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Deceased Donor Split Liver Transplantation In Adult Recipients: Is The Learning Curve Over?

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Abstract

Background—Infants have the highest waitlist mortality of all liver transplant candidates. Deceased-donor split liver transplantation, a technique that provides both an adult and pediatric graft, may be the best way to decrease this disproportionate mortality. Yet concern for an increased risk to adult split recipients has discouraged its widespread adoption. We aimed to determine the current risk of graft failure in adult recipients following split liver transplantation.

Study Design—United Network for Organ Sharing (UNOS) data from 62,190 first-time adult recipients of deceased-donor liver transplants (1995–2010) were analyzed (889 split grafts). Bivariate risk factors ($p < 0.2$) were included in cox proportional hazards models of the effect of transplant type on graft failure.

Results—Split liver recipients had an over-all hazard-ratio (HR) of graft failure of 1.26 ($p < .001$) compared to whole liver recipients. The split liver HR was 1.45 ($p < .001$) in the pre-MELD era (1995–2002), and 1.10 ($p = .28$) in the MELD era (2002–2010). Interaction analyses suggested an increased risk of split graft failure in Status 1 recipients and those given an exception for hepatocellular carcinoma (HCC). Excluding higher-risk recipients, split and whole grafts had similar outcomes (HR .94, $p = .59$).

Conclusions—The risk of graft failure is now similar between split and whole liver recipients in the vast majority of cases – demonstrating that the expansion of split liver allocation may be possible without increasing the overall risk of long-term graft failure in adult recipients. Further

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prospective analysis should examine if selection bias may account for the possible increase in risk for recipients with HCC or designated Status 1.

Keywords

Liver transplantation; adult; partial liver grafts; deceased donor; risk factors; multivariate analysis; United Network for Organ Sharing

Introduction

Infants awaiting liver transplantation have the highest mortality rate of all liver transplant candidates (1–3) and may be at the greatest risk for long-term morbidities.(4–6) Facing a severe shortage of size matched pediatric whole organs, living-donor (LD) and deceased-donor (DD) partial liver grafts have increasingly been used as a means to expand the pediatric donor pool.(2, 5) Split liver transplantation, in which a single DD liver is shared between two recipients, has been demonstrated to be a safe alternative for small children when a whole or living donor liver is unavailable.(2, 7–10) An increase in the splitting of adult donor organs would potentially shorten pediatric waitlist times and could decrease the disproportionately high waitlist morbidity and mortality in this age group.(11)

Despite an increase in the number of DD adult livers that were split in the past decade, the current liver allocation system is not designed to optimize the use of this valuable resource; fewer than 10% of donors that met criteria between 1996 and 2006, including age 40 years and a body mass index 28, were actually made available for splitting.(8) Efforts to change liver allocation policy to increase the number of split liver transplants have been hampered by past analyses showing an increased risk of split graft failure in adult recipients. Studies have estimated that the adjusted-risk of graft failure in adult split liver recipients may be up to 1.51–2.55 times that experienced by whole liver recipients.(7, 12, 13) Furthermore, it has been suggested that some high-risk individuals, such as those with a higher MELD score or a Status 1A designation, may be at disproportionately increased risk when accepting split grafts.(8, 14) Other studies have suggested that the diagnosis of hepatocellular carcinoma (HCC) may be also associated with poorer outcomes when accepting living-donor partial grafts,(15–17) an association that has never been investigated in DD split grafts. Although more recent studies have shown improved outcomes in split liver transplantation, (8, 10, 13, 14, 18, 19) there has been no significant increase in its use over the past decade (1, 20)

The aims of this study were: (i) to estimate the current risk of graft failure in adult recipients of split liver grafts relative to whole liver grafts, (ii) to identify the effects of other known risk factors on the risk of split liver graft failure; and (iii) to explore if recipient selection can be optimized to mitigate any possible adverse effects on adult recipients of split grafts.

Methods

Data

All DD liver transplants reported in the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research Files were considered for analysis. IRB Approval was obtained from Boston Children's Hospital.

All DD transplants in adults (≥ 18-years) from 1995–2010 were analyzed. We excluded recipients of living-donor transplants, multi-organ transplants, re-transplants and transplants using organs procured after circulatory death of the donor. The follow-up period extended from 1/1/1995–8/31/2011. Overall median follow-up time was 1289 days (95% CI=374–2546), and did not differ by graft type. Adult candidates with fulminant hepatic failure judged to have a life-expectancy < 7 days were designated status 1A, the highest priority on the liver transplantation waitlist.(21) Non-status 1A candidates were listed on the waitlist according to the Model of End-Stage Liver Disease (MELD) score in descending order. The MELD score (introduced 3/1/2002), based on common laboratory values (bilirubin, creatinine, International Normalized Ratio) predicts the probability of pre-transplant death, with higher scores signifying higher risk.(21) The MELD era includes all transplants performed after 2/28/2002. The “HCC Exception,” introduced in 2002, provides additional status points for candidates suspected to have HCC based on clinical and radiologic findings. (21, 22) “Lab MELD Score” was calculated purely by lab values and was not point adjusted for exceptions.

All variables considered to be possible risk factors for graft failure in previous analyses were considered for investigation. (8, 12, 23) Split livers were first subdivided by split type and side including: (1) *in situ* (split in vivo, before cross clamp of the aorta) and *ex vivo* (split on bench) and (2) right and left sided grafts. As all split grafts had comparable outcome on bivariate analysis, type and side of split graft were not specified in the adjusted models. Missing values of included variables were categorized as “missing.” All variables included in the analysis had less than 20% missing data. The primary outcome variable of interest was time to graft loss as defined by re-transplant or death determined by the Social Security Master Death File. This outcome was available for all recipients in the study. Patients were followed until they were lost to follow-up, the date of graft loss or the end of the study follow-up period. As the stated reason for graft failure was often left incomplete, this data was not included in the analysis in accordance with previous studies.(8, 12)

Analysis

Recipient and donor demographic and clinical characteristics were compared between the whole and split liver groups using Chi-square tests for categorical variables. Normally distributed data were compared with student’s t-tests, while skewed continuous variables (e.g. MELD score, waitlist and cold ischemia time) were compared with Wilcoxon rank-sum tests.

Kaplan-Meier survival curves and log-rank tests were used to examine the unadjusted association of each variable with graft failure. Due to the differential in median donor age by transplant type, we used donor-age-restricted subsets (≤ 40 years) to reveal the unadjusted effects of previously suggested risk factors of split graft outcome. The proportion of functioning grafts at 3 months, 1 year and 3 years was estimated from the survival curve analysis and compared using fisher’s exact tests as in previous studies of the UNOS database (Table 3). (12)

Factors suggestive of an association with graft failure on bivariate analysis ($p<0.2$) were included in the multivariate analysis. A Cox proportional hazards model was used to

estimate the adjusted association of all variables with graft failure. Interaction tests were used to determine the effect of independent risk factors on the adjusted risk of split liver grafts. To validate these results, a propensity-adjusted cox proportional hazards model was then used to estimate the relative hazard of split liver graft failure. Logistic regression was used to derive a propensity score for the use of split liver grafts using a forward selection process ($p < 0.1$), considering all covariates from the initial Cox model.(24) Using both models we examined the effects of split liver transplantation overall and in high and lower risk subgroups. Ten-fold cross-validation was used to evaluate the stability of the multivariate model estimates.(25, 26)

A p-value .05 was considered to be significant. Analyses were performed with JMP-Pro 10.0.0 (SAS Institute Inc, Cary, NC) and SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Transplant Characteristics

The characteristics of all donor and recipient variables, stratified by transplant type, are shown in Table 1. There was an average of 45.9 split livers transplanted into our cohort per year in the pre-MELD era (1995–2001), and 63.1 split livers transplanted per year in the MELD era (2002–2010), comprising 1.4% and 1.5% of all transplants respectively in the pre-MELD and MELD eras ($p = .29$). Donors of split liver grafts tended to be significantly younger and were associated with a lesser burden of comorbid disease than their whole liver graft counterparts. Recipients of split liver grafts also had a lower median lab MELD score compared to those receiving whole liver grafts. In our cohort, median time from registration to transplant in the MELD era was significantly longer for recipients of split liver grafts compared to whole liver grafts, even when adjusting for lab MELD score. In the MELD era, left-sided and right-sided split grafts had similar graft survival (3 month: Right 88.6% versus Left 87.8% $p = 0.84$; 1 year: Right 82.4% versus Left 83.3%, $p = 1.0$). In the MELD era, regions with increased waitlist time for transplanted patients had greater rates of split liver transplantation; regions with median waitlist times of < 75 , 75–100, and > 100 days were associated with 0.7%, 1.3% and 2.5% split liver transplants, respectively ($p < 0.001$).

Over time, there have been significant changes in both recipient and donor selection in split liver transplantation (Table 2). Compared to the pre-MELD era, split liver recipients in the MELD era have tended to be slightly older ($p < 0.001$), were more likely being transplanted for hepatic malignancy ($p < 0.001$), were less likely to be status 1 ($p < 0.001$), and less likely to be in the ICU prior to transplantation ($p < 0.001$). However, time between registration and transplant was comparable in both eras ($p = .20$).

Bivariate Analysis

Kaplan-Meier curves of crude graft survival were comparable between split and whole grafts ($p = .66$, Figure 1A). However over-all split graft survival was revealed to be significantly lower than whole graft survival when restricting donor age (donors < 40 y, $p = .007$, figure 1B). In this young donor cohort split liver transplant recipients in the pre-MELD period had poorer graft survival than all whole liver recipients ($p < .001$, figure 1C), whereas there was

no difference in survival in the MELD era. While there was a suggestion of a difference in graft survival by split liver type (*ex vivo* and *in situ*) in the pre-MELD era ($p=.004$, figure 1D), this difference became negligible in the MELD era ($p=.27$, figure 1E). Status 1A recipients of split liver grafts were significantly more likely to experience early graft failure than all recipients with any other status score ($p<.001$, figure 1F). Importantly, recipients qualifying for an HCC exception experienced significantly reduced graft survival when accepting split liver grafts compared to whole liver grafts ($p=.003$, figure 1G). Furthermore, split liver recipients with HCC were associated with worse graft survival than recipients without a diagnosis of HCC ($p=.01$). When the apparently higher risk recipients with a status 1A designation or a HCC exception were excluded from age-restricted survival analysis in the MELD era, split livers were noted to have similar graft survival to whole livers ($p=.84$, figure 1H).

In a donor age-restricted (< 40 years) comparison of graft survival at 3-months, 1-year and 3-years post-transplant, split grafts were noted to have a lower rate of graft survival overall, in the pre-MELD and MELD eras, in status 1A recipients, and in patients given an exception for HCC compared to those transplanted with whole grafts (Appendix). In non-HCC and non-status 1 recipients in the MELD era, there was similar graft survival between split and whole grafts at all time-points.

Cox Proportional Hazards Model

The multivariate associations of selected donor and recipient characteristics overall (1995–2010) and in the pre-MELD (1995–2/2002) and MELD eras (3/2002–2010) are shown in Table 3. The most significant independent predictors of graft failure appeared consistent across all time periods; including recipients and donors over 70 years, CIT over 11 hours, recipient diabetes, diagnosis of primary hepatic malignancy, pre-operative mechanical ventilation, hepatitis C status, and preoperative dialysis. Overall, final status score was not highly associated with graft function when adjusting for case-mix. Split liver transplants were associated with a case-mix adjusted HR of graft failure of 1.26 compared with whole livers overall (Table 3 and 4, $p<.001$), and in the pre-MELD era (HR 1.45, $p<.001$). However in the cohort of patients treated in the MELD era, the risk of graft failure was comparable between graft types (Split HR 1.10, $p=.28$, Interaction Term comparing Pre-MELD to MELD: $p=.07$). Status 1A designation was noted to have a significant interaction with transplant type in the full Cox proportional hazards model ($p=.02$). However, no MELD category had a significant interaction with transplant type, including MELD >35 . Additionally, there was no significant interaction between transplant type and important prognostic indicators such as longer CIT (>11 hours), recipient age >70 , medical condition, preoperative ventilation or dialysis. Recipients with a Status 1A designation or HCC exception were found to have significantly greater adjusted risks of failure when transplanted with a split liver compared to a whole liver (Table 4, interaction $p=.02$ and $p=.01$ respectively).

Propensity Score-Adjusted Cox Proportional Hazards Model with Subsets

The propensity score model was highly discriminatory; the predicted graft type was concordant with the actual graft type in 86% of cases (c-statistic = .86). Using this

propensity score-adjusted model on the entire cohort, our hazard estimate of split graft failure was similar to that given by the standard Cox proportional hazards model (Table 5, HR 1.25 $p<.001$).

While there was a significant propensity adjusted risk associated with split livers in the pre-MELD era (HR 1.32, $p<.001$), there was only a trend towards an increased risk in the MELD era (HR 1.18, $p=.06$). In subsets of only status 1A recipients and only recipients with an HCC exception, split liver transplants were associated with adjusted hazards of graft failure of 2.01 ($p<.001$) and 1.84 ($p<.001$) respectively. Conversely, when only examining recipients without an HCC exception, split grafts were shown to have comparable outcomes to whole grafts (HR 1.00, $p=.98$). In the vast majority of patients in the current post-MELD era, the risk of graft failure in split grafts was similar to that of whole grafts (HR .98, $p=.87$).

Cross-K group validation demonstrated that the estimates were highly stable across the study sample.

Discussion

The development of surgical techniques to transplant reduced sized liver grafts from adult donors promised to increase the number of organs available for children. However, this also resulted in an equivalent reduction of liver grafts available for adults.(27, 28) The technique to split a liver for use in two recipients was hailed as a solution to this problem.(29) It is estimated that if even half of potentially appropriate split liver donors were made available for split liver transplantation, the pediatric liver waitlist could be eliminated.(11) However, early reports of inferior results with split liver transplantation in adult recipients have discouraged efforts to maximize the use of this technique. (7, 12, 13) We sought to estimate the current risk of graft failure in adult recipients of split liver grafts, and to determine if any potential risk in the adult transplant population could be mitigated by further optimizing recipient selection.

There was significant regional variation in the rates of split liver transplantation. In the MELD era (3/2002–2010), regions with increased waitlist time for transplanted patients had greater rates of split liver transplantation. Similar to previous analyses, (7, 12, 13) we noted a significantly increased risk of graft failure in split grafts compared to whole grafts in the pre-MELD era. However, in the MELD era we found a risk of graft failure among split liver recipients that was not significantly different from that of whole liver recipients. In the MELD era all types of split liver grafts were associated with comparable outcomes, including left and right sided grafts and grafts split *in situ* and *ex vivo*. Recipients with a status 1A designation experienced over twice the adjusted-risk of graft failure when allocated a split liver as compared to a whole liver. Furthermore, we noted a disproportionate risk of graft loss in split liver recipients who had an exception for HCC. When excluding higher-risk groups, we found that graft survival of split and whole liver grafts was similar in the majority of adult recipients.

Although the risk of split liver transplantation appeared to be significantly reduced in the current era, we aimed to determine if any specific patient cohorts were associated with a

higher risk of graft failure when transplanted with a split graft. On cox proportional hazards analysis we confirmed that older donor age was independently associated with decreased liver graft survival.(9, 30) Grafts from donors >40 years had a significantly increased risk of failure compared to grafts from donors ≤40 years of age. As split grafts tended to come from significantly younger donors than whole grafts, and thus were less associated with medical comorbidities, donor age was an important confounder of outcome by transplant type (figure 1A+B). We also noted a significantly higher MELD score in the whole liver cohort. As recent studies have suggested that greater recipient medical risk can increase the likelihood of split graft failure,(14, 18, 31) there may have been a tendency to provide split livers to recipients with lower status scores. While we found that status 1A recipients of split livers were associated with a disproportionate risk of graft failure, we did not identify a disproportionate risk when patients with higher MELD scores (>35) were given a split liver. Furthermore, other patients presumed to be high-risk in previous analyses, including ICU patients, those requiring mechanical ventilation or dialysis, and older recipients, also did not have a disproportionately increased risk of failure when transplanted with a split liver graft. Importantly, other than recipients with a status 1 designation or an HCC exception, we did not identify any other cohorts that had a higher risk of failure when given a split liver transplant instead of a whole liver transplant.

Malignancy has become an increasingly common diagnosis requiring liver transplantation. In the MELD era the HCC exception has been given to 23.3% and 26.8% of recipients of whole and split grafts, respectively. On both donor age-restricted survival analysis and multivariate regression analysis, we found that recipients qualifying for an HCC exception appeared to have a greater risk of graft failure when receiving split grafts compared to whole grafts. While no previous study has noted an increased risk of deceased-donor split grafts in recipients with HCC, it has been suggested that partial grafts from living donors may have an increased risk of disease recurrence in this population.(15–17) The increased risk of disease recurrence seen in living donor recipients has been hypothesized to result from either selection bias or the release of growth factors involved in regeneration of the partial graft. (32–35) Observations supporting selection bias include: (i) living donor recipients are more likely to fall outside of Milan criteria, (16) (ii) they often have more poorly differentiated tumors (15, 17) and (iii) they are associated with significantly shorter wait-times than deceased donor recipients – possibly eliminating the pre-transplant dropout seen in whole grafts due to high-risk disease. (17, 36) While selection bias is a possible explanation for our findings, we found that recipients with an HCC exception who were allocated split livers were largely similar to those given whole livers by the risk factors measured in the UNOS database, including by waitlist time. Additionally, unlike recipients of LD partial grafts, most deceased-donor recipients with HCC should fall within the Milan criteria before receiving an exception for HCC.(22) In fact, recent studies have found that 94% of patients with an HCC exception fall within the Milan Criteria and 99% fall within the University of California at San Francisco criteria, making tumors in recipients given an HCC exception lower risk than those in recipients without an exception.(37) While the proportion of patients diagnosed with HCC, who qualified for an HCC exception, was similar across graft types - other tumor specific factors may also contribute to tumor risk. Even the previously noted

increase in recurrence in living donor partial grafts has not been found to affect graft or patient survival when careful selection is employed.(16, 17, 38).

To determine if recurrence of disease might have explained the increased risk of graft failure in split grafts, we examined the primary causes of death for recipients with HCC exceptions. As the proportion of deaths assumed to be due to malignancy appeared comparable between graft types, it is possible that differences in graft failure risk may have been unrelated to malignancy. However as the specific cause of death was missing in over 25% of mortalities after split and whole liver transplantation, the UNOS database alone may be inadequate to definitively answer this question. Future prospective research will be needed to validate the present study's findings of increased risk in recipients with an HCC exception and to determine the etiology of this potential risk.

Several factors may have influenced the reduction in relative risk of split liver transplantation in the modern era: (1) Changes in recipient and donor selection and matching, (2) changes in allocation and logistics, and (3) improved technical proficiency. While we have adjusted for the effects of possible changes in selection criteria in a multivariate subset analysis, there may be additional unmeasured factors that could explain the reduction in our risk estimates over time. Although we speculate that all three factors may have played a significant part, further analysis may be needed to determine the precise reasons for this improvement.

Using an array of analytical techniques, we have demonstrated that while split liver grafts were associated with a significantly increased risk of failure in the pre-MELD era, they have significantly improved over time. In the current MELD era, split and whole grafts have a similar risk of graft failure on both bivariate and case-mix adjusted analysis. Although further analysis will be required to determine the etiology of the increased risks noted in some groups, this study demonstrates that the risk of split graft failure may be similar to the risk of whole graft failure in the vast majority of individuals. Our study suggests that an allocation policy that encourages the use of split liver transplantation may be possible without significantly increasing the risk of graft failure in adult recipients. Through the expansion of split liver transplantation, the transplant community may be able to both increase the organ pool and decrease the current disparities in waitlist morbidity and mortality in infants and young children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation

All abbreviations used in this manuscript are explained directly within the text

CIT	Cold Ischemia Time
DD	Deceased Donor
HCC	Hepatocellular Carcinoma
ICU	Intensive Care Unit
INR	International Normalized Ratio
LD	Living Donor
MELD	Model of End-Stage Liver Disease
UNOS	United Network for Organ Sharing

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Figure 1. (A–H). Unadjusted Analysis

Kaplan Meier curves of graft survival in split and whole liver transplantation. (A) All donors (1995–2010). (B) Donor Age Restricted (Only Donors < 40 years, 1995–2010). (C) Effect of MELD on Transplant Type, (Donors < 40 years, 1995–2010). (D) Split Type in Pre-MELD era (Donors < 40 years, 1995–1/2002). (E) Split Type in Post-MELD era (Donors < 40 years, 2/2002–2010). (F) Effect of Status 1 on Transplant Type (Donors < 40 years, 1995–2010). (G) Effect of HCC Exception on Transplant Type (Donors < 40 years, 2002–2010).

(H) Excluding recipients with the HCC Exception and Status 1 Donors 40 years, 2002–2010).

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Table 1

Differences in split and whole liver transplantation based on selected variables found to be significant predictors of graft survival. N= 62,190.

Variables	Whole (N=61301)	Split (N=889)	p-value
Donor Factors:			
Age (yrs, mean, SD)	40.6 ± 17.4	24.0 ± 10.2	<.001
Body Mass Index (BMI; median, IQR)	25.4 (22.4–29.1)	23.6 (21.5–26.0)	<.001
Gender Male (%)	36489 (59.6)	649 (73.0)	<.001
Donor vasopressors (1) (%)	54250 (88.5)	764 (86.0)	.02
Diabetes (%)	4977 (8.1)	13 (1.5)	<.001
Previous Malignancy (%)	2004 (3.3)	4 (0.04)	<.001
Cold Ischemia (Hrs, median, IQR)	7.2 (5.5–9.3)	8 (6–10.1)	<.001
Split Type			
In SITU (Split before cross clamp)	N/A	510 (57.4)	N/A
Ex VIVO (Split on Bench)	N/A	379 (42.6)	
Split Graft Side			
Left-Sided	N/A	185 (20.8)	N/A
Right-Sided	N/A	704 (79.2)	
Share Type			
Local	44344 (72.3)	605 (68.1)	<.001
Regional	13254 (21.6)	256 (28.8)	
National	3702 (6.0)	28 (3.2)	
Recipient Factors:			
Age (yrs, mean, SD)	52.2 ± 10.2	52.1 ± 11.2	.82
Gender Male (%)	40554 (66.2)	412 (46.3)	<.001
Weight (kg, median, IQR)	81.8 (70–95.3)	68.5 (59.3–81.3)	<.001
Body Mass Index (BMI) (median, IQR)	27.6 (24.4–31.7)	25.1 (22.2–28.3)	<.001
Final Status Score (%)			
MELD > 30 (Post MELD)	6897 (17.4)	80 (14.4)	.06
Status 1	3350 (5.5)	37 (4.2)	.10
Lab MELD Score (median, IQR)	19 (13–26)	16 (11–23)	<.001
Primary Diagnosis (%)			.01

Variables	Whole (N=61301)	Split (N=889)	p-value
Acute	3630 (5.9)	43 (4.8)	
Biliary Atresia/Hypoplasia	109 (0.2)	5 (0.6)	
Cancer	8047 (13.1)	129 (14.5)	
Cirrhosis	33751 (55.1)	511 (57.5)	
Alcoholic Cirrhosis	12046 (19.7)	142 (16.0)	
Metabolic	1761 (2.9)	25 (2.8)	
Other	1957 (3.2)	34(3.8)	
Primary Diagnosis HCC (2002–2010) (%)			
With HCC Exception	5158 (74.3)	77 (77.0)	.64
Without HCC Exception	1784 (25.7)	23 (23.0)	
HCC Exception (2002–2010) (%)			
<i>Primary diagnosis listed as:</i>			
Cancer	5237 (56.6)	78 (52.4)	.18
Non-ETOH Cirrhosis	2921 (31.6)	46 (30.9)	
Other	1096 (11.8)	25 (16.8)	
Medical Condition (%)			
Home	42902 (70.0)	631 (71.0)	.61
Inpatient	10128 (13.4)	136 (13.7)	
ICU	8231 (16.5)	122 (15.3)	
Ventilator (%)			
	4067 (6.6)	54 (6.1)	.54
Dialysis (%)			
	3210 (5.2)	28 (3.1)	.004
Diabetes (%)			
	12024 (19.6)	169 (19.0)	.76
Confirmed HCV Positive (%)			
	24193 (39.5)	339 (38.1)	.63
Previous Malignancy (%)			
	4189 (6.8)	67 (7.5)	.23
Time between Registration and Transplant, Days, