

Chapter IV

Liver Transplantation in the United States, 1999-2008

Overview

- 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.
- 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 1998-2007.
- 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, included is a more detailed analysis of liver transplantation for hepatitis C, retransplantation and simultaneous liver-kidney transplantation.

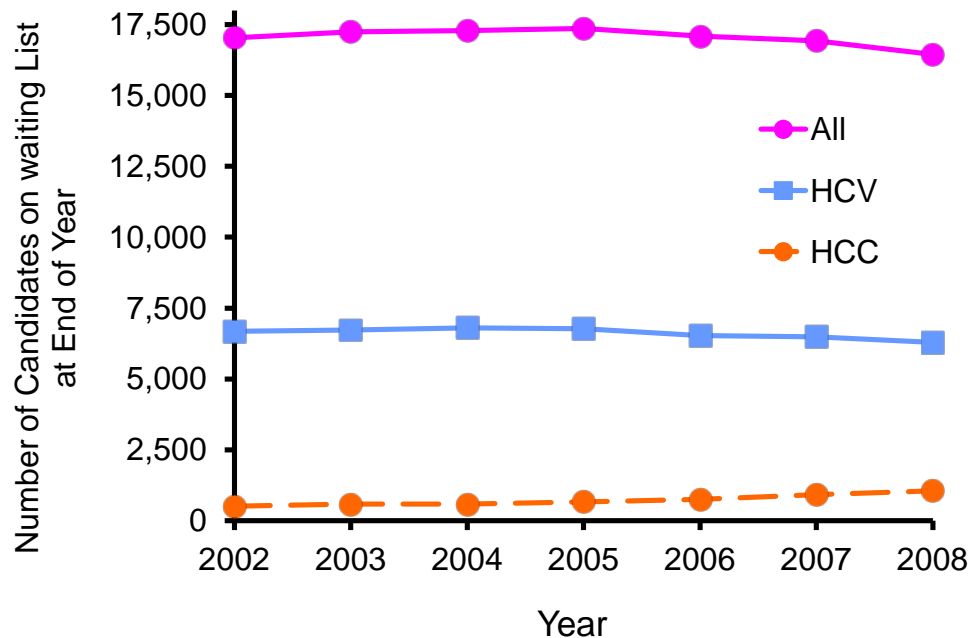
Introduction

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. This review summarizes the current status of liver transplantation in the United States using an analysis of the Scientific Registry of Transplant Recipients (SRTR) data on patients transplanted between 1999-2008. In addition to providing a general overview of the current state of liver transplantation in the United States, 3 specific topics are addressed in detail, liver transplantation for HCV, retransplantation, and SLK. Previously detailed topics (in the last 3 years [1-3]) were avoided. The data is presented as frequency, percentage or mean (\pm 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 IV-1, between 2002-2008, the number of candidates remaining on the waiting list at the end of the calendar year decreased by 3.4 percent. During the same time period, the number of candidates with hepatitis C decreased marginally (5.9 percent) and the number of candidates with HCC increased by 108 percent.

Figure IV-1: Number of Candidates on the Liver Waiting List by the End of the Calendar Year



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

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 IV-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 percent in 2002 down to 44.6 percent in 2008, but the number of candidates on the waiting list at the end of the year with a non-standard MELD exception for HCC increased considerably from 1.0 percent in 2002 to 20.6 percent in 2008. Between 2002-2008, the proportion of candidates on the waiting list at the end of the calendar year with other exceptions fluctuated between 29.3 percent and 41.4 percent, without any clear trends (Table IV-1).

Table IV-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

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 IV-2). The proportion of candidates with a standard HCC MELD exception score ranged between 15.0 percent (Region 10) to 63.5 percent (Region 7). For example, for Region 10, 80 percent 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 2 out of 3 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 to 28.5 points).

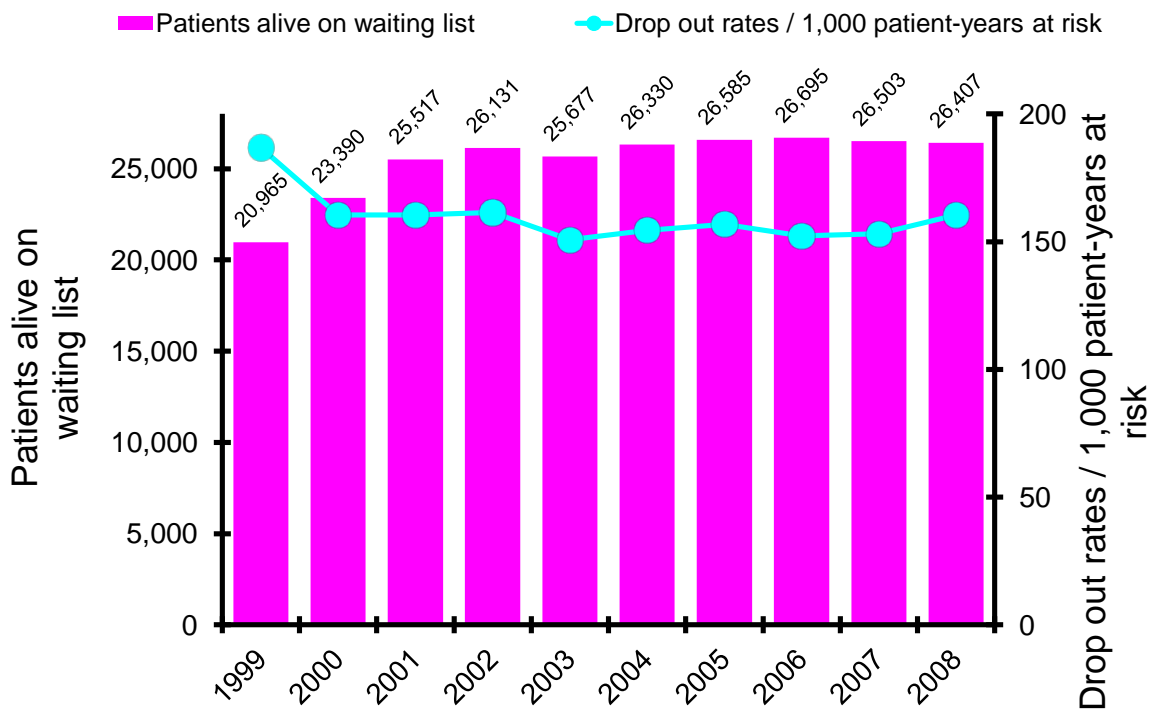
Table IV-2. MELD Exceptions for Candidates on the Waiting List at the End of 2008 by Region

	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

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 1,000 patient-years at risk) remained relatively stable over the decade as shown in Figure IV-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 dropout rate (removals for death or being too sick per 1,000 patient-years at risk) was greatest in 1999 at 186.8 compared to 160.5 in 2008.

Figure IV-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 1,000 patient-years



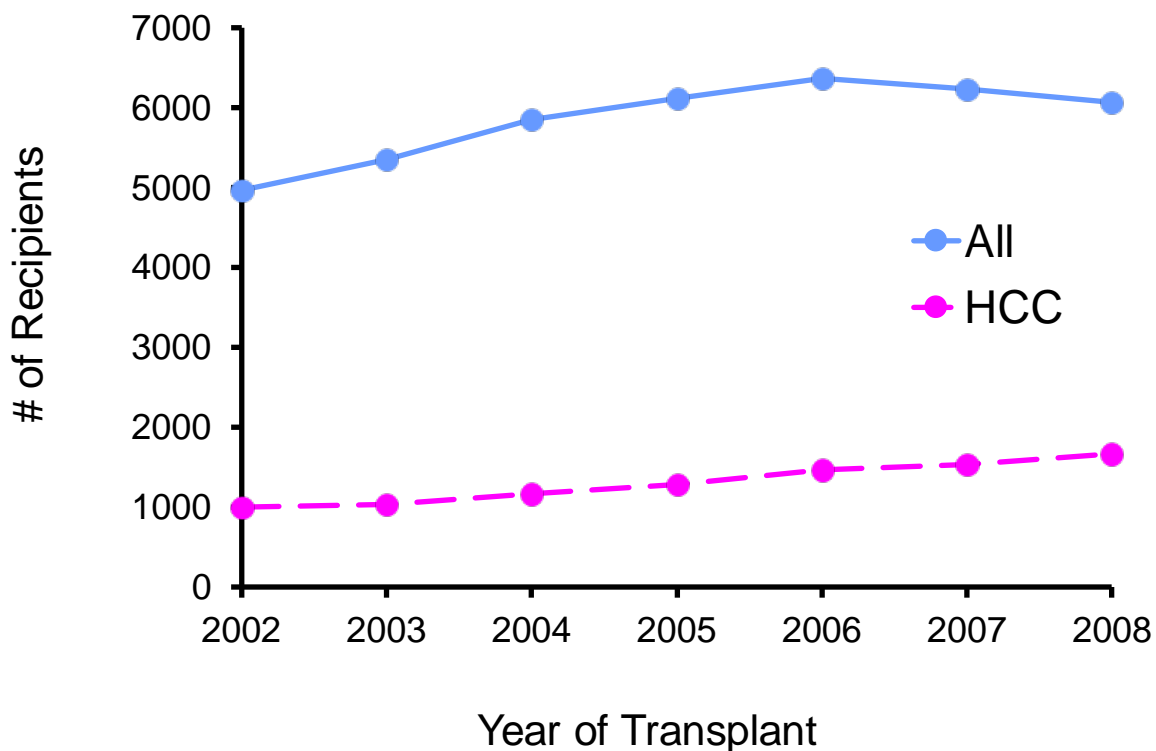
Source: SRTR Analysis, Data as of May 2009.

Liver Transplant Recipient Characteristics

The number of transplant recipients steadily increased from 4,969 in 2002 to 6,363 in 2006, but there was a decline in 2007 (n=6,228) and in 2008 (n=6,069) (Figure IV-3). During the same period, the number of transplant recipients with HCC increased steadily from 999 in 2002 to 1,656 in 2008 (Figure IV-3). The retransplantation rates decreased during this period for both HCV positive (from 8 percent to 5 percent) and HCV negative (from 11 percent-12 percent to 9

percent) recipients. The age and race distribution of patients who received deceased donor liver transplants is shown in Figures 4A & 4B.

