During this period, there was an increase in donor age, the Donor Risk Index, the number of candidates receiving MELD exception scores and the number of recipients with hepatocellular carcinoma. In contrast, there was a decrease in retransplantation rates, and the number of patients receiving grafts from either a living donor or from donation after cardiac death. The proportion of patients with severe obesity, diabetes and renal insufficiency increased during this period. Despite increases in donor and recipient risk factors, there was a trend towards better 1-year graft and patient survival between 1998 and 2007. Of major concern, however, were considerable regional variations in waiting time and post-transplant survival. The current status of liver transplantation in the United States between 1999 and 2008 was analyzed using SRTR data. In addition to a general summary, we have included a more detailed analysis of liver transplantation for hepatitis C, retransplantation and SLK transplantation.

Key words: Deceased donors, deceased donor liver transplant, donation after cardiac death, hepatitis C, liver, liver transplant, living donors, living donor liver transplant, organ donation, Organ Procurement and Transplantation Network, organ procurement, retransplantation, Scientific Registry of Transplant Recipients, simultaneous liver–kidney, United Network For Organ Sharing

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Introduction

Adoption of model for end-stage liver disease (MELD) scores, pediatric end-stage liver disease (PELD) scores and further provision of priority scores for hepatocellular carcinoma (HCC) in 2002 reduced the number of adult patients on the liver transplant waiting list, changed the characteristics of transplant recipients and increased the number of patients receiving simultaneous liver–kidney (SLK) transplantation. During this period, the donor age increased, the retransplantation rates for hepatitis C (HCV) decreased, and the number of patients receiving grafts from either a living donor liver transplantation (LDLT) or a donation after cardiac death (DCD) donor decreased. In this review, we will summarize the current status of liver transplantation in the United States using our analysis of the Scientific Registry of Transplant Recipients (SRTR) data on patients transplanted between 1999 and 2008. In addition to providing a general overview of the current state of liver transplantation in the United States, three specific topics are addressed in detail, liver transplantation for HCV, retransplantation and SLK. We have attempted to avoid topics that were detailed in the previous 3 years (1–3). The data is presented as frequency, percentage or mean (±SEM) as appropriate. Survival rates were adjusted for age, sex, race and etiology of liver disease unless otherwise mentioned. The data provided are for patients who received grafts from deceased donors unless otherwise specified.

Liver Transplant Waiting List

The introduction of the MELD liver allocation system in February 2002 changed the dynamics of the liver transplant waiting list. As seen in Figure 1, between 2002 and 2008, the number of candidates remaining on the waiting list at the end of the calendar year decreased by 3.4%. During the same time period, the number of candidates with hepatitis C decreased marginally (5.9%) and the number of candidates with HCC increased by 108%.

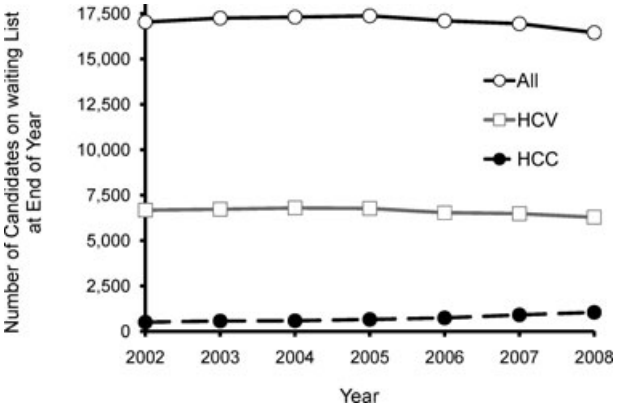


Figure 1: Number of candidates on the liver waiting list by the end of the calendar year.

MELD exception and scores

These scores were assigned to patients with mortality risk that was not adequately addressed by their MELD/PELD scores. In general, these groups have included candidates with HCC or other diagnoses. Candidates with HCC within the Milan criteria are awarded standard MELD exception scores with the intent to limit the risk of removal from the waiting list for cancer progression. Patients outside of the Milan criteria were awarded MELD exception scores only if approved by the appropriate Regional Review Board. Exceptions for indications other than HCC were also awarded through a Regional Review Board if a candidate's risk for death was not felt to be appropriately reflected by their laboratory MELD score.

As seen in Table 1, the number of candidates remaining on the waiting list with a MELD exception at the end of the calendar year increased from 382 in 2002 up to 890 in 2008. The proportion of standard HCC exceptions decreased from 69.6% in 2002 down to 44.6% in 2008, but the number of candidates on the waiting list at the end of the year with a nonstandard MELD exception for HCC increased considerably from 1.0% in 2002 to 20.6% in 2008. Between 2002 and 2008, the proportion of candidates on the waiting list at the end of the calendar year with other exceptions fluctuated between 29.3% and 41.4%, without any clear trends (Table 1).

The number of candidates with MELD exceptions remaining on the waiting list at the end of 2008 varied considerably between Regions with only 20 in Region 10 and up to 229 in Region 5 (Table 2). The proportion of candidates with a standard HCC MELD exception score ranged between 15.0% (Region 10) to 63.5% (Region 7). For example, for Region 10, 80% of the candidates with MELD exception scores on the waiting list at the end of 2008 were for indications other than HCC. In contrast, almost two of three exceptions for candidates in Region 7 were standard HCC MELD exceptions. The mean exception scores also ranged considerably between Regions. Between Regions, standard HCC exception scores for candidates on the waiting list at the end of 2008 ranged between 21.4 through 24.2 points and nonstandard (other) HCC exceptions ranged between 22 through 26.2 points. There was an even greater range for other exceptions (range of 19.1–28.5 points).

Removal from waiting list

The annual drop-out rates from the waiting list (number of patients removed for death or for being too sick per 1000 patient-years at risk) remained relatively stable over the decade as shown in Figure 2. Between 1999 and 2008, the number of patients alive on the waiting list at any time during the year ranged between 20 965 in 1999 and 26 695 in 2006. The drop out rate (removals for death or being too sick per 1000 patient-years at risk) was greatest in 1999 at 186.8 compared to 160.5 in 2008.

Liver Transplant Recipient Characteristics

The number of transplant recipients steadily increased from 4969 in 2002 to 6363 in 2006, but there was a decline in 2007 (n = 6228) and in 2008 (n = 6069) (Figure 3). During the same period, the number of transplant recipients with HCC increased steadily from 999 in 2002 to 1656 in 2008 (Figure 3). The retransplantation rates decreased during this period for both HCV positive (from 8% to 5%) and HCV negative (from 11–12% to 9%) recipients. The age and race distribution of patients who received deceased donor liver transplants is shown in Figure 4A, B.

MELD exception rates and scores

The distribution of HCC exception scores among liver transplant recipients between 2002 and 2008 is shown in Table 3. In 2002, 71.1% of liver recipients with exception scores received a standard exception for a T2 tumor, 15.3% received a T1 standard exception score and only 1.7% received an exception score for HCC other than a standard exception. In contrast, the number of patients transplanted with a nonstandard exception for HCC increased to 18.2% in 2008. From 2005, MELD exception scores were not

Table 1: Liver candidates on the waiting list at the end of the year with a MELD exception

	2002	2003	2004	2005	2006	2007	2008
N	382	485	490	535	599	755	890
Standard HCC (%)	69.6	57.7	52.9	54.2	53.4	53.4	44.6
Other HCC (%)	1.0	5.4	5.7	5.4	11.5	12.3	20.6
Other exceptions (%)	29.3	36.9	41.4	40.4	35.1	34.3	34.8

Table 2: MELD exceptions for candidates on the waiting list at the end of 2008 by Region

	Standard HCC exception	Other HCC exception	Other exception
Distribution by region (N)			
1 (66)	51.5%	25.8%	22.7%
2 (118)	44.9%	11.0%	44.1%
3 (48)	35.4%	2.1%	62.5%
4 (109)	44.0%	16.5%	39.4%
5 (229)	39.3%	39.7%	21.0%
6 (21)	23.8%	19.0%	57.1%
7 (85)	63.5%	5.9%	30.6%
8 (40)	55.0%	2.5%	42.5%
9 (127)	49.6%	24.4%	26.0%
10 (20)	15.0%	5.0%	80.0%
11 (27)	29.6%	3.7%	66.7%
Mean exception score received by region			
1	23.8	26.2	26.9
2	22.9	23.8	28.5
3	21.4	–	19.1
4	22.7	22.8	20.5
5	23.7	24.3	24.3
6	23.8	22.0	24.3
7	23.6	24.2	23.1
8	23.3	22.0	22.8
9	24.2	25.7	27.2
10	22.0	22.0	22.8
11	22.4	22.0	21.7

routinely given for T1 tumors, which led to a decrease in the proportion of liver recipients with a standard T1 exception in 2008 to only 0.4%. In 2002, 11.9% of the HCC recipients were transplanted without a MELD exception score and this increased to 18.8% in 2008.

Loco-regional therapy for HCC

The proportion of liver transplant recipients receiving loco-regional therapy prior to transplant has increased steadily from 2003 (37.3%) through 2008 (58.1%; Figure 5A). Transarterial chemoembolization (TACE) and radio-frequency ablation (RFA) were the most common modalities utilized (Figure 5B). Of the patients receiving pretransplant loco-regional therapy, the proportion receiving TACE increased from 65.7% in 2003 to 74.4% in 2008. Details regarding the type of TACE were not available. In contrast, the proportion of patients receiving RFA decreased from 38.1% in 2003 down to 32.1% in 2008. Other modalities, including chemical ablation and cryotherapy were used infrequently throughout all years from 2003 to 2008.

Waiting time

With the initiation of the MELD system for liver allocation in February 2002, the emphasis on waiting time had markedly diminished. As seen in Figure 6, the proportion of patients transplanted within 30 days of being listed was relatively steady between 1999 to 2001. While only 23% were transplanted within a month after listing in 2001, 29.2% were transplanted in 2002 after the introduction of the MELD score for organ allocation. This proportion of patients transplanted within 1 month increased to 39% in 2005 and decreased marginally to 36.8% in 2008. In contrast, the proportion of liver transplant recipients waiting for more than 6 months on the waiting list has generally decreased in the MELD era when compared to those transplanted before February 2002.

Considerable variation existed between waiting times for recipients in different Regions. As noted in Figure 7, only 42.8% of recipients waited 90 days or less in Region 5 compared to 70.9% of liver recipients in Region 3.

Comorbidities and renal insufficiency

The proportion of liver transplant recipients with significant comorbidities has increased over the decade (Table 4). In

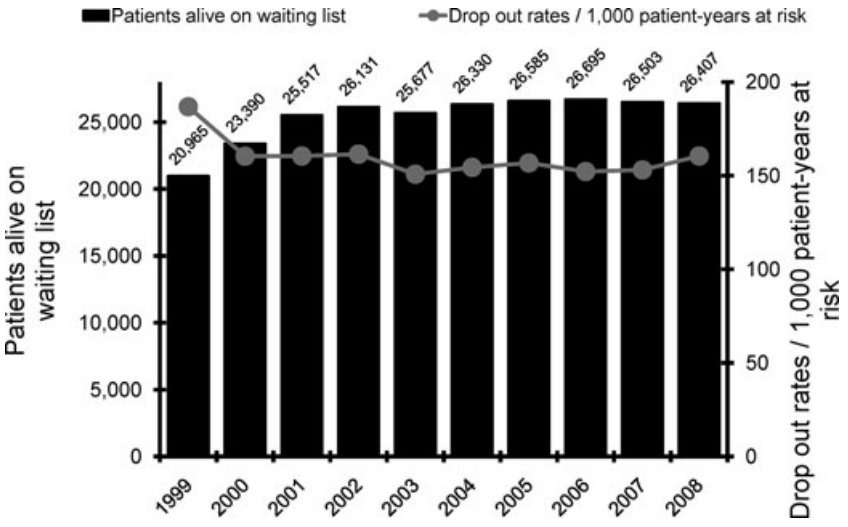


Figure 2: Patients alive on the waiting list at any time during the year and annual drop out (removal for death or being too sick) rates from the liver waiting list per 1000 patient-years.

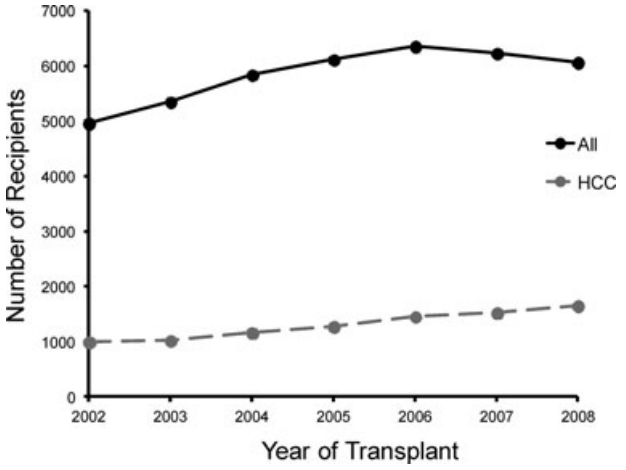


Figure 3: Comparison of HCC liver recipients to all liver recipients by year of transplant.

1999, 7.8% of recipients were noted to have a body mass index (BMI) ≥35 kg/m^2 (severe or morbid obesity) compared to 11.0% in 2008. In addition, the proportion of liver recipients with diabetes increased from 14.9% in 1999 up to 21.5% in 2008. Patients with renal insufficiency (defined as serum creatinine ≥1.5 mg/dL) increased from 26.1% in 2002 to 32.5% in 2005. This proportion has been relatively steady since that time with 29.8% of recipients having renal insufficiency in 2008. The number of patients with hepatopulmonary syndrome, transplanted with MELD exception scores, increased from 54 in 2002 to 90 in 2008.

Recipients of DCD grafts

As the supply of organs has failed to meet the demand of candidates on the waiting list, interest in using DCD organs increased over the decade. As seen in Table 5, the number of DCD donors increased and peaked in 2007 at 307 (compared to 23 in 1999). Perhaps as a result of several reports demonstrating inferior graft survival of DCD livers when compared to donation following brain death, this number decreased to 276 in 2008.

Post Liver Transplant Survival and Predictors of Survival

Liver transplant survival increased over the decade. For those who received a liver from a deceased donor, the 3-month, 1-year, 5-year and 10-year unadjusted graft survival rates were 91.2%, 84.3%, 68.4% and 54.1% respectively, and unadjusted patient survival rates were 94.3%, 88.4%, 73.8% and 60.0% respectively (Figure 8A). Please note that for 3-month and 1-year transplantation, only those transplanted in 2006 and 2007 (GS n = 11 458, PS n = 10 551) were analyzed, while for 5-years and 10-years, only those transplanted between 2002–2007 (GS n = 32 307, PS n = 29 604) and 1997–2007 (GS n = 53 673, PS n = 48 827) were analyzed *[Table 9.10a]*. For patient survival, only primary liver transplant was considered, and for graft survival all transplants were analyzed. For LDLT, unadjusted graft and patient survival at 3-months, 1-year, 5-years and 10-years are shown in Figure 8B; in this analysis, for 3-months and 1-year transplantation, only those who were transplanted in 2006 and 2007 (GS n = 537, PS n = 532) were analyzed, while for 5-years and 10-years, those who were transplanted between 2002–2007 (GS n = 1854, PS n = 1821) and 1997–2007 (GS n = 3201, PS n = 3126) were analyzed *[Table 9.10b]*. Compared to deceased donors, the outcomes were better for LDLT at 1-year, 5-years and 10-years (Figure 8A, B).

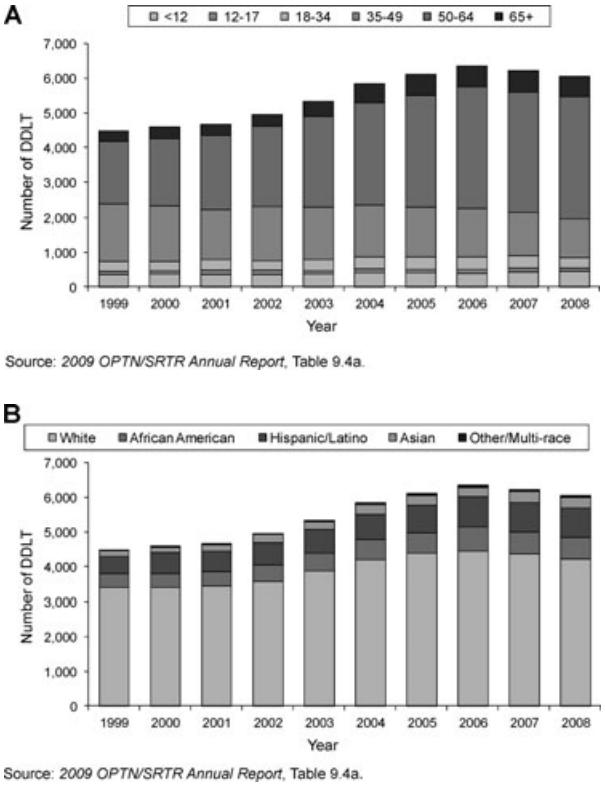


Figure 4: (A) The age distribution of patients who received deceased donor liver transplants during 1999–2008. (B) The race distribution of patients who received deceased donor liver transplants during 1999–2008.

There has been a trend toward better 1-year adjusted (adjusted for age, sex, race and etiology) graft and patient survival rates during the decade (Figure 9A and 9B). One year graft survival improved from 79.5% in 1998 to 85.6% in 2007 while patient survival improved from 85.4% in 1998 to 89.4% in 2007. This improvement was seen irrespective of age, race, sex, etiology, BMI, presence of diabetes and renal insufficiency. One year adjusted graft survival (68.1% in 1998 to 86.7% in 2007) and patient survival (78.9% in 1998 to 91.7% in 2007) for those who received grafts from a living donor also improved over the decade (Figure 9B).

Table 3: Distribution of HCC exceptions among liver transplant recipients by year of transplant

	2002	2003	2004	2005	2006	2007	2008
N	999	1027	1165	1284	1458	1534	1656
Type of exception							
T1 (%)	15.3	13.3	5.8	0.6	0.4	0.3	0.4
T2 (%)	71.1	68.5	69.6	68.8	68.2	67.8	62.7
Other (%)	1.7	5.2	8.2	9.8	9.5	13.0	18.2
None (%)	11.9	13.0	16.5	20.8	21.9	18.9	18.8

Recipient factors such as age, race, etiology of liver disease including HCC, BMI, presence of diabetes, previous liver transplantation and donor factors such as age and race had an effect on 1-year patient survival. Hospitalized patients and those on mechanical support had a lower survival *[Table 9.10a]*. Blood type and sex had no effect. Data were available for recipient serum sodium and organ preservation solution between 2005 and 2008; neither recipient serum sodium (<130 vs. ≥130 mmol/L) nor the type of preservation solution (University of Wisconsin [UW] solution Viaspan vs. Custodiol® histidine-tryptophan-ketogluterate [HTK]) had an impact on survival. Please note that over the past 4 years (2005–2008), approximately 27% of all liver allografts utilized Custodial® HTK preservation solution compared to 68% for UW solution (SRTR analysis 2009).

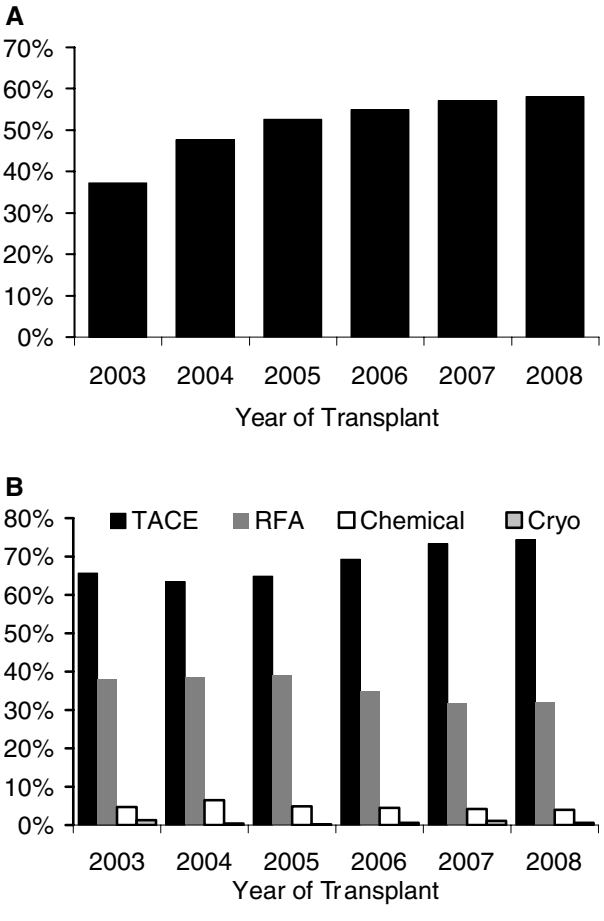


Figure 5: (A) Proportion of HCC liver recipients receiving any pretransplant loco-regional therapy by year of transplant. (B) Comparison of different modalities utilized for loco-regional therapy by year of transplant for treated liver recipients.

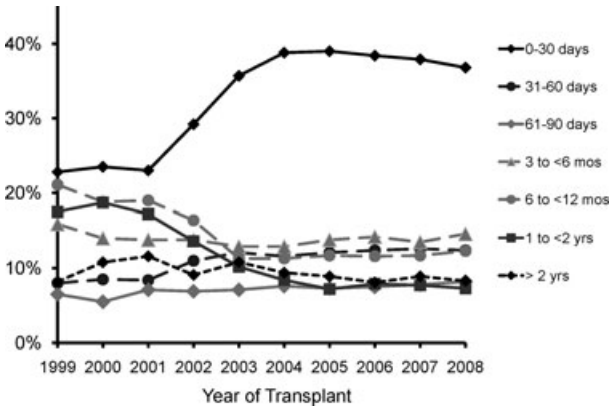


Figure 6: Distribution of time from listing until transplant among liver recipients by year of transplant.

Recipient age

Age remained an important predictor of short and long-term adjusted graft and patient survival *[Tables 9.8a and 9.12a]*. In children (aged <18 years), the best survival outcomes were seen in the age group 6–11 years at 1, 5 and

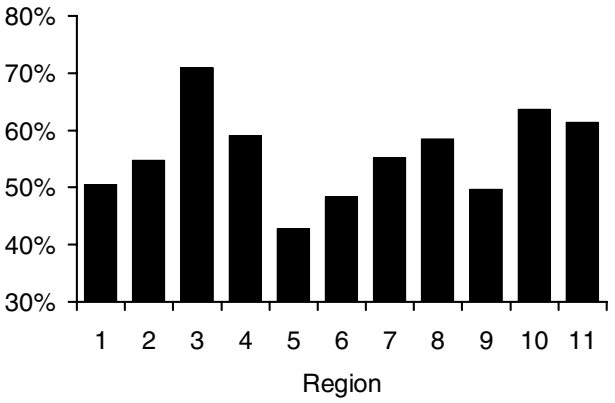


Figure 7: Proportion of liver transplant recipients with a waiting time of 90 days or less by Region.

Table 4: Incidence of comorbidities among liver recipients by year of transplant

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Number of patients	4498	4595	4672	4969	5351	5848	6121	6363	6228	6069
Obesity (BMI $\geq$ 35 kg/m^2; %)	7.8	8.5	8.3	6.9	8.2	8.9	8.3	8.4	9.8	11.0
Diabetes (%)	14.9	15.6	17.8	16.8	18.1	18.9	18.9	21.6	22.0	21.5
Renal insufficiency (Cr $\geq$ 1.5 mg/dL; %)	–	–	–	26.1	29.1	30.8	32.5	30.2	31.1	29.8

10-years. Five year graft survival ranged between 75.1% and 78.5% for children, and 10-year survival ranged between 59.6% and 71.4%. For adults, 1-year graft survival ranged between 82.0% and 85.6%; 5-year survival ranged between 61.5% and 69.9% and 10-year survival was between 41.1% and 56.0%. The worst 5-year (61.5%) and 10-year (41.1%) graft survival was seen in those who were aged $\geq$65 years and older. The impact of age on graft and patient survival was also observed for adults who received LDLT, but the overall outcomes were better for those who received LDLT *[Tables 9.8b and 9.12b]*.

Sex and race

Among the liver transplant recipients, male:female ratio was 2:1. Sex did not have any impact on survival. Race continues to have a major impact on long-term graft and patient survival *[Tables 9.8a and 9.12a]*. African Americans had the worst graft outcomes at 5-years (60.0%) and 10-years (45.4%) whereas Asians had the best outcomes at 1-year (88.1%), 5-years (73.7%) and 10-years (63.1%). These differences were also observed for LDLT *[Tables 9.8b and 9.12b]*.

Etiology of liver disease

Etiology remained a major predictor of adjusted graft survival *[Table 9.8a]*. Whereas cholestatic liver diseases, biliary atresia and metabolic diseases had the best outcomes at all time intervals, malignant diseases had the worst outcomes at 5-years (63.5%) and 10-years (45.9%). Similar observations were noted for those who received LDLT *[Tables 9.8b]*. For patients who were transplanted between 2002 and 2007 with HCC, 5-year unadjusted graft survival was better for T1 stage (n = 357; 71.1%) compared to T2 stage (n = 4934; 65.7%) *[Table 9.10a]*. The survival of patients who received loco-regional therapy for HCC versus no therapy prior to liver transplantation is shown in Table 6.

Table 5: Liver transplants from DCD donors by year of transplant

Year of transplant	Total donors N	DCD N	DCD donors of total (%)
1999	4498	23	0.5
2000	4595	39	0.8
2001	4672	69	1.5
2002	4969	79	1.6
2003	5351	111	2.1
2004	5848	185	3.2
2005	6121	271	4.4
2006	6363	289	4.5
2007	6228	307	4.9
2008	6069	276	4.5

Hospitalization status

There was a decrease in the number of hospitalized patients receiving transplants during this period. This decrease was seen both for HCV positive (31–24%) and HCV negative (42-34%) recipients. A similar trend was seen for both HCV positive (19–7%) and HCV negative (28–16%) patients transplanted from the intensive care unit. The rates for patients on mechanical support also declined for both HCV positive (7% to 3–4%) and HCV negative (16–9%) groups (SRTR analysis 2009). Patients who were hospitalized (1-year unadjusted graft survival 82.2% vs. 86.8%) had approximately 4% lower survival than those who were not hospitalized. The impact was higher for those who were in the intensive care unit (1-year unadjusted graft survival 73.3% vs. 86.8% for nonhospitalized) or on mechanical support at the time of transplant (67.5% vs. 85.5% for those who were not on mechanical support) *[Table 9.10a]*.

Transplantation by state

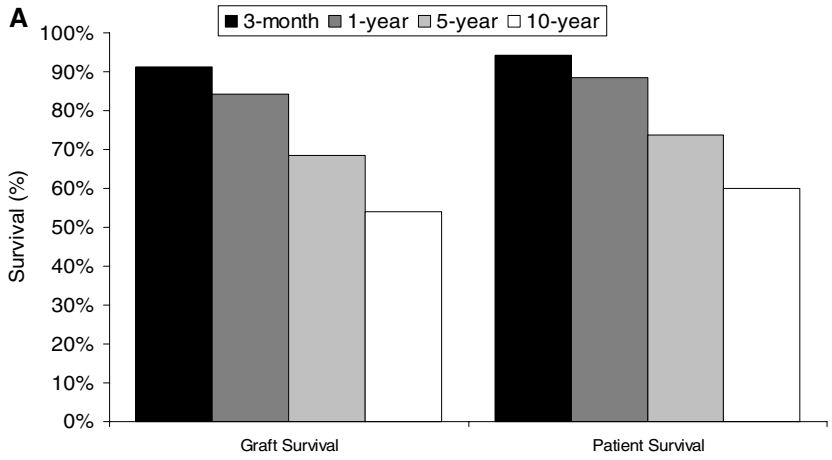
Data were analyzed according to the state instead of the center for the sake of confidentiality. Highest numbers of transplants were performed in California followed by Florida, New York, Texas and Pennsylvania. Adjusted graft and patient survival showed differences at all time intervals among the states *[Tables 9.8a and 9.12a]*. One year graft survival ranged between 73.1% (Maryland) and 96.2% (Arkansas). Yearly center volume had only minimal impact on outcomes, but there was a trend toward lower unadjusted graft survival among centers that transplanted less than 10 patients per year, or more than 57 patients per year *[Table 9.10a]*.

MELD and PELD scores

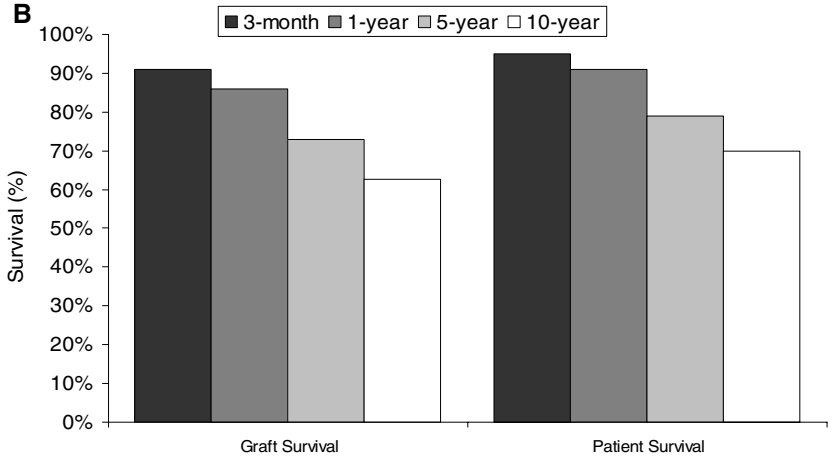
The MELD and PELD score at the time of transplantation had a significant effect on survival. Recipients with MELD scores between 11 and 20 had the best unadjusted graft and patient survival rates at 3-months, 1-year and 5-years, with the worst outcomes in those with MELD scores >30. Similarly, those with PELD scores >30 had the worst outcomes *[Tables 9.10a and 9.14a]*.

Donor age

Best outcomes were observed for donors aged between 1 and 34 years, and worst outcomes were observed for donors who were aged <1-year or aged $\geq$65 years. As



Source: *2009 OPTN/SRTR Annual Report*, Tables 9.10a and 9.14a.



Source: *2009 OPTN/SRTR Annual Report*, Tables 9.10b and 9.14b.

Figure 8: (A) Unadjusted 3-month, 1-year, 5-year and 10-year graft and patient survival after deceased donor liver transplantation. Please note that graft survival is for all transplants and patient survival is only for primary transplants. (B) Unadjusted 3-month, 1-year, 5-year and 10-year patient survival after living donor liver transplantation. Please note that graft survival is for all transplants and patient survival is only for primary transplants.

donor age increased, there was a trend towards lower 5-year and 10-year unadjusted graft survival *[Tables 9.10a]*.

Cold ischemia time

Few patients received grafts with cold ischemia time (CIT) >15 h. Between 2006 and 2007, 948 grafts had CIT between 11 and 15 h, 83 had CIT between 16 and 20 h and 71 had CIT >21 h; 1-year unadjusted graft survival was 80.1%, 77.1% and 81.7% respectively for these groups *[Table 9.10a]*. In contrast 1-year unadjusted graft survival was 87.9% when CIT was between 0 and 5 h (n = 3287), and 83.7% for CIT between 6 and 10 h (n = 6042) *[Table 9.10a]*. For both HCV and non-HCV recipients, CIT became progressively shorter over time. The percentage of transplants with CIT less than 6 h increased from 16% to 34% by 2008 for HCV patients, and nearly identical trends and rates for CIT were seen in HCV negative recipients.

Liver Transplantation for Hepatitis C

HCV is the most common indication for liver transplantation in the United States. From 1999 through 2007, the number of recipients with HCV increased to a peak of 2481 in 2006 representing more than one third (37–41%) of all recipients. In the second half of the decade, the rates remained relatively stable at around 2400 transplants annually. Unless otherwise stated, the following analysis includes only deceased donor transplantation.

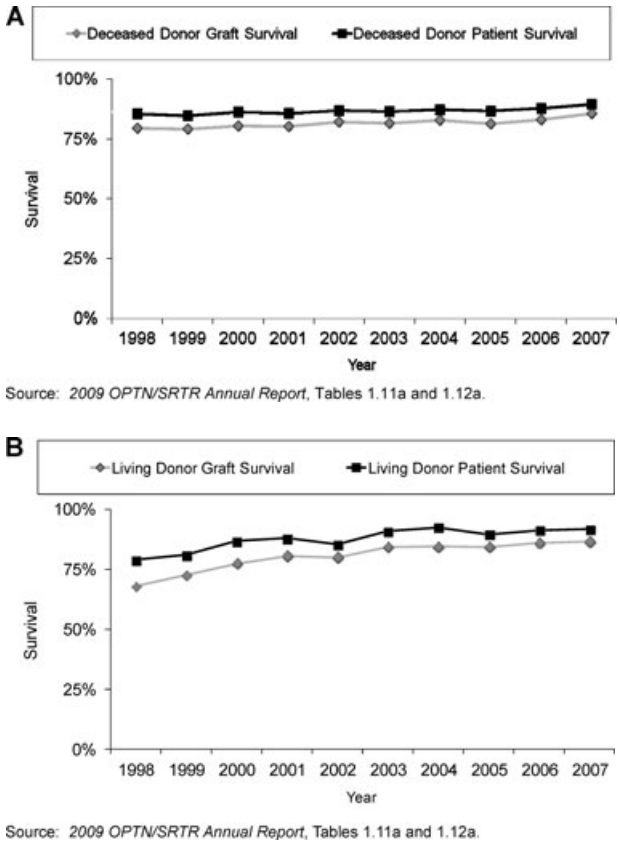


Figure 9: (A) 1-year adjusted (adjusted for age, sex, race and etiology) graft and patient survival rates for deceased donor liver transplantation by year of transplantation. (B) 1-year adjusted (adjusted for age, sex, race and etiology) living donor graft and patient survival by year of transplantation.

Recipient characteristics

The age of patients transplanted for HCV increased between 1999 and 2008. The most prominent shift occurred in the 50–64 years of age group, which increased from 37% (n = 667) in 1999 to 74% (1746) in 2008. The number of transplants for HCV patients aged ≥65 years, however, remained small during this period (100–160 per year or 6–7%) and similarly, only a small number (<50 per year) of transplants were performed in patients aged ≤35 years. Most transplants for HCV were for men (70–80%) and in contrast, 40–45% of HCV negative recipients were women. During this period, the proportion of white recipients with HCV decreased (from 77% in 1999 to 70% in 2008) while the proportion of African American recipients increased (from 7–8% to 10–11%). This increase was substantial as it represented a doubling in the absolute numbers of transplants performed in African Americans, from 125 in 1999 to 249 in 2008. The rates for Hispanic/Latinos (12–15%) and Asians (3–4%) remained stable throughout the decade. In HCV negative recipients, a similar decrease in the proportion of white recipients was seen during the decade (from 75% to 69%). The redistribution, however, occurred mostly in the Hispanic/Latinos group, where the rates increased from 9% to 14%. With rates hovering at around 10% steadily throughout the decade, the rates for HCV negative African Americans remained stable.

There was a decrease in transplantation for hospitalized patients, and those in the intensive care unit or on mechanical support as discussed earlier. Rates of transplantation for low MELD scores decreased steadily since the institution of MELD for both HCV positive and HCV negative patients. Among HCV recipients, transplantation rates decreased from 3–4% to 1% for patients with MELD scores of 6–10, and for those with MELD scores of 11–14 rates decreased from 8% to 2%. The rates remained steady for those with MELD scores 15–20 (17–20%) and MELD scores >30 (14–19%), but increased from 40% to 61% in those with MELD scores of 21–30. The distributions and trends for HCV negative patients were similar to that of HCV positive patients except that there were about 10% fewer recipients in the 21–30 MELD group and somewhat more recipients at the extremes (in the MELD <14 and >30 groups).

Partial or split liver transplants were done infrequently for HCV positive recipients (n ≤40 transplants, <2% per year). In contrast, partial and split livers were used more frequently in HCV negative patients (n = 150–200, 5–6% per year). The number of LDLT for HCV positive recipients decreased from 176 in 2001 to 64 in 2008. Although the number of LDLT decreased in HCV negative recipients also during this period, the decrease was relatively less (348 in 2001 to 185 in 2008).

Table 6: Unadjusted patient survival at 1 year, 3 years, and 5 years by ablation therapy

	1-Year			3-Years			5-Years		
Ablation therapy	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
No ablation	1032	89.1%	1.0%	2005	75.3%	1.1%	2398	67.4%	1.4%
Any ablation therapy	1301	88.9%	0.9%	2277	76.6%	1.1%	2507	69.9%	1.5%
Chemo ablation	932	88.6%	1.0%	1563	76.8%	1.3%	1715	69.7%	1.9%
Radio ablation	430	89.5%	1.5%	805	77.4%	1.7%	891	72.3%	2.4%
Cryo ablation	11	81.8%	11.6%	14	78.6%	11.0%	17	57.4%	18.3%
Chemical ablation	56	92.9%	3.4%	110	74.5%	4.9%	121	63.4%	6.5%

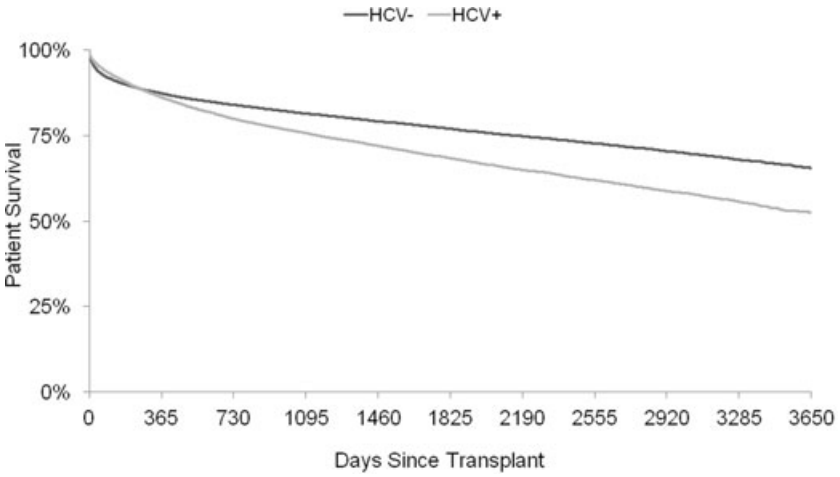


Figure 10: Patient survival in HCV patients compared to HCV negative patients.

Survival

Patient survival was lower in HCV patients compared to non-HCV patients (Figure 10). One-year adjusted patient survival improved marginally for HCV positive recipients (85–88%) during this decade. Additionally, 1-year survival of HCV patients aged >64 years showed a relatively strong improvement (from 78% to 89%). Donor age was an important risk factor, demonstrating significantly worse 1-year patient survival in recipients of donors aged >34 years. There was not much change in this effect over the decade, except perhaps a suggestion of improving results over time for recipients of donors aged >64. Among LDLT recipients, there was a significant difference in unadjusted 3-year and 5-year patient survival between HCV positive (82%, 75%) and HCV negative (86%, 81%, $p < 0.0001$) recipients. One year patient survival after retransplantation did not change much over the decade for recipients with HCV; it oscillated around 70%. In contrast, outcomes for retransplantation in HCV negative recipients steadily improved during this era, increasing from 64% to 81%.

Independent Predictors of Survival Among HCV Recipients

Recipient factors

In this analysis, we performed a multivariate analysis of patient survival using all variables that were found to be statistically significant in the univariate model. Recipient age was found to be an important risk factor for two recipient age groups, the 35–49 year old cohort, where the risk of death at 1-year was 13% lower (relative risk [RR] = 0.87, $p = 0.0013$) than that of patients in the 50–64 year age group (the reference group), and for the over 65 year age group, where the risk of death at 1-year was 20% greater than that of the reference group (RR = 1.20, $p = 0.01$). Interestingly, female recipients with HCV were at significantly greater risk of death: 15% greater within 1-year, 14% greater at 3-years and 14% greater at 5-years (all $p < 0.01$). The presence of diabetes (RR = 1.2 for all three time points, $p \leq 0.0003$), being on mechanical support (RR = 2.1 for death at 1-year, $p < 0.0001$), a history of previous abdominal surgery (RR = 1.1 at 1 year, $p = 0.007$), a previous transplant other than a liver transplant (RR = 3.7 at 1-year, $p < 0.0001$), a history of a previous malignancy (RR = 1.1 at 3-years and 1.2 at 5-years, $p < 0.01$) and a specific diagnosis of HCC (RR = 1.2 at 1-year, 3-years and 5-years, $p < 0.008$) were all independent predictors of mortality. Interestingly, a history of portal vein thrombosis did not appear to be a significant risk factor at 1-year posttransplantation (RR = 1.2, $p = 0.08$) in the HCV positive cohort unlike HCV negative recipients (RR = 1.7 at 1-year, $p < 0.0001$). Similarly, in contrast to the HCV negative population, dialysis within the week prior to transplant was not a statistically significant risk factor. Notably, recipients with private insurance were at lower risk of death at 1-year (RR = 0.89, $p = 0.006$).

Donor factors

Donor sex was not a risk factor, but donor age was an important risk factor for death after transplantation in the HCV positive transplant population (Table 7). For recipients of donors aged >34 years, the risk of death was significantly greater than that of recipients of livers from donors aged 18–34 years (the reference group). Specifically, the risk was 16% higher for liver recipients from donors aged 35–49 years, 45% higher for liver donors aged 50–64 years and 84% higher when the donor was aged >64 years (all $p < 0.006$). The deleterious effect of advanced donor age increased over the time from transplantation, such that there was a 20% increased risk of death at 5-years for recipients of donors in the 35–49 year old donor age group, a 57% increased risk in the 50–64 year old donor age group and a 114% increased risk in the over 64 year old donor age group. DCD grafts significantly increased the risk for death and graft loss, furthermore, the risk was similar for HCV positive (RR = 1.6 for patient survival at 1-year, $p < 0.0001$) and HCV negative (RR = 1.5, $p = 0.0002$) recipients. The effect of CIT was significant and similar in HCV positive and negative recipients.

Table 7: The impact of donor age on patient survival in recipients with HCV

	1-year			3-year			5-year		
Donor age	RR	CI	p-Value	RR	CI	p-Value	RR	CI	p-Value
<12 years	0.69	0.46–1.04	0.078	0.66	0.48–0.92	0.015	0.68	0.50–0.92	0.012
12–17 years	0.92	0.77–1.10	0.36	0.92	0.80–1.06	0.23	0.93	0.82–1.05	0.25
35–49 years	1.16	1.05–1.29	0.0058	1.19	1.09–1.29	<0.0001	1.20	1.12–1.30	<0.0001
50–64 years	1.45	1.30–1.61	<0.0001	1.50	1.38–1.63	<0.0001	1.57	1.45–1.69	<0.0001
>65 years	1.84	1.60–2.11	<0.0001	2.01	1.80–2.23	<0.0001	2.14	1.94–2.35	<0.0001

Race and donor–recipient race matching

Both recipient and donor race were important predictors of survival. When compared to white recipients (the reference group), the RR was 1.4 for African American recipients ($p < 0.0001$), 0.84 for Hispanic/Latino recipients ($p < 0.0001$) and 0.85 for Asian recipients ($p = 0.04$). Donor race also was a risk factor for poor survival; when compared to white donors (reference group), the RR was 1.08 for Hispanic/Latino donors ($p = 0.05$), 1.18 for Asian donors ($p = 0.04$) and 0.93 for African American donors ($p = 0.06$).

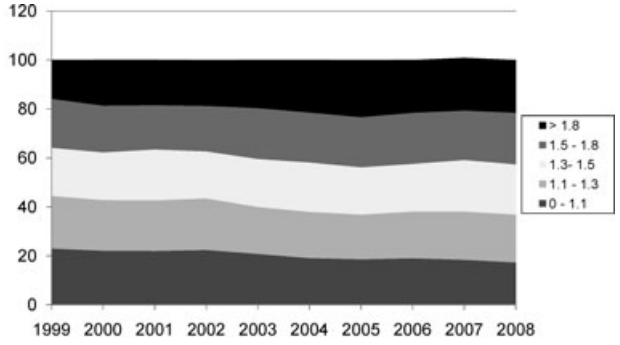
An intriguing observation was the impact of donor–recipient mismatching on survival, especially the survival benefit among African American HCV positive recipients when the donor was also African American (Table 8). Unadjusted 5-year patient survival was better among HCV positive African American recipients when the donor was also African American when compared to African American recipients who received a liver from a white donor (72.8% vs. 56.3%). In a multivariate analysis of 5-year patient survival, the RR by donor–recipient race matching for HCV positive African American recipients was 1.5 for those with a white donor (compared to the reference group of white recipients of white donors), 1.4 for those with a Hispanic/Latino donor and 1.8 for those with an Asian donor (all p values < 0.006). The interaction of recipient and donor race was evident even at 1-year (RR = 1.2 for African American recipients of a liver from a white donor, $p = 0.005$). Similarly, white HCV recipients had lower survival when the donor was Asian (Table 8). For white recipients, patient mortality at 1, 3 and 5 years was significantly higher when the donor was Asian (RR = 1.3, 1.3, 1.3, all $p < 0.10$). The risk also increased for white recipients (RR = 1.2) at 3 and 5 years (but not at 1 year) when the donor was Hispanic ($p < 0.01$). For Hispanic/Latino recipients, the 5-year unadjusted patient survival was lower when the donor was Asian and this was true for both HCV positive (66.8% vs. 71.0–77.7% for other donor races) and HCV negative (68.9% vs. 79.0–82.3% for other races) Hispanic/Latino recipients. It is important to note that the number of Asian recipients was relatively small for this analysis (for 5-years, there were 269 Asian donors for HCV positive recipients and 297 for HCV negative recipients), and therefore, the interaction with Asian donors should be interpreted with caution.

Retransplantation

The debate on retransplantation as a measure of organ utilization and cost has only heightened in this age of increasing organ shortage. The difference between patient and graft survival curves represents the utilization of retransplantation for failed life-saving allografts. This section provides an overview and analysis of the patterns and causes

Table 8: Unadjusted patient survival by recipient and donor race in HCV positive and negative recipients

	HCV negative			HCV positive		
Recipient/donor race	1-year	3-year	5-year	1-year	3-year	5-year
White/White	88.8	81.8	77.8	88.3	76.7	70.1
White/African American	88.0	80.2	75.0	88.1	77.0	70.4
White/Hispanic	86.0	79.9	75.3	84.8	74.0	63.3
White/Asian	91.8	80.0	73.7	72.0	67.9	57.2
African American/White	91.0	83.5	77.0	82.6	65.9	56.3
African American/African American	87.0	80.8	73.8	86.0	78.6	72.8
African American/Hispanic	87.8	76.3	67.7	90.9	62.5	60.5
African American/Asian	94.4	69.0	60.2	75.0	57.3	51.4
Hispanic/White	89.3	85.1	79.2	90.6	78.6	71.3
Hispanic/African American	89.0	82.1	82.3	88.0	78.2	77.7
Hispanic/Hispanic	91.0	81.2	79.0	88.3	78.5	71.0
Hispanic/Asian	83.3	66.4	68.9	72.2	62.2	66.8
Asian/White	92.8	85.0	82.0	90.5	79.2	73.4
Asian/African American	95.3	82.3	78.1	85.0	81.6	73.1
Asian/Hispanic	93.7	80.9	78.8	74.2	75.7	62.1
Asian/Asian	91.2	86.8	81.0	81.8	66.5	77.8



Source: *SRTR Analysis*, Data as of May 2009.

Figure 11: Donor risk index for livers used for primary liver transplant (1999–2008).

for liver retransplantation over the past 10 years, and seeks to further understand the factors that influence the need for retransplantation. Factors that impact the need for retransplantation are assessed at the donor, recipient and program level. Outcomes, including patient and graft survival, as well as utility of transplantation are also analyzed.

Retransplantation trends by donor characteristics

The quality of a donor in terms of the risk for graft loss can be accurately characterized using the donor risk index (DRI), an algorithm derived from a comprehensive risk analysis of the SRTR database. As shown in Figure 11, the DRI profile of livers used in primary liver transplantation changed during the period from 1999 to 2008, with a decrease in the percentage of donors with DRI <1.3 (17% decrease) and a corresponding increase in the percentage of donors with DRI >1.8 (36% increase). The risk for retransplantation based on the DRI of the primary liver is shown in Figure 12, where a stepwise increase in the risk for retransplantation can be seen for each category of increasing DRI during all years (1999–2008). Nevertheless, over this period, the risk for retransplantation following primary liver transplantation decreased from 9.6% to 7.6% and this was particularly true for the higher DRI livers (DRI 1.5–1.8 and DRI >1.8). In contrast to the increasing DRI of livers used in primary liver transplantation, the DRI for livers used for retransplantation decreased over time with an increase in the percentage of donors with DRI <1.3 (18% increase) and a corresponding decrease in the percentage of donors with DRI >1.8 (36% decrease) (Figure 13). Analysis of the impact of the serum sodium quintiles in the donor population analyzed during this period did not show any correlation between higher levels of serum sodium with the risk for retransplantation. On the other hand, a well-acknowledged component of DRI is whether the liver was from a DCD. As shown in Figure 14, while the utilization of DCD liver for primary liver transplant increased from 1999 to 2007, the retransplantation rates after DCD did not change in recent years. Compared to donation after brain death (DBD), the retransplantation rate was 54% higher with DCD liver (7.1% vs. 13.0%). Predictably, use of DCD was lower among retransplanted patients (1.1% vs. 4.8%) than primary transplants.

Retransplantation trends by recipient characteristics

For the purposes of this overview of retransplantation, we have defined utility of liver for transplantation as the ratio of primary liver transplants to liver retransplantation and do not take into consideration life-years saved (4). As seen in Figure 15, retransplantation has declined over the last 10 years, as noted by the increase in the ratio of primary liver transplants to retransplants being performed. In the first 5 years (1999–2003), 1 of every 10.4 grafts was utilized for retransplantation, whereas in the latter 5 years (2004–2008), only 1 of every 12 grafts was utilized for retransplantation (an overall improvement in utility of 15%). This was particularly evident in certain age groups (Figure 15). In the group of recipients aged 1–5 years, utilization improved 60%, from 1 of 6.0 grafts utilized for retransplantation from 1999–2003 to 1 of 9.6 grafts from 2004–2008. Similarly in the <1 year age group, utility improved from 1 in 10.5 grafts for retransplants to 1 in 15.2 grafts during the latter 5 years (48% improvement) during the same

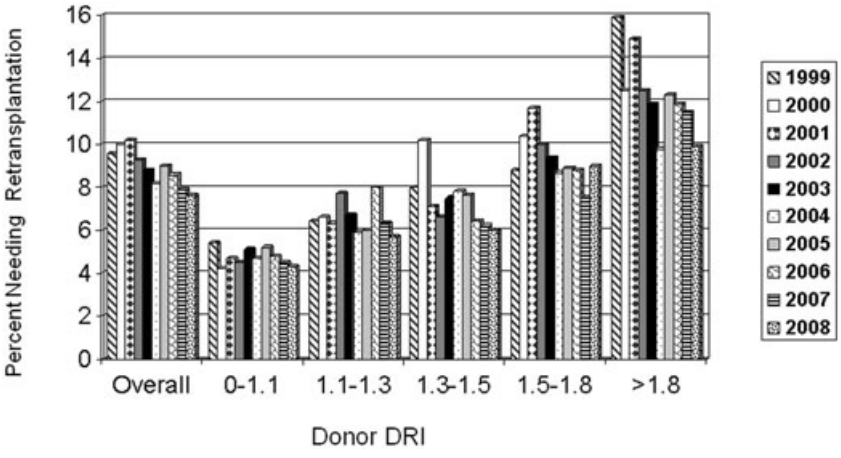


Figure 12: Retransplantation rates based on DRI for primary liver transplants.

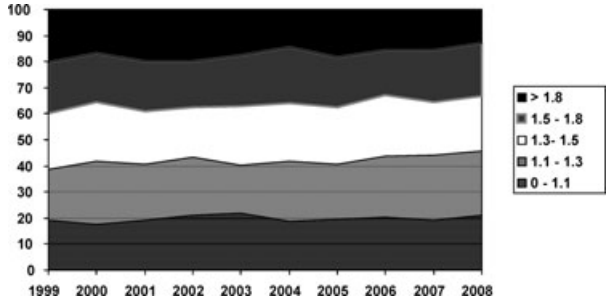


Figure 13: Donor risk index for livers used for retransplantation (1999–2008).

time periods. Improvements were seen in all age groups, with the 18 to 34 year age group having the lowest degree of improvement, from 1 in 5.4 grafts used for retransplantation from 1999 to 2003 to 1 in 5.8 grafts from 2004 to 2008 (an increase of 7% utility). Over the past 10 years the highest utility of liver allograft use in primary liver transplantation was in the oldest and youngest age groups (1 in 21.7 grafts utilized for retransplantation in the age group >65 years and 1 in 12.6 grafts for the age group <1 year), compared to the lowest utility (highest retransplantation rates) in the groups aged 6–11, 18–34 and 12–17 years (Table 9).

The race of the recipient was also associated with differential rates for retransplantation (Table 9). Over the past 10 years the highest rate of retransplantation was seen in African American recipients with a ratio of primary liver transplants to liver retransplants of 7.8 to 1. The highest utility of liver allograft use was seen in Asian recipients with 1 retransplant for every 15.1 liver allografts used. In the first 5 years compared to the second half of the analysis period, the rates increased for all groups except for the recipients designated as 'Other/Multi-race' where utilization actually decreased from 1 in 10.6 grafts utilized for retransplantation to 1 in 8.9 grafts (a decrease of 16% utility). The greatest increase in the utilization of liver allograft was seen in Asian designated recipients with an increase in utility from 1 in 11.3 grafts for retransplants in the first

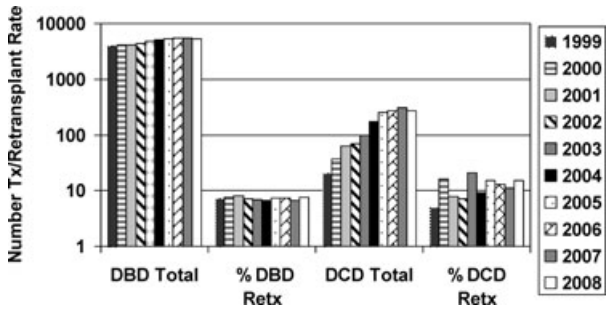


Figure 14: DCD utilization and impact on retransplantation from 1999 to 2008.

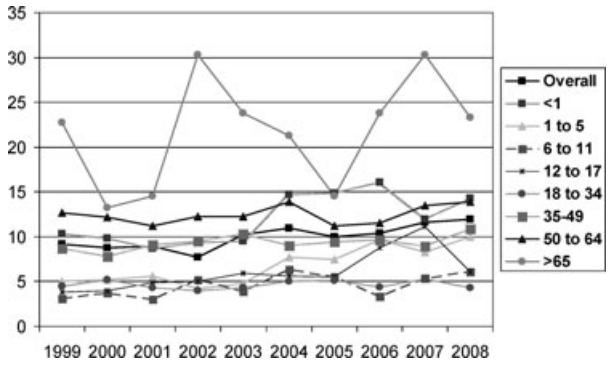


Figure 15: Ratio of primary liver transplants to liver retransplants by recipient age (1999–2008).

5 year period to 1 in 19.3 grafts during the latter 5 years (70% improvement).

Although the proportion of retransplants utilized by sex (37.4% female/62.6% male) appeared similar to the proportion of males and females undergoing primary transplantation (34.9% female/65.1% male) over the 10 year period, females had a slightly higher retransplant rate compared to males, with 1 liver in every 10.5 utilized for retransplantation in females, compared to 1 in 11.6 livers utilized for males (12% less utility when transplanting female recipients compared to male recipients) (SRTR analysis 2009).

Utilizing the diagnosis designation codes employed by the Organ Procurement and Transplantation Network, the retransplant rate by diagnosis was also notable for a wide range of utility over the 10-year period (Table 9). Aside from transplant recipients designated as 'other', where the retransplant rate was 1 in 3.3 grafts, the lowest utility of livers transplanted was for those with acute hepatic necrosis, where 1 in 7.2 grafts was used for retransplantation; only 1 in 41.1 grafts for malignant neoplasms was utilized for retransplantation.

The United Network for Organ Sharing Region where the primary liver transplant was performed was also associated with differential rates of retransplantation with an almost 3-fold difference in the utilization of liver retransplantation (Table 9). Over the past 10 years the highest rate of retransplantation was seen in recipients transplanted in Region 7 with a ratio of primary liver transplants to liver retransplants of 7.3:1. In contrast, the highest utility of liver allograft use was seen in Region 6 recipients with 1 retransplant for every 21.4 liver allografts used.

Timing and indications for liver retransplantation

The majority of liver retransplants were for first retransplants. Retransplantation for the second or greater remained constant throughout the 10-year period, with

Table 9: Ratio of primary liver transplants to liver retransplants from 1999 to 2008

Age		Race		Diagnosis		Region	
Age groups	UR	Race	UR	Primary diagnosis	UR	Region	UR
Overall	10.2	Overall	10.2	Overall	10.2	Overall	10.2
<1 year	11.6	White	10.3	Noncholestatic	16.6	Region 1	13.2
1–5	6.5	African American	7.8	Cholestatic	7.1	Region 2	9.6
6–11	4.2	Other/Multi-Race	8.5	AHN	6.2	Region 3	9.7
12–17	5.6	Asian	14.1	Biliary atresia	7.0	Region 4	18.0
18–34	4.6	Hispanic/Latino	11.1	Metabolic	12.3	Region 5	10.7
35–49	9.2			Malignant	40.1	Region 6	20.4
50–64	12.5			Others	2.3	Region 7	7.3
>65	20.7					Region 8	10.3
						Region 9	7.5
						Region 10	11.0
						Region 11	10.5

UR, Utility ratio is the ratio of primary liver transplants to liver retransplantation; AHN, acute hepatic necrosis.

approximately 10% of all allografts utilized for retransplantation being used for second or rarely third retransplants. The timing of retransplantation was quite broad. The mean time to retransplantation was 962 ± 1453 days, while the median time to retransplantation was 222 days. Only 25% of retransplants fell into the immediate posttransplant period of 14 days. The quartile with the longest time to retransplant received their retransplant more than 3.5 years following their prior transplant.

The indications for retransplantation are listed in Table 10. As was noted in a previous SRTR analysis (5), the most common cause for retransplantation in the first 14 days after transplantation was primary nonfunction, followed by vascular thrombosis. After the mid-point, the most common causes for retransplantation were: recurrent diseases, chronic rejection and biliary complications. As the number of patients whose primary liver transplant was for diseases known to recur, (e.g. primary biliary cirrhosis, primary sclerosing cholangitis, nonalcoholic steatohepatitis, Hepatitis C, Hepatitis B, autoimmune hepatitis), have continued to grow, it is not surprising to see the shift in retransplantation for those patients well into the third and fourth quartile periods.

Outcomes of retransplantation

Survival outcomes following retransplantation were inferior to primary liver transplantation. Figure 16 demonstrates the differences between the 1-year patient survivals between primary transplants and retransplants. Over the 10-year period, however, while 1-year primary liver transplant patient survival improved by 4.1%, the corresponding survival for first retransplant recipients increased by 13.0%. As has been reported before, the timing from primary liver transplant to retransplantation may play an important role in determining survival outcome (6). Over the 10-year period from 1998 to 2007, the 1-year patient survival for first retransplants in the lowest follow-up quartile was 65.8%; for the second quartile, it was 68.1%; for the third quartile, it was 70.0% and the highest was in the fourth quartile at 77.3%. As seen in Figure 17, the trend in the second half of the analytic period was

Table 10: Causes of graft failure in liver retransplant recipients by time from first transplant to retransplant (n = 3969 recipients with a first retransplant between 1999 and 2008)

	Quartiles/time from primary transplant to retransplant							
	Quartile 1 0–14 days		Quartile 2 15–222 days		Quartile 3 223–1307 days		Quartile 4 >1308 days	
Cause of graft failure[1]	N	%	N	%	N	%	N	%
Primary graft failure	653	64.1	204	21.1	100	10.1	88	8.9
Vascular thrombosis	283	27.8	318	32.9	114	11.5	53	5.3
Biliary tract complication	14	1.4	142	14.7	146	14.7	53	5.3
Hepatitis: *de novo*	0	0.0	1	0.1	10	1.0	10	1.0
Hepatitis: recurrent	5	0.5	51	5.3	243	24.5	200	20.2
Recurrent disease	1	0.1	12	1.2	103	10.4	175	17.6
Acute rejection	42	4.1	67	6.9	50	5.0	22	2.2
Chronic rejection	1	0.1	34	3.5	183	18.5	204	20.6
Infection	15	1.5	83	8.6	51	5.1	25	2.5
Patient noncompliance	0	0.0	0	0.0	8	0.8	6	0.6
Missing	126	12.4	265	27.4	277	27.9	367	37.0

[1]Cause of graft failure of the primary transplant. Some patients may have multiple causes of graft failure.

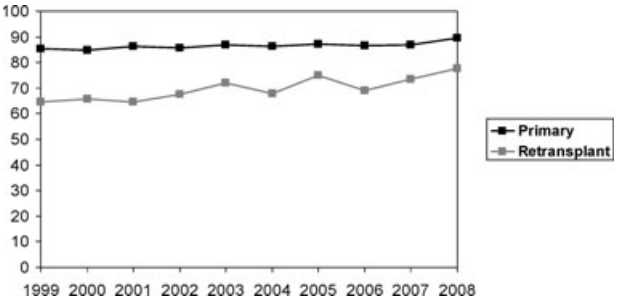


Figure 16: One-year patient survival for primary and retransplantation by year of transplantation.

notable for a shift away from early retransplantation to late retransplantation with a corresponding increase in survival.

Several single center reports have indicated that the overall incidence of retransplantation has fallen over time (7). Reduction in graft loss due to acute rejection, technical complications and patient death may have been behind this trend. Nevertheless, with an increasing DRI, meeting the challenge of improving early graft function in the face of increasing donor age, and the use of DCD livers and fatty livers, efforts must focus on reducing early retransplantation. Reducing the impact of recurrent disease, in particular HCV, remains a major challenge in reducing the need for late retransplantation. In addition, as indicated in this analysis, there are also regional practices that appear to influence the risk of retransplantation that have not been clarified.

SLK Transplantation

The number of SLK transplants has increased from 100 in 1999 to a peak of 445 in 2007. The upward trend was broken in 2008 when there was a decrease to 379 combined liver–kidney transplants performed, which represented 6.2% of all liver transplants performed. As expected, MELD score SLK patients transplanted in the past decade was higher (mean 29.2, range 25.4–32.1) than those who were transplanted for liver only (mean 23.6, range 21.7–25.3). The difference in the mean MELD score between these two groups varied between Regions (range 4.2 [in Regions 6, 8, 10] to 6.0 [in Region 7]). Regions 1 (11.9%), 7 (11.4%) and 5 (8.2%) had a relatively higher percentage of SLK. In other centers, the percentage of SLK ranged between 3.3% (Region 6 and 5) and 6% (Region 4). While the total number of liver transplants increased by 35% over the last 10 years (from 4498 to 6069), the number of SLK transplants increased by over 279% (from 100 to 379) (Table 11). Reasons for this increase in SLK over the last decade were likely multifactorial, however, two significant factors may have played an important role. First, evidence of increased postoperative mortality with liver transplant alone in patients with renal insufficiency shaped clinical practice patterns in many transplant centers to consider SLK in patients with renal insufficiency and cirrhosis. This practice was particularly prevalent in patients with acute renal failure due to hepatorenal syndrome, especially when those patients required hemodialysis. The second factor was the introduction of the MELD system for liver allocation in 2002. Creatinine was included as a major determinant of the score and thus renal insufficiency prioritized patients for liver allocation. Selection criteria for SLK have evolved over the last 5 years as our understanding of the profile of patients likely to have renal recovery after transplantation began to evolve. In addition, in 2006, a consensus conference on SLK was held in the United States, which helped to define the recipients in need of SLK. Specifically, the conference conclusions recommended SLK for patients with chronic renal failure and creatinine clearance <30 mL/min. In patients with acute renal failure, the need for dialysis >6 weeks was believed to merit SLK consideration (8,9). Perhaps because of these recommendations, the annual increase in the number of SLK transplants finally declined in 2008, but it remains to be seen whether this decline will continue in the next few years.

Cause of liver disease

The primary diagnosis of liver disease in over 70% of patients undergoing SLK was noncholestatic cirrhosis (Table 11). Commonly, patients referred for renal

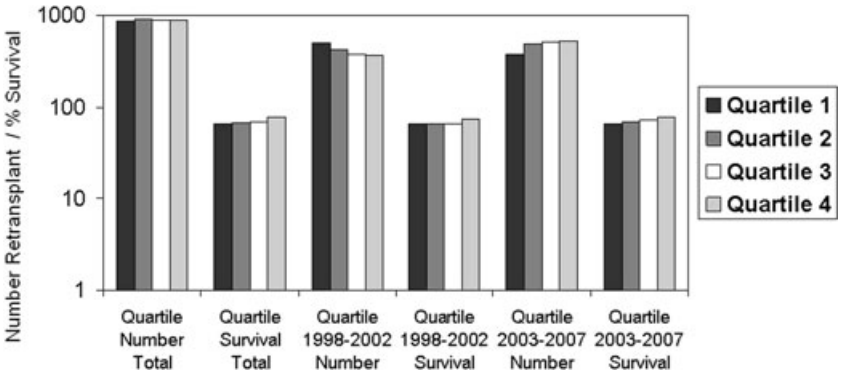


Figure 17: Number and patient survival outcome following retransplantation by quartile —1998 to 2007.

Table 11: SLK transplantation by etiology of liver disease

	Year of transplant									
Primary liver diagnosis	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total number (%)	100	135	135	210	247	279	340	400	445	379
Non-cholestatic cirrhosis	51 (51)	87 (64.4)	89 (65.9)	151 (71.9)	173 (70.0)	206 (73.8)	246 (72.4)	286 (71.5)	298 (67.0)	273 (72.0)
Cholestatic liver disease	13 (13)	7 (5.2)	8 (5.9)	12 (5.7)	15 (6.1)	17 (6.1)	18 (5.3)	31 (7.8)	22 (4.9)	23 (6.1)
Acute hepatic necrosis	5 (5)	7 (5.2)	10 (7.4)	6 (2.9)	14 (5.7)	14 (5.0)	11 (3.2)	15 (3.8)	23 (5.2)	6 (1.6)
Biliary atresia	–	2 (1.5)	–	1 (0.5)	2 (0.8)	3 (1.1)	3 (0.9)	–	2 (0.4)	1 (0.3)
Metabolic diseases	11 (11)	9 (6.7)	8 (5.9)	11 (5.2)	6 (2.4)	12 (4.3)	12 (3.5)	13 (3.3)	21 (4.7)	10 (2.6)
Malignant neoplasms	–	2 (1.5)	1 (0.7)	4 (1.9)	6 (2.4)	5 (1.8)	11 (3.2)	12 (3.0)	20 (4.5)	16 (4.2)
Others	20 (20)	21 (15.6)	19 (14.1)	25 (11.9)	31 (12.6)	22 (7.9)	39 (11.5)	43 (10.8)	59 (13.3)	50 (13.2)

transplantation with chronic HCV are deemed poor candidates for renal transplant alone and are then referred for SLK consideration. Even without advanced liver disease, the contribution to the MELD score from creatinine alone would enable these wait-listed candidates to gain priority on the allocation list for a SLK. This circumstance, however, does not account for all differences in the incidence of SLK in patients with noncholestatic cirrhosis, as the total number of transplants received by patients with noncholestatic cirrhosis in 2008 was approximately 56%, while 72% of SLK were performed in patients with noncholestatic cirrhosis *[Table 9.4a].* Thus, there is a greater requirement for SLK in patients with noncholestatic liver disease than would be predicted by the requirement for liver transplant alone. Certainly, some glomerular diseases and diabetes are known to have a higher association with HCV than with other primary liver diagnoses. For essentially all primary liver diagnoses, the peak number of SLK occurred between 2002 and 2006. For some diagnoses such as biliary atresia, the number of SLK transplants has remained minuscule over the last 10 years and represents a smaller proportion of SLK than the percentage of patients receiving liver transplant alone for this indication. For cholestatic liver disease, however, the number of SLK transplants has remained consistently between 5% and 6% of total liver transplants performed for that indication (Table 11). For patients with metabolic disease, the number of SLK transplants has been comparable peaking at approximately 5% of all SLK. In 2008, 18.4% of patients who did not receive SLK transplantation had malignant disease, and only 4.2% of patients who received SLK had malignant disease. The smaller proportion of SLK in this group is likely influenced by the MELD exception points awarded to tumor patients which allowed access to liver transplant at an earlier physiologic stage in their underlying liver disease. Acute hepatic necrosis represented the indication with the greatest decline in SLK transplants. Most likely, this is a result of centers rethinking the indications for SLK in the setting of acute renal failure when patients are not on dialysis or on dialysis for less than 60 days. In 2007, 23 SLK transplants were performed in patients with acute hepatic necrosis representing 5.2% of total SLK, while in 2008 only 6 SLKs (1.6%) were performed in patients with acute hepatic necrosis. The influence of current data demonstrating the likely return of renal function when there is acute renal failure with limited dialysis exposure has likely influenced the precipitous decline in SLK in acute hepatic necrosis. Most of these patients are transplanted within 7 days of listing and thus fall into the category of limited or no dialysis with acute renal failure.

Table 12: SLK transplantation—primary kidney diagnosis

	Year of transplant									
Primary kidney diagnosis	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total number (%)	100	135	135	210	247	279	340	400	445	379
Glomerular diseases	12 (12.0)	23 (17.0)	16 (11.9)	24 (11.4)	40 (16.2)	41 (14.7)	54 (15.9)	57 (14.3)	30 (6.7)	41 (10.8)
Diabetes	11 (11.0)	16 (11.9)	19 (14.1)	25 (11.9)	39 (15.8)	38 (13.6)	48 (14.1)	73 (18.3)	74 (16.6)	67 (17.7)
Hypertensive nephrosclerosis	3 (3.0)	9 (6.7)	8 (5.9)	8 (3.8)	15 (6.1)	18 (6.5)	33 (9.7)	27 (6.8)	41 (9.2)	33 (8.7)
Polycystic kidneys	16 (16.0)	7 (5.2)	15 (11.1)	18 (8.6)	16 (6.5)	19 (6.8)	15 (4.4)	19 (4.8)	21 (4.7)	23 (6.1)
Tubular and interstitial diseases	22 (22.0)	21 (15.6)	17 (12.6)	37 (17.6)	36 (14.6)	30 (10.8)	40 (11.8)	41 (10.3)	70 (15.7)	58 (15.3)
Renovascular & vascular diseases	5 (5.0)	2 (1.5)	4 (3.0)	2 (1.0)	5 (2.0)	4 (1.4)	5 (1.5)	5 (1.3)	5 (1.1)	4 (1.1)
Congenital, familial, & metabolic disorders	–	1 (0.7)	–	–	3 (1.2)	2 (0.7)	–	–	–	2 (0.5)
Neoplasms	1 (1.0)	–	1 (0.7)	2 (1.0)	–	–	2 (0.6)	–	1 (0.2)	2 (0.5)
Others	24 (24.0)	51 (37.8)	49 (36.3)	80 (38.1)	91 (36.8)	122 (43.7)	137 (40.3)	172 (43.0)	200 (44.9)	146 (38.5)
Unknown	6 (6.0)	5 (3.7)	6 (4.4)	14 (6.7)	2 (0.8)	5 (1.8)	6 (1.8)	6 (1.5)	3 (0.7)	3 (0.8)

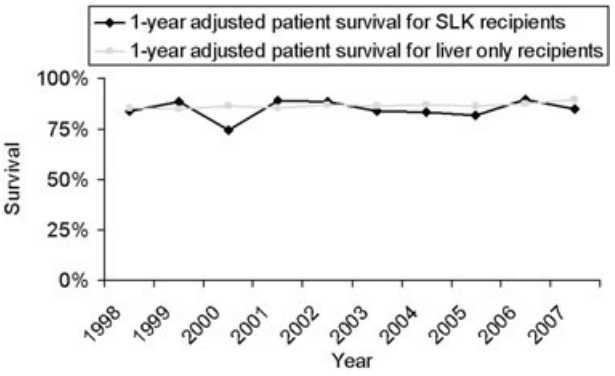


Figure 18: One year adjusted patient survival by year of transplantation for SLK and liver only recipients.

Cause of renal disease

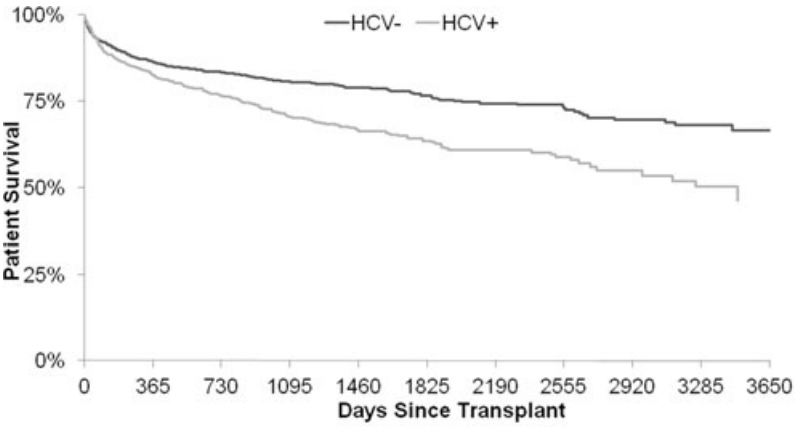
The primary kidney disease of SLK recipients was listed as 'other' in approximately 40% (Table 12). Since acute renal failure and hepatorenal syndrome are not listed indications for SLK transplantation, many of these SLK recipients with a primary renal diagnosis listed as 'other' might have had acute renal failure or hepatorenal syndrome. Diabetes was the most common cause of chronic renal disease in the liver transplant population, representing 11–18% of total SLK transplants. Tubular and interstitial diseases accounted for 10–15% most recently. Other diagnoses in 2008 such as polycystic renal disease, hypertension and glomerular diseases accounted for 6.1%, 8.7% and 10.8%, respectively. The patients receiving SLK represented by primary renal diagnoses not designated as chronic renal disease precipitously declined from 200 to 146 transplants between 2007 and 2008. This decline represented a change from 44.9% of all SLK to 38.5%. The most likely explanation is the reduction of transplants performed for hepatorenal syndrome and acute renal failure as would be expected from the selection changes undertaken at many U.S. transplant centers after the consensus conference on SLK in 2006, and other data supporting revisions of selection criteria for SLK.

Survival

One year adjusted patient survival for patients undergoing liver transplant alone has generally increased over the decade between 1999 and 2007 (Figure 9A and 9B). For SLK transplantation, there was no such improvement in patient survival (Figure 18). In fact, the patient survival of SLK recipients in 2007 at 84.7% was almost the same as that observed in SLK recipients in 1999 at 84.1%. The reflection of the selection changes that generally occurred in 2007 and 2008 will not impact the survival analyses until a later date, and thus the impact of these actions will be determined by future survival analyses. As expected, patients with HCV (n = 954) had a lower patient survival after SLK compared to those without HCV (n = 1431) (Figure 19).

Summary

The introduction of MELD and PELD for organ allocation in 2002 changed the dynamics of liver transplantation in the United States. During the decade from 1999 through 2008, the number of liver transplants increased and reached a peak in 2006, and waiting time for liver transplantation, especially for the sickest patients, decreased. The number of liver transplants for HCC increased significantly over the decade after the introduction of MELD exception scores. Similarly, introduction of MELD increased the number of SLK, since serum creatinine is a major determinant of MELD score. Despite an increase in the recipient comorbidities (severe obesity, diabetes, renal insufficiency) and an increased DRI, there was a trend toward a better 1-year graft and patient survival over the decade with a decrease in retransplantation rates. These trends are reassuring, but there was significant regional variation in the waiting time and postliver transplant survival. Only 43% of recipients were transplanted within



Source: *SRTR Analysis*, Data as of May 2009.

Figure 19: Patient survival in HCV positive (n = 954) and HCV negative (n = 1431) patients after SLK.

90 days or less in Region 5, while 71% of liver recipients in Region 3 were transplanted within that time frame. Similarly, there was considerable geographic variation in 1-year graft survival ranging from 73% in Maryland to 96% in Arkansas. Such differences could not be explained by yearly center volume as it had only a minimal impact on outcomes. As described in previous reports (10), recipient race is an important predictor of survival, and we have shown that there may be an interaction between recipient and donor race matching on posttransplant survival in HCV positive recipients. These observations merit further investigations.

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Conflict of Interest Statement

The authors have no conflicts of interest.

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