Figure IV-3: Comparison of HCC Liver Recipients to All Liver Recipients by Year of Transplant



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

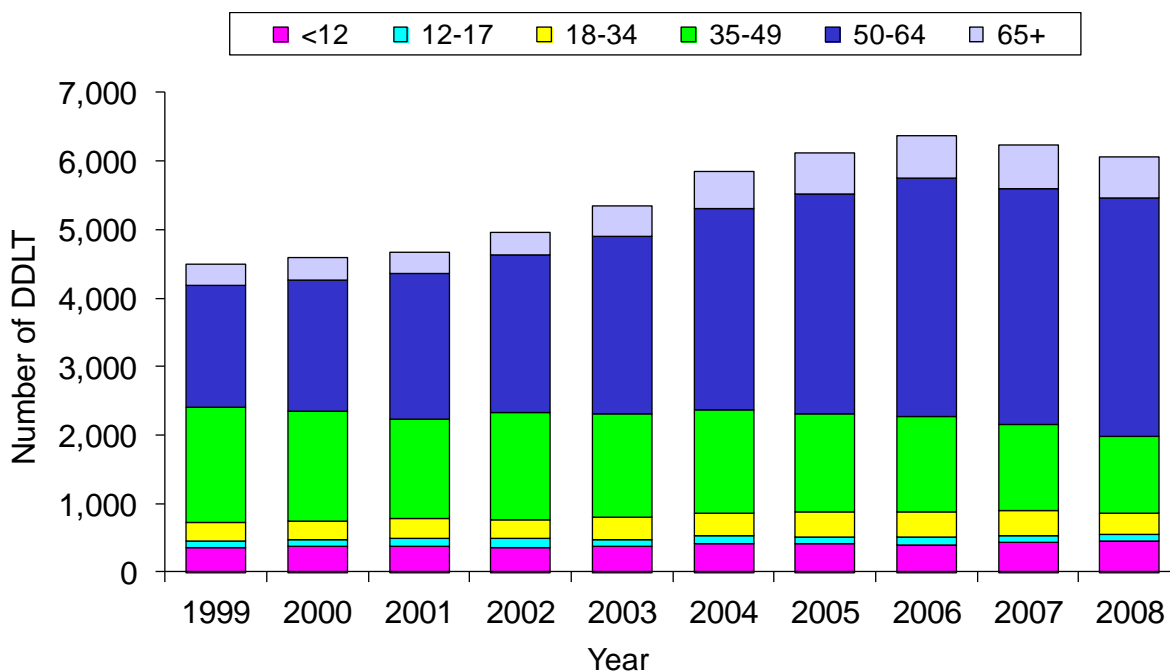
MELD Exception Rates and Scores

The distribution of HCC exception scores among liver transplant recipients between 2002-2008 is shown in Table IV-3. In 2002, 71.1 percent of liver recipients with exception scores received a standard exception for a T2 tumor, 15.3 percent received a T1 standard exception score, and only 1.7 percent received an exception score for HCC other than a standard exception.

Table IV-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

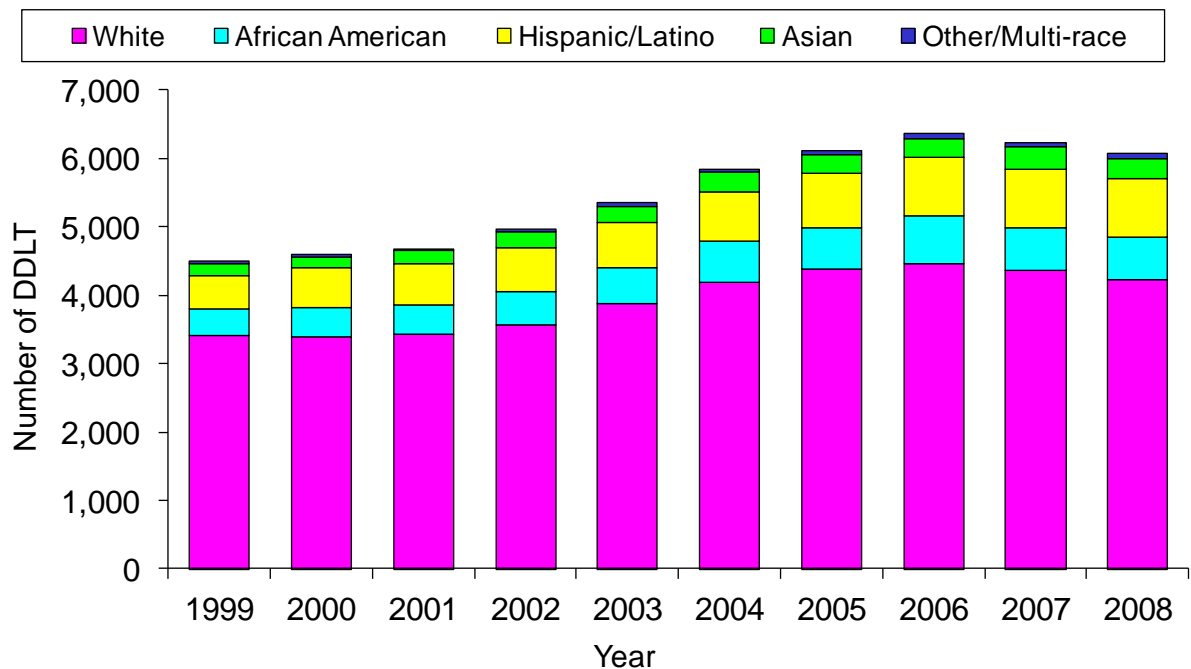
Figure IV-4A: Number of Deceased Donor Liver Transplants by Age, 1999-2008



Source: 2009 OPTN/SRTR Annual Report, Table 9.4a.

In contrast, the number of patients transplanted with a nonstandard exception for HCC increased to 18.2 percent in 2008. From 2005, MELD exception scores were not 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 percent. In 2002, 11.9 percent of the HCC recipients were transplanted without a MELD exception score and this increased to 18.8 percent in 2008.

Figure IV-4B: Number of Deceased Donor Liver Transplants by Recipient Ethnicity/Race, 1999-2008

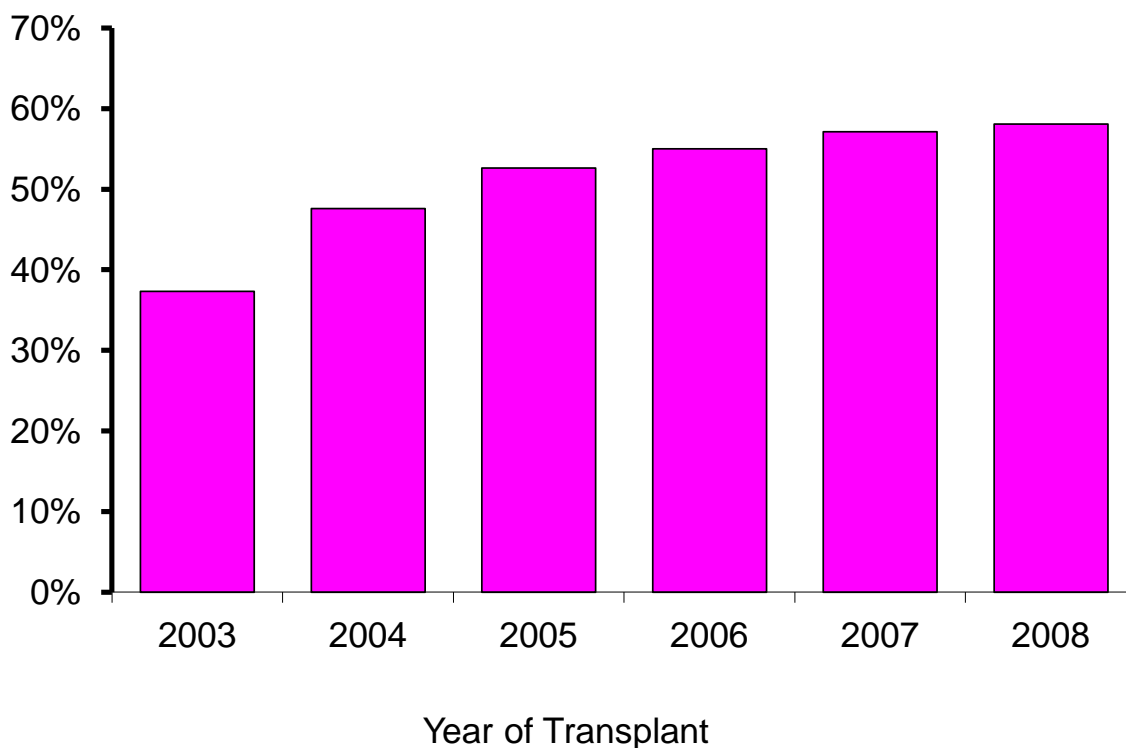


Source: 2009 OPTN/SRTR Annual Report, Table 9.4a.

Loco-regional Therapy for HCC

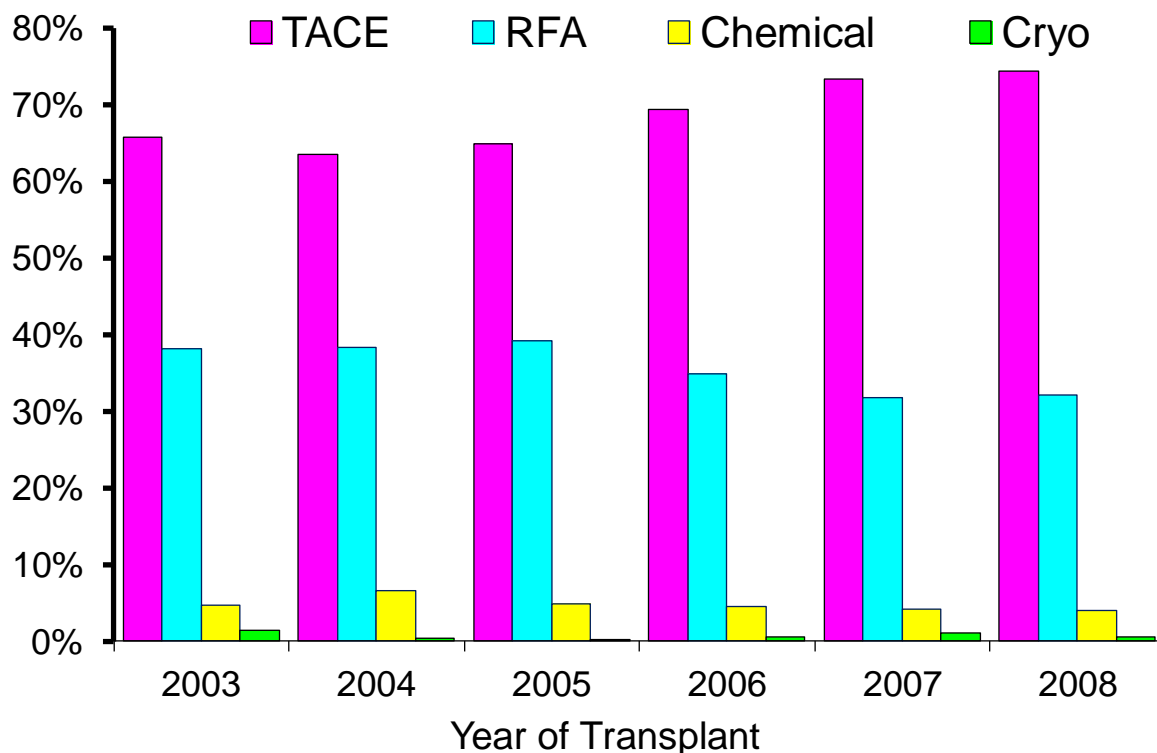
The proportion of liver transplant recipients receiving loco-regional therapy prior to transplant has increased steadily from 2003 (37.3 percent) through 2008 (58.1 percent; Figure IV-5A). Transarterial chemoembolization (TACE) and radio-frequency ablation (RFA) were the most common modalities utilized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

Figure IV-5A: Proportion of HCC Liver Recipients Receiving any Pretransplant Loco-regional Therapy by Year of Transplant



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

Figure IV-5B: Comparison of Different Modalities Utilized for Loco-regional Therapy by Year of Transplant for Treated Liver Recipients

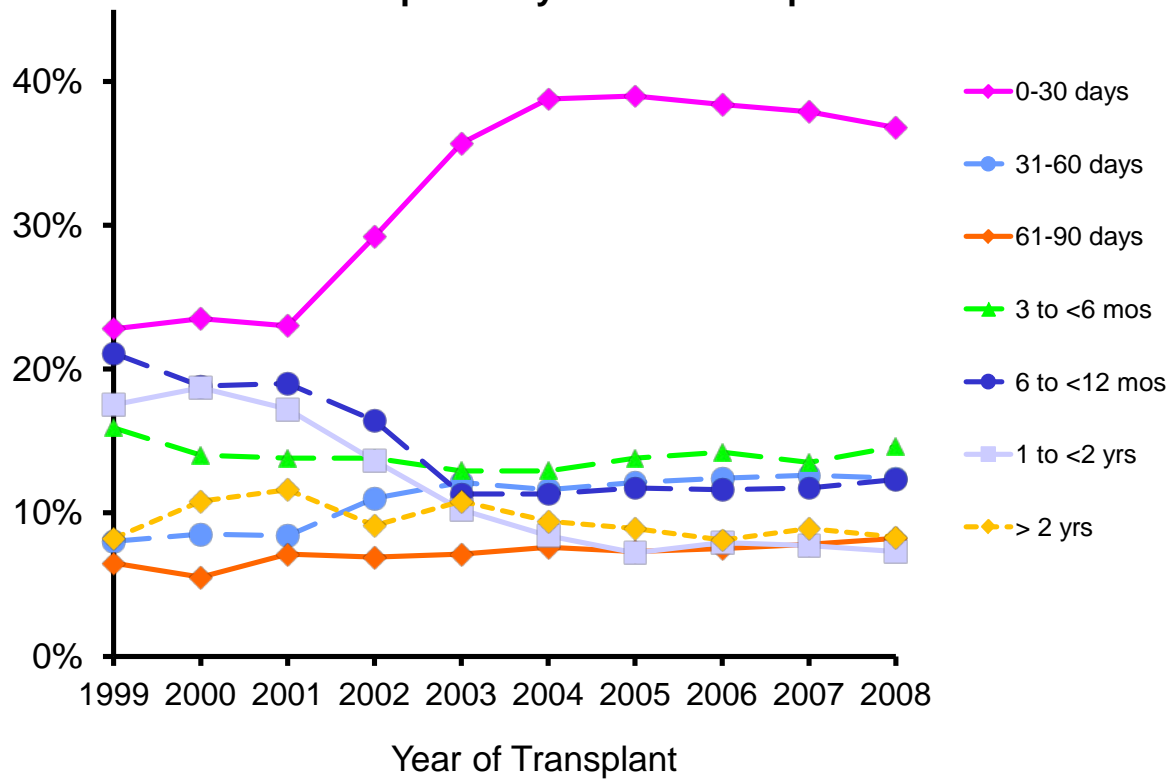


Source: *SRTR Analysis*, Data as of May 2009.

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 IV-6, the proportion of patients transplanted within 30 days of being listed was relatively steady between 1999-2001. While only 23 percent were transplanted within a month after listing in 2001, 29.2 percent 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 percent in 2005 and decreased marginally to 36.8 percent in 2008. In contrast, the proportion of liver transplant recipients waiting more than 6 months on the waiting list has generally decreased in the MELD era when compared to those transplanted before February 2002.

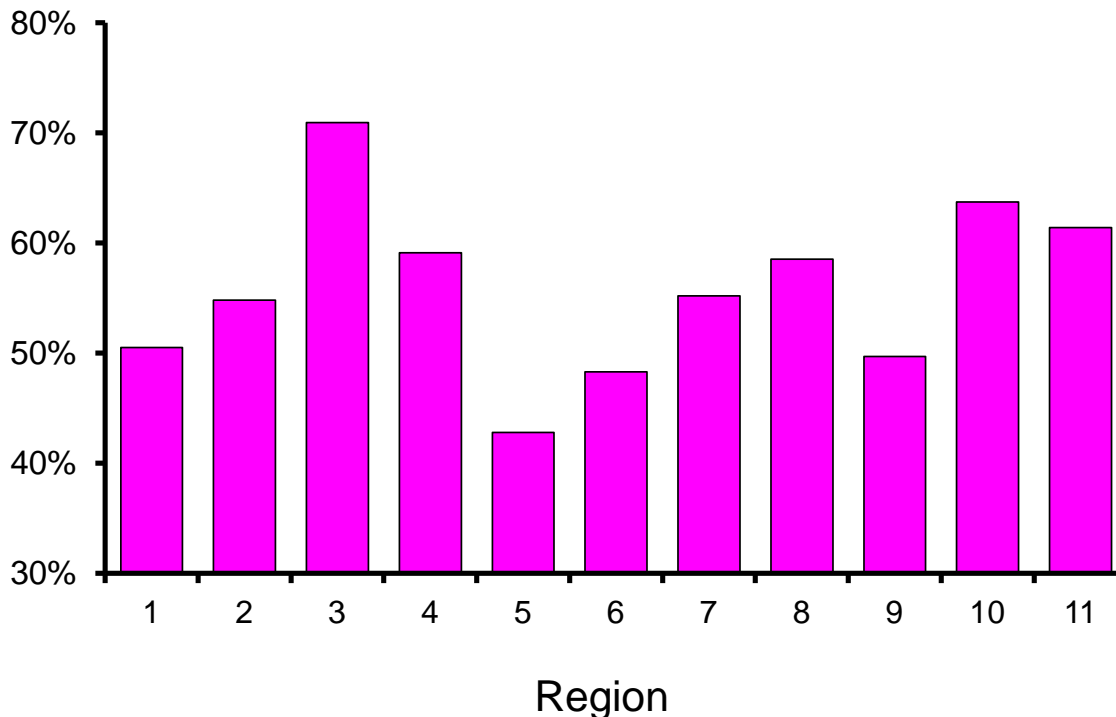
Figure IV-6: Distribution of Time From Listing Until Transplant Liver Recipients by Year of Transplant



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

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

Figure IV-7: Proportion of Liver Transplant Recipients with a Waiting Time of 90 days or Less by Region



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

Comorbidities and Renal Insufficiency

The proportion of liver transplant recipients with significant comorbidities has increased over the decade (Table IV-4). In 1999, 7.8 percent of recipients were noted to have a body mass index (BMI) ≥ 35 kg/m² (severe or morbid obesity) compared to 11.0 percent in 2008. In addition, the proportion of liver recipients with diabetes increased from 14.9 percent in 1999 up to 21.5 percent in 2008. Patients with renal insufficiency (defined as serum creatinine ≥ 1.5 mg/dL) increased from 26.1 percent in 2002 to 32.5 percent in 2005. This proportion has been relatively steady since that time with 29.8 percent 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.

Table IV-4. Incidence of Comorbidities Among Liver Recipients by Year of Transplant

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Number of patients	4,498	4,595	4,672	4,969	5,351	5,848	6,121	6,363	6,228	6,069
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

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 IV-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.

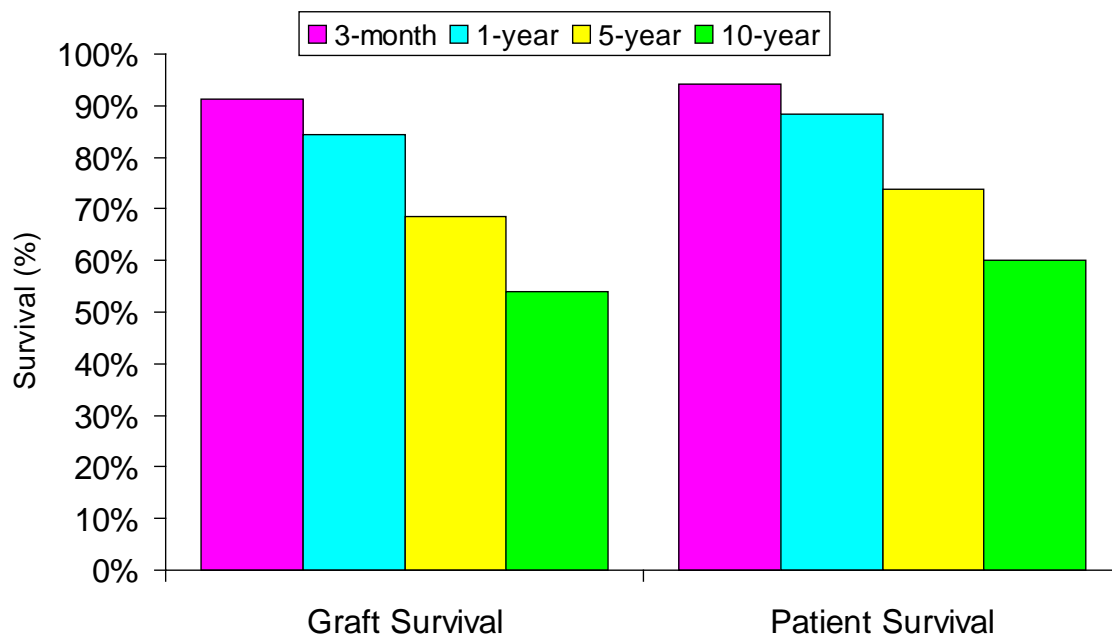
Table IV-5. Liver Transplants From DCD Donors by Year of Transplant

Year of Transplant	Total Donors	DCD	DCD Donors
	N	N	% of Total
1999	4,498	23	0.5
2000	4,595	39	0.8
2001	4,672	69	1.5
2002	4,969	79	1.6
2003	5,351	111	2.1
2004	5,848	185	3.2
2005	6,121	271	4.4
2006	6,363	289	4.5
2007	6,228	307	4.9
2008	6,069	276	4.5

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 percent, 84.3 percent, 68.4 percent and 54.1 percent respectively, and unadjusted patient survival rates were 94.3 percent, 88.4 percent, 73.8 percent and 60.0 percent respectively (Figure IV-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].

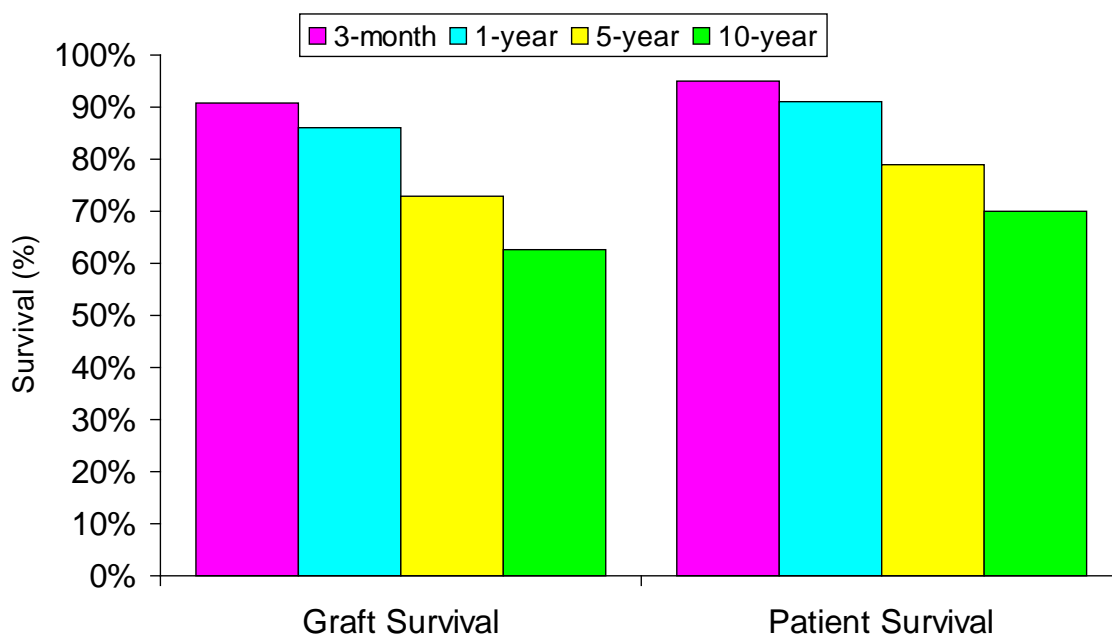
Figure IV-8A: Unadjusted 3-month, 1-year, 5-year and 10-year Graft and Patient Survival – Deceased Donor



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

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 IV-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=1,854, PS n=1,821) and 1997-2007 (GS n=3,201, PS n=3,126) were analyzed [Table 9.10b]. Compared to deceased donors, the outcomes were better for LDLT at 1-year, 5-years and 10-years (Figure IV-8A & Figure IV-8B).

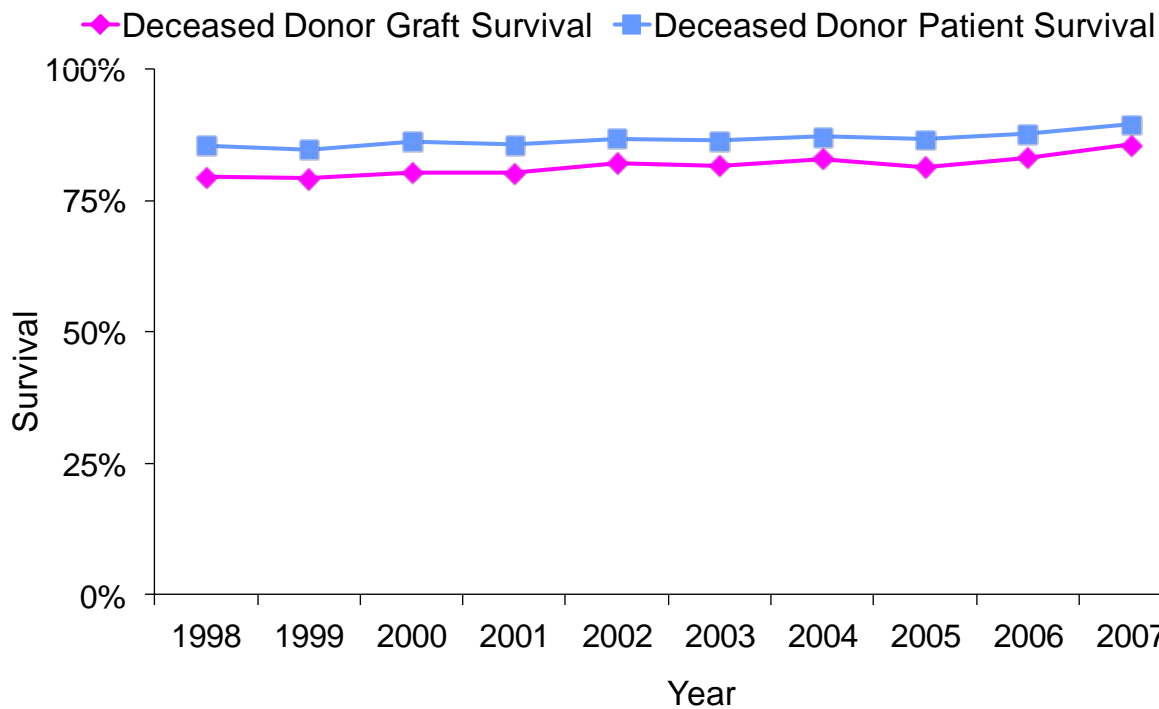
Figure IV-8B. Unadjusted 3-month, 1-year, 5-year and 10-year Graft and Patient Survival – Living Donor



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

There has been a trend towards better 1-year adjusted (adjusted for age, sex, race and etiology) graft and patient survival rates during the decade (Figure IV-9A & Figure IV-9B). One-year graft survival improved from 79.5 percent in 1998 to 85.6 percent in 2007 while patient survival improved from 85.4 percent in 1998 to 89.4 percent in 2007.

Figure IV-9A: One-Year Adjusted Deceased Donor Graft and Patient Survival by Year of Transplantation

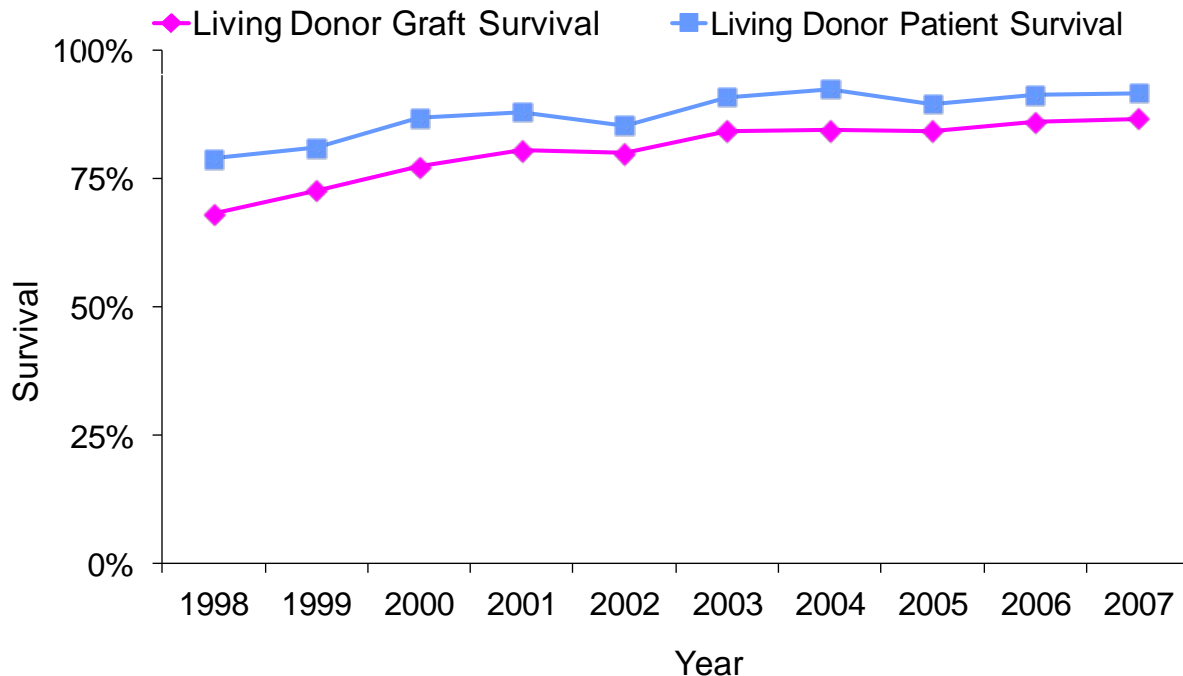


Source: 2009 OPTN/SRTR Annual Report, Tables 1.11a and 1.12a.

This improvement was seen irrespective of age, race, sex, etiology, BMI, presence of diabetes and renal insufficiency. One-year adjusted graft survival (68.1 percent in 1998 to 86.7 percent in 2007) and patient survival (78.9 percent in 1998 to 91.7 percent in 2007) for those who received grafts from a living donor also improved over the decade (Figure IV-9B).

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 2005-2008; neither recipient serum sodium (<130 vs. \geq 130 mmol/l) nor the type of preservation solution (University of Wisconsin [UW] solution Viaspan vs. Custodiol® histidine-tryptophan-ketoglutarate [HTK]) had an impact on survival. Please note that over the past 4 years (2005-2008), approximately 27 percent of all liver allografts utilized Custodial® HTK preservation solution compared to 68 percent for UW solution [SRTR analysis 2009].

Figure IV-9B: One-Year Adjusted Living Donor Graft and Patient Survival by Year of Transplantation



Source: 2009 OPTN/SRTR Annual Report, Tables 1.11a and 1.12a.

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 10-years. Five year graft survival ranged between 75.1 percent and 78.5 percent for children, and 10-year survival ranged between 59.6 percent and 71.4 percent. For adults, 1-year graft survival ranged between 82.0 percent and 85.6 percent; 5-year survival ranged between 61.5 percent and 69.9 percent and 10-year survival was between 41.1 percent and 56.0 percent. The worst 5-year (61.5 percent) and 10-year (41.1 percent) graft survival was seen in those who were aged ≥ 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 percent) and 10-years (45.4 percent) whereas Asians had the best outcomes at 1-year (88.1 percent), 5-years

(73.7 percent) and 10-years (63.1 percent). 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 percent) and 10-years (45.9 percent). Similar observations were noted for those who received LDLT [Tables 9.8b]. For patients who were transplanted between 2002-2007 with HCC, 5-year unadjusted graft survival was better for T1 stage (n=357; 71.1 percent) compared to T2 stage (n=4,934; 65.7 percent) [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 IV-6.

Table IV-6. Unadjusted Patient Survival at 1-Year, 3-Years, and 5-Years by Ablation Therapy

Ablation Therapy	1-Year			3-Years			5-Years		
	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%

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 percent to 24 percent) and HCV negative (42 percent to 34 percent) recipients. A similar trend was seen for both HCV positive (19 percent to 7 percent) and HCV negative (28 percent to 16 percent) patients transplanted from the intensive care unit. The rates for patients on mechanical support also declined for both HCV positive (7 percent to 3 percent-4 percent) and HCV negative (16 percent to 9 percent) groups [SRTR analysis 2009]. Patients who were hospitalized (1-year unadjusted graft survival 82.2 percent vs. 86.8 percent) had approximately 4 percent lower survival than those who were not hospitalized. The impact was higher for those were in the intensive care unit (1-year unadjusted graft survival 73.3 percent vs. 86.8 percent for non-hospitalized) or on mechanical support at the time of transplant (67.5 percent vs. 85.5 percent 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 percent (Maryland) and 96.2 percent (Arkansas). Yearly center volume had only minimal impact on outcomes, but there was a trend towards 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 1-34 years, and worst outcomes were observed for donors who were aged <1-year or aged ≥65 years. As 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 hours. Between 2006 and 2007, 948 grafts had CIT between 11-15 hours, 83 had CIT between 16-20 hours, and 71 had CIT >21 hours; 1-year unadjusted graft survival was 80.1 percent, 77.1 percent and 81.7 percent respectively for these groups [Table 9.10a]. In contrast 1-year unadjusted graft survival was 87.9 percent when CIT was between 0-5 hours (n=3,287), and 83.7 percent for CIT between 6-10 hours (n=6,042) [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 hours increased from 16 percent to 34 percent 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 2,481 in 2006 representing more than 1/3 (37 percent to 41 percent) of all recipients. In the second half of the decade, the rates remained relatively stable at around 2,400 transplants annually. Unless otherwise stated, the following analysis includes only deceased donor transplantation.

Recipient characteristics

The age of patients transplanted for HCV increased between 1999 and 2008. The most prominent shift occurred in the 50-64 year old age group, which increased from 37 percent (n=667) in 1999 to 74 percent (1,746) in 2008. The number of transplants for HCV patients aged ≥65 years, however, remained small during this period (100 to 160 per year or 6 percent -7 percent) and

similarly, only a small number (<50/year) of transplants were performed in patients aged ≤ 35 years. Most transplants for HCV were for men (70 percent -80 percent) and in contrast, 40 percent to 45 percent of HCV negative recipients were women. During this period, the proportion of White recipients with HCV decreased (from 77 percent in 1999 to 70 percent in 2008) while the proportion of African-American recipients increased (from 7 percent-8 percent to 10 percent-11 percent). 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 percent-15 percent) and Asians (3 percent-4 percent) 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 percent to 69 percent). The redistribution, however, occurred mostly in the Hispanic/Latinos group, where the rates increased from 9 percent to 14 percent. With rates hovering at around 10 percent steadily throughout the decade, the rates for HCV negative African-Americans remained stable.

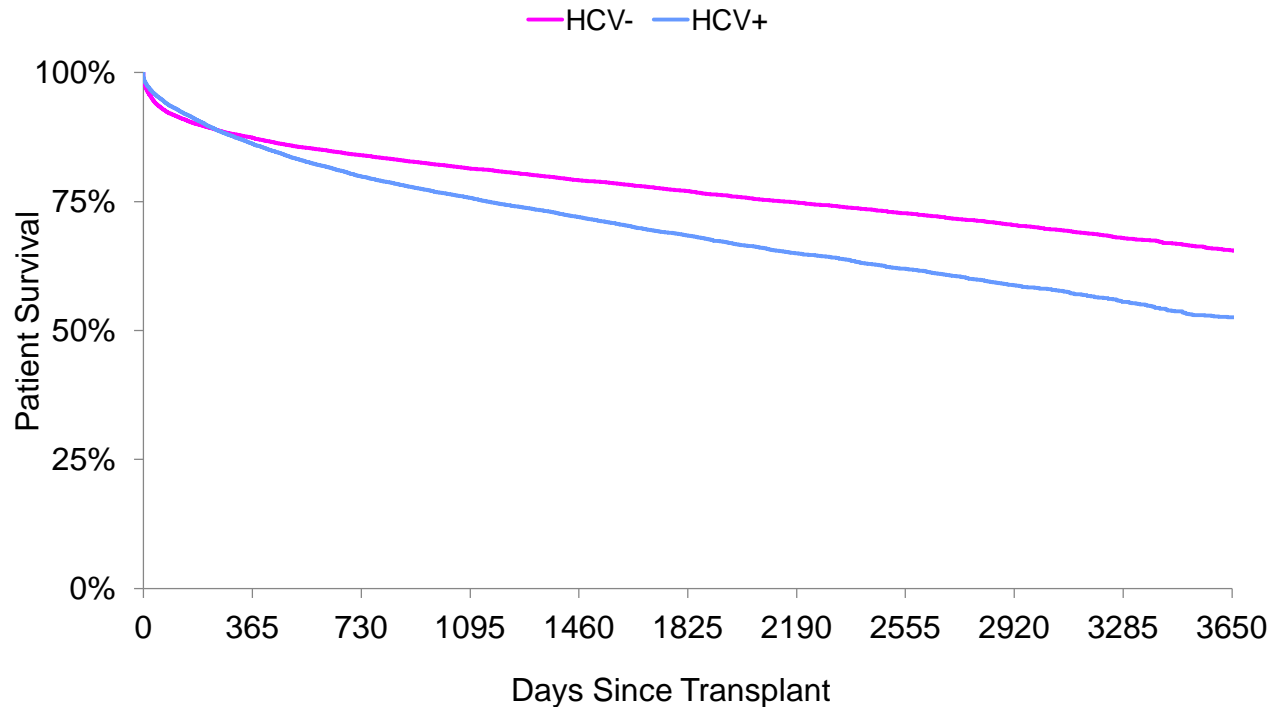
There was a decrease in transplantation for hospitalized patients, and those in the intensive care unit or on mechanical support as discussed earlier. Rates of transplantation for low MELD scores decreased steadily since the institution of MELD for both HCV positive and HCV negative patients. Among HCV recipients, transplantation rates decreased from 3 percent-4 percent to 1 percent for patients with MELD scores of 6-10, and for those with MELD scores of 11-14 rates decreased from 8 percent to 2 percent. The rates remained steady for those with MELD scores 15-20 (17 percent -20 percent) and MELD scores >30 (14 percent-19 percent), but increased from 40 percent to 61 percent 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 percent 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 percent per year). In contrast, partial and split livers were used more frequently in HCV negative patients ($n = 150-200$, 5 percent-6 percent 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).

Survival

Patient survival was lower in HCV patients compared to non-HCV patients (Figure IV-10). One-year adjusted patient survival improved marginally for HCV positive recipients (85 percent to 88 percent) during this decade. Additionally, 1-year survival of HCV patients aged >64 years showed a relatively strong improvement (from 78 percent to 89 percent). 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 percent, 75 percent) and HCV negative (86 percent, 81 percent, $p < 0.0001$) recipients. One-year patient survival after retransplantation did not change much over the decade for recipients with HCV; it oscillated around 70 percent. In contrast, outcomes for retransplantation in HCV negative recipients steadily improved during this era, increasing from 64 percent to 81 percent.

Figure IV-10: Patient survival in HCV patients compared to HCV negative patients



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

Independent predictors of survival among HCV recipients

Recipient factors

This analysis used 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 2 recipient age groups, the 35-49 year old cohort, where the risk of death at 1-year was 13 percent 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 percent 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 percent greater within 1-year, 14 percent greater at 3-years, and 14 percent greater at 5-years (all $p < 0.01$). The presence of diabetes (RR = 1.2 for all 3 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 post-transplantation (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 IV-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 percent higher for liver recipients from donors aged 35-49 years, 45 percent higher for liver donors aged 50-64 years and 84 percent higher when the donor was aged >64 years (all p < 0.006).

Table IV-7. The Impact of Donor Age on Patient Survival in Recipients with HCV

Donor Age	1-year			3-year			5-year		
	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

The deleterious effect of advanced donor age increased over the time from transplantation, such that there was a 20 percent increased risk of death at 5-years for recipients of donors in the 35-49 year old donor age group, a 57 percent increased risk in the 50-64 year old donor age group, and a 114 percent 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.

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 relative risk 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 relative risk 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 IV-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 percent vs. 56.3 percent).

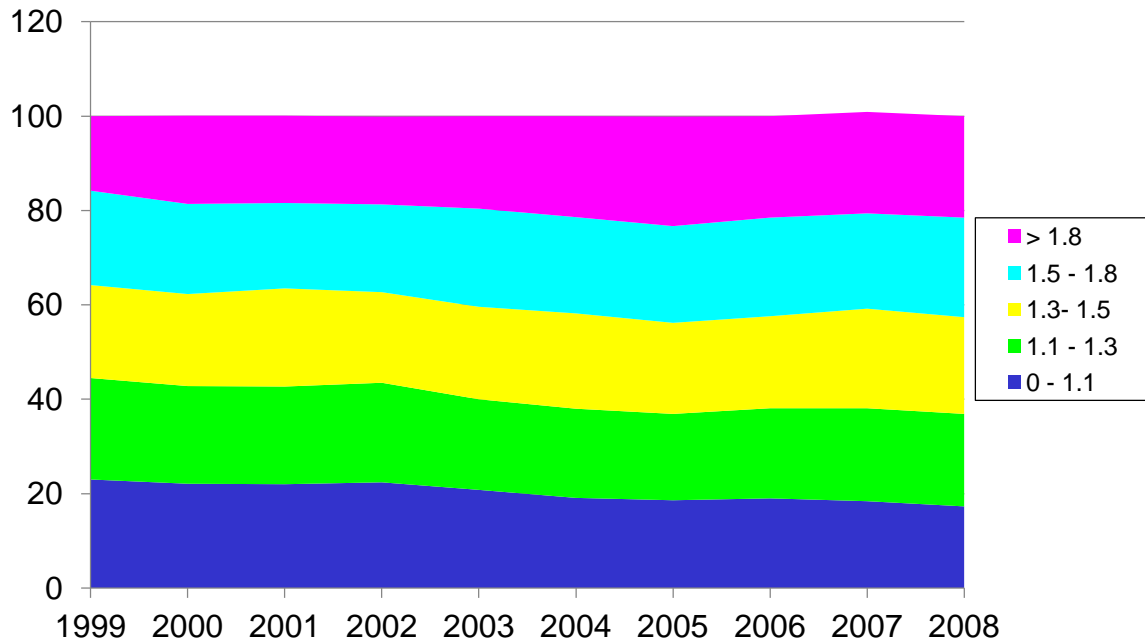
Table IV-8. Unadjusted Patient Survival by Recipient and Donor Race in HCV Positive and Negative Recipients

Recipient/Donor Race	HCV Negative			HCV Positive		
	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

In a multivariate analysis of 5-year patient survival, the relative risk 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 IV-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 percent vs. 71.0 percent-77.7 percent for other donor races) and HCV negative (68.9 percent vs.

79.0 percent-82.3 percent 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.

Figure IV-11: Donor Risk Index for Primary Liver Transplants from 1999-2008



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

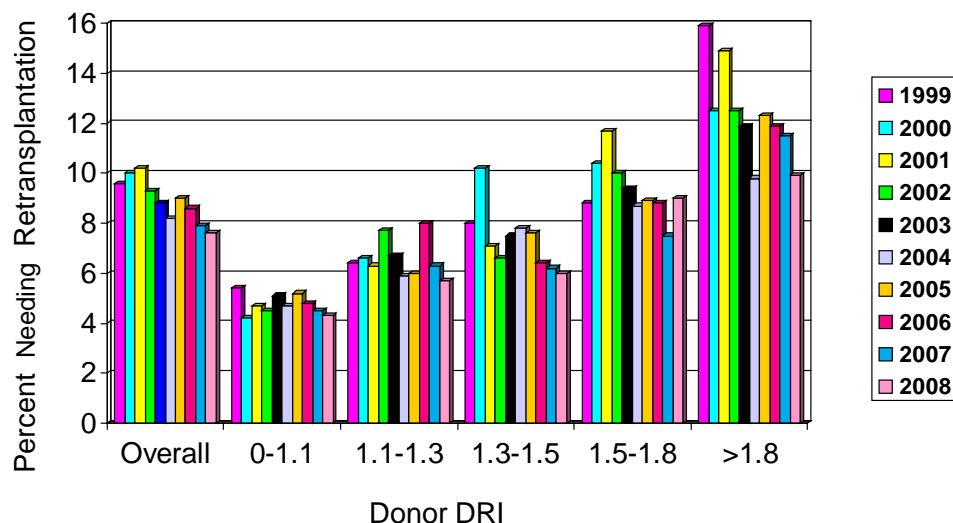
Retransplantation

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 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 IV-11, the DRI profile of livers used in primary liver transplantation changed during the period from 1999-2008, with a decrease in the percentage of donors with DRI <1.3 (17 percent decrease) and a corresponding increase in the percentage of donors with DRI >1.8 (36 percent increase). The risk for retransplantation based on the DRI of the primary liver is shown in Figure IV-12, where a stepwise increase in the risk for retransplantation can be seen for each category of increasing DRI during all years (1999-2008).

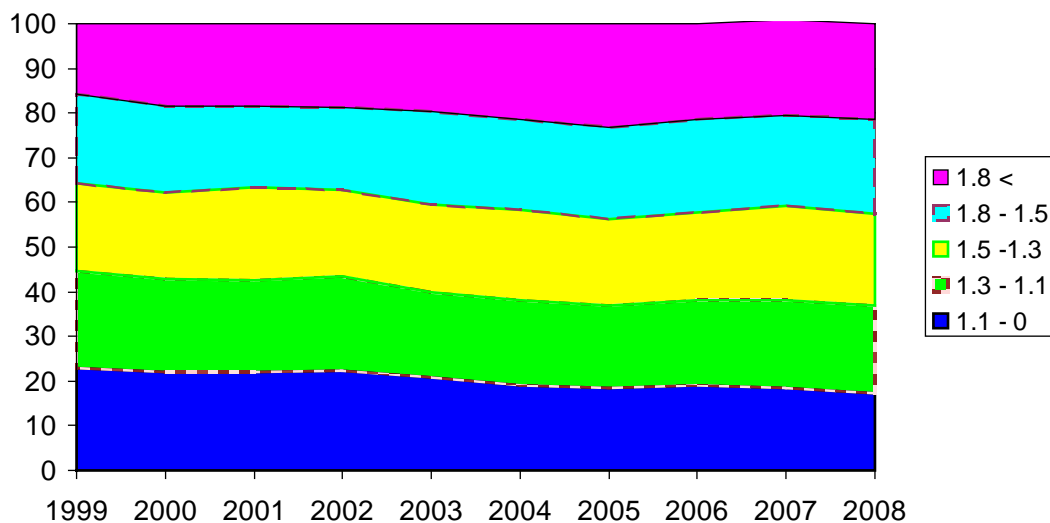
Figure IV-12: Retransplantation Rate Based on Donor DRI in Primary Liver Transplantation



Source: SRTR Analysis, Data as of May 2009.

Nevertheless, over this period, the risk for retransplantation following primary liver transplantation decreased from 9.6 percent to 7.6 percent 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 percent increase) and a corresponding decrease in the percentage of donors with DRI >1.8 (36 percent decrease) (Figure IV-13).

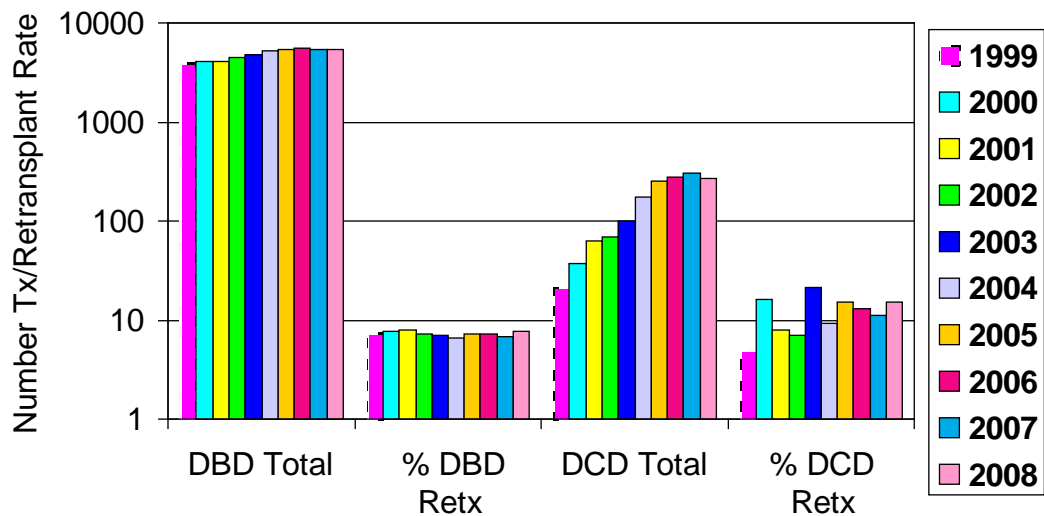
Figure IV-13: Donor Risk Index for Livers Used for Retransplantation from 1999-2008



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

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 IV-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 percent higher with DCD liver (7.1 percent vs. 13.0 percent). Predictably, use of DCD was lower among retransplanted patients (1.1 percent vs. 4.8 percent) than primary transplants.

Figure IV-14: DCD Utilization and Impact on Retransplantation from 1999-2008



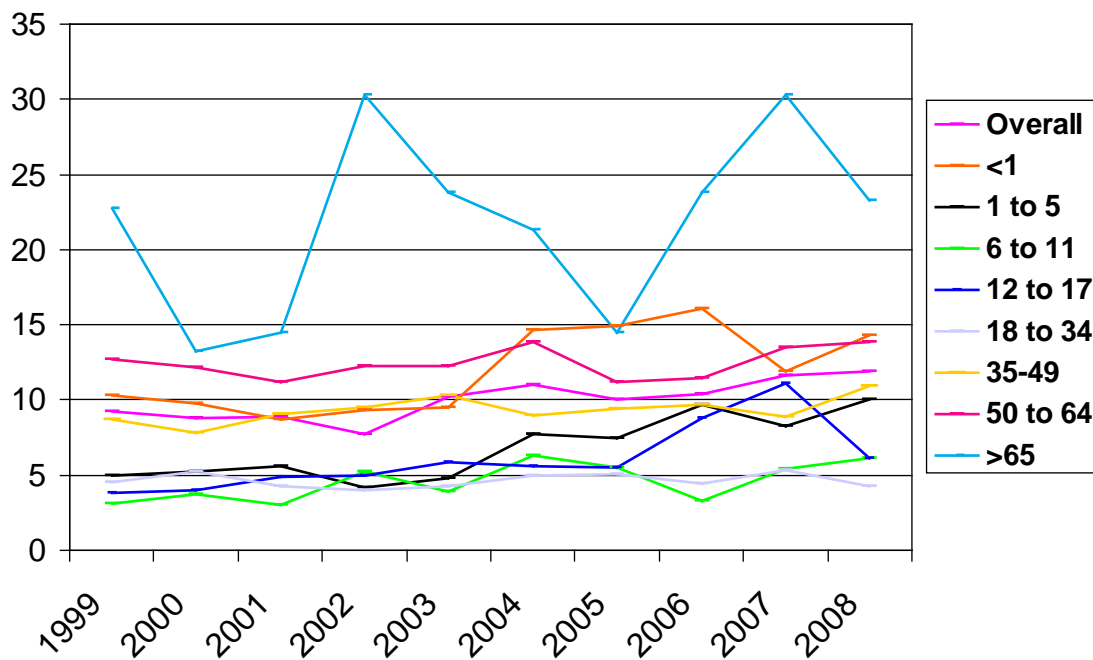
Source: *SRTR Analysis*, Data as of May 2009.

Retransplantation Trends by Recipient Characteristics

For the purposes of this overview of retransplantation, utility of liver for transplantation was defined as the ratio of primary liver transplants to liver retransplantation and does not take into consideration life-years saved (4). As seen in Figure IV-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 out of every 10.4 grafts was utilized for retransplantation, whereas in the latter 5 years (2004-2008), only 1 out of every 12 grafts was utilized for retransplantation (an overall improvement in utility of 15 percent).

This was particularly evident in certain age groups (Figure IV-15). In the group of recipients aged 1-5 years, utilization improved 60 percent, from 1 out of 6.0 grafts utilized for retransplantation from 1999-2003 to 1 out 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 percent improvement) during the same time periods.

Figure IV-15: Ratio of Primary Liver Transplants to Liver Retransplants by Recipient Age from 1999-2008



Source: SRTR Analysis, Data as of May 2009.

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 1999-2003 to 1 in 5.8 grafts from 2004-2008 (an increase of 7 percent 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 to 17 years (Table IV-9). The race of the recipient was also associated with differential rates for retransplantation (Table IV-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 percent 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 5 year period to 1 in 19.3 grafts during the latter 5 years (70 percent improvement).

Table IV-9. Ratio of Primary Liver Transplants to Liver Retransplants from 1999-2008

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 to 5	6.5	African-American	7.8	Cholestatic	7.1	Region 2	9.6
6 to 11	4.2	Other/Multi-Race	8.5	AHN	6.2	Region 3	9.7
12 to 17	5.6	Asian	14.1	Biliary atresia	7.0	Region 4	18.0
18 to 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 to 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

Although the proportion of retransplants utilized by sex (37.4 percent female/62.6 percent male) appeared similar to the proportion of males and females undergoing primary transplantation (34.9 percent female/65.1 percent 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 percent 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 IV-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 threefold difference in the utilization of liver retransplantation (Table IV-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 approximately 10 percent 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 days \pm 1453 days, while the median time to retransplantation was 222 days. Only 25 percent of retransplants fell into the immediate post-transplant 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 IV-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 non-function, 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, non-alcoholic 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.

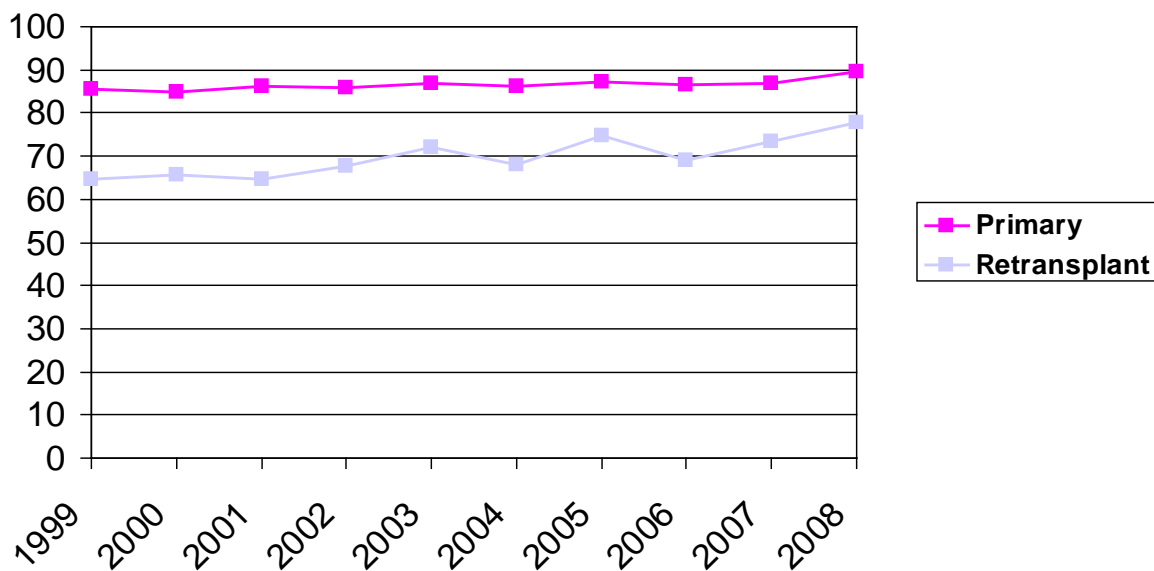
Table IV-10. Causes of Graft Failure in Liver Retransplant Recipients by Time from First Transplant to Retransplant (N=3,969 recipients with a first retransplant between 1999 and 2008)

Cause of Graft Failure*	Quartiles/Time from Primary Transplant to Retransplant							
	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	0 – 14 days		15 – 222 days		223 – 1307 days		>1308 days	
	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: <i>DeNovo</i>	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

Outcomes of Retransplantation

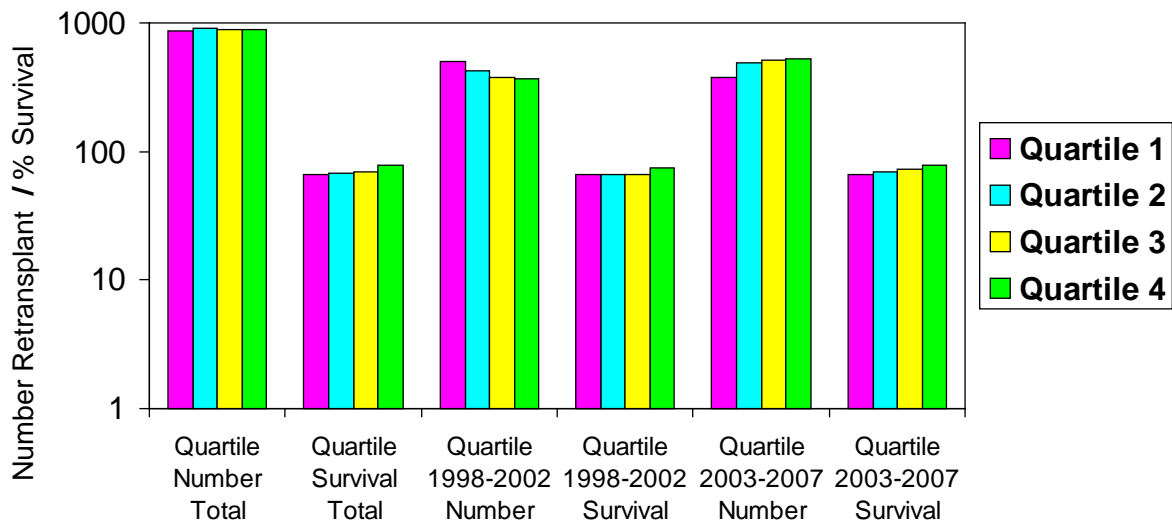
Survival outcomes following retransplantation were inferior to primary liver transplantation. Figure IV-16 demonstrates the differences between the 1-year patient survivals between primary transplants and retransplants. Over the 10-year period, however, while 1-year primary liver transplant patient survival improved by 4.1 percent, the corresponding survival for first retransplant recipients increased by 13.0 percent. 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 1998-2007, the 1-year patient survival for first retransplants in the lowest follow-up quartile was 65.8 percent; for the second quartile, it was 68.1 percent; for the third quartile, it was 70.0 percent; and the highest was in the fourth quartile at 77.3 percent. As seen in Figure IV-17, the trend in the second half of the analytic period was notable for a shift away from early retransplantation to late retransplantation with a corresponding increase in survival.

Figure IV-16: One-Year Patient Survival Following Primary Liver or First Re-Transplantation by Year



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

Figure IV-17: Number and Patient Survival Outcome Following Retransplantation by Quartile - 1998-2007



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

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.

Simultaneous Liver-Kidney Transplantation

The number of simultaneous liver-kidney (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 percent 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 2 groups varied between Regions [range 4.2 (in Regions 6,8,10) to 6.0 (in Region 7)]. Regions 1 (11.9 percent), 7 (11.4 percent) and 5 (8.2 percent) had a relatively higher percentage of SLK. In other centers,

the percentage of SLK ranged between 3.3 percent (Region 6 and 5) and 6 percent (Region 4). While the total number of liver transplants increased by 35 percent over the last 10 years (from 4,498 to 6,069), the number of SLK transplants increased by over 279 percent (from 100 to 379) (Table IV-11). Reasons for this increase in SLK over the last decade were likely multi-factorial, however, 2 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 the 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 <30ml/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.

Table IV-11. SLK Transplantation by Etiology of Liver Disease

Primary Liver Diagnosis	Year of Transplant									
	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)

Cause of liver disease

The primary diagnosis of liver disease in over 70 percent of patients undergoing SLK was non-cholestatic cirrhosis (Table IV-11). Commonly, patients referred for renal 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 non-cholestatic cirrhosis, as the total number of transplants received by patients with non-cholestatic cirrhosis in 2008 was approximately 56 percent, while 72 percent of SLK were performed in patients with non-cholestatic cirrhosis [Table 9.4a]. Thus, there is a greater requirement for SLK in patients with non-cholestatic 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 percent and 6 percent of total liver transplants performed for that indication (Table IV-11). For patients with metabolic disease, the number of SLK transplants has been comparable peaking at approximately 5 percent of all SLK. In 2008, 18.4 percent of patients who did not receive SLK transplantation had malignant disease, and only 4.2 percent 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 percent of total SLK, while in 2008 only 6 SLKs (1.6 percent) 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 IV-12. SLK Transplantation – Primary Kidney Diagnosis

Primary Kidney Diagnosis	Year of Transplant									
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total Number (%)	100	135	135	210	247	279	340	400	445	379
Glomerular Diseases		23	16	24	40	41	54	57		41
	12 (12.0)	(17.0)	(11.9)	(11.4)	(16.2)	(14.7)	(15.9)	(14.3)	30 (6.7)	(10.8)
Diabetes		16	19	25	39	38	48	73	74	67
	11 (11.0)	(11.9)	(14.1)	(11.9)	(15.8)	(13.6)	(14.1)	(18.3)	(16.6)	(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			15							
	16 (16.0)	7 (5.2)	(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		21	17	37	36	30	40	41	70	58
	22 (22.0)	(15.6)	(12.6)	(17.6)	(14.6)	(10.8)	(11.8)	(10.3)	(15.7)	(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		51	49	80	91	122	137	172	200	146
	24 (24.0)	(37.8)	(36.3)	(38.1)	(36.8)	(43.7)	(40.3)	(43.0)	(44.9)	(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)

Cause of renal disease

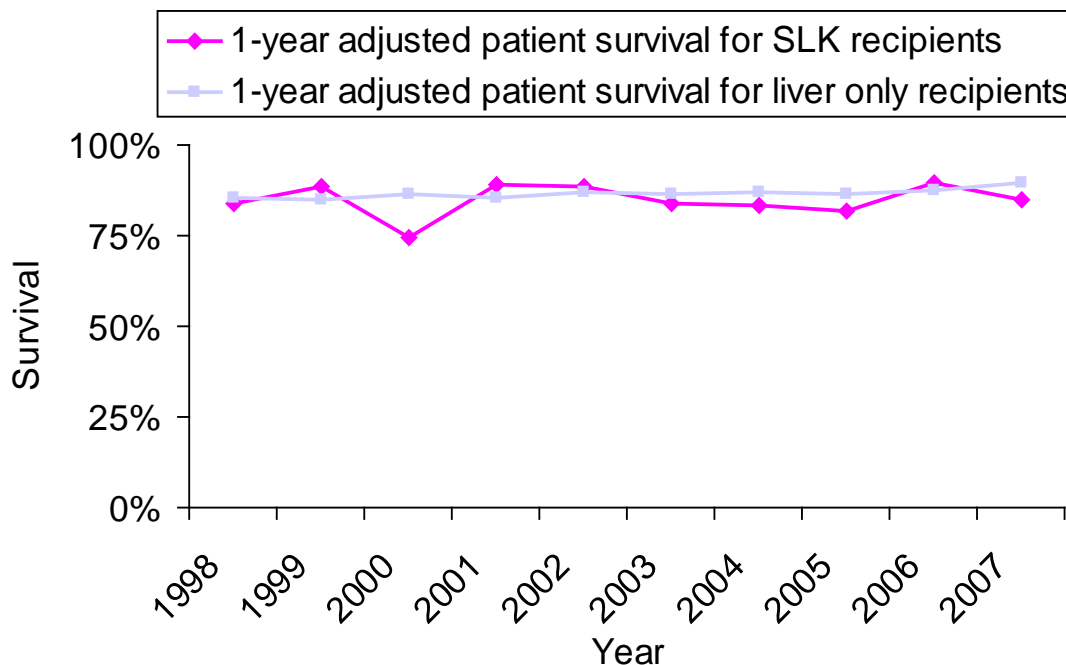
The primary kidney disease of SLK recipients was listed as “other” in approximately 40 percent (Table IV-12). Since acute renal failure and hepatorenal syndrome are not listed indications for SLK transplantation, many of these SLK recipients with a primary renal diagnosis listed as “other” might have had acute renal failure or hepatorenal syndrome. Diabetes was the most common cause of chronic renal disease in the liver transplant population, representing 11 percent to 18 percent of total SLK transplants. Tubular and interstitial diseases accounted for 10 percent to 15 percent most recently. Other diagnoses in 2008 such as polycystic renal disease, hypertension, and glomerular diseases accounted for 6.1 percent, 8.7 percent and 10.8 percent, 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 percent of all SLK to 38.5 percent. 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 United States

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 IV-9A & Figure IV-9B). For SLK transplantation, there was no such improvement in patient survival (Figure IV-18).

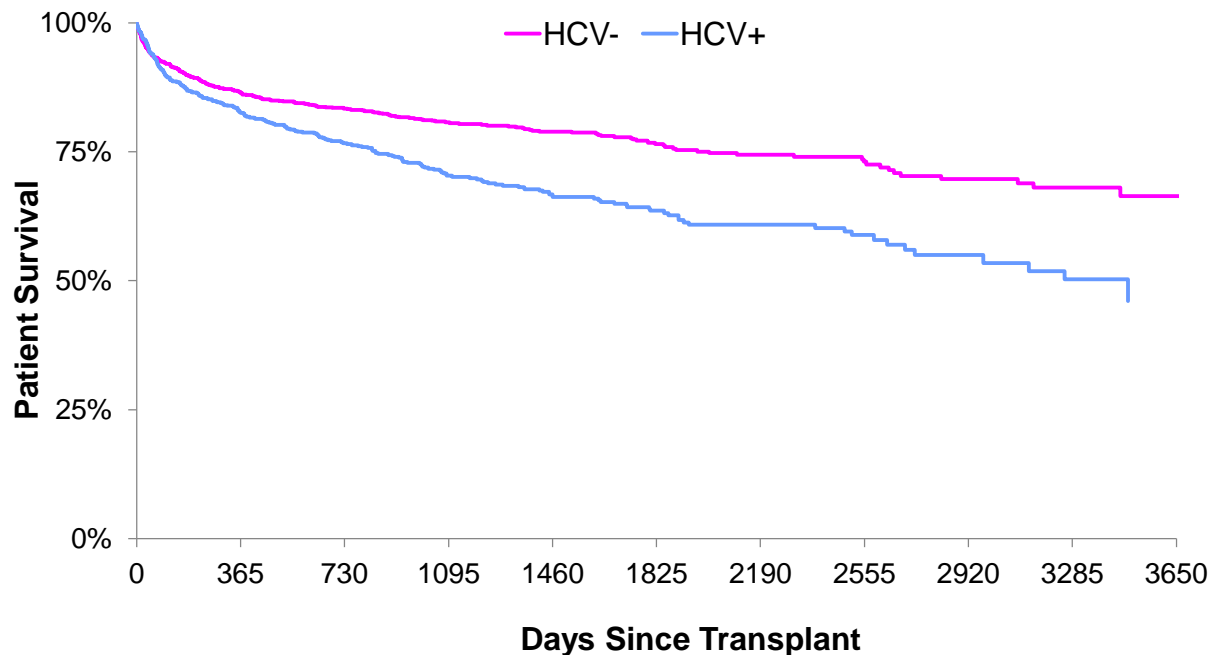
Figure IV-18: One-year Adjusted Patient Survival by Year of Transplantation for Simultaneous Liver-Kidney and Liver only Recipients



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

In fact, the patient survival of SLK recipients in 2007 at 84.7 percent was almost the same as that observed in SLK recipients in 1999 at 84.1 percent. 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 IV-19).

Figure IV-19: Unadjusted Patient Survival By HCV Status Among SLK Recipients



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

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 towards 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 post-liver transplant survival. Only 43 percent of recipients were transplanted within 90 days or less in Region 5, while 71 percent 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 percent in Maryland to 96 percent 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 this study has shown that

there may be an interaction between recipient and donor race matching on post-transplant survival in HCV positive recipients. These observations merit further investigations.

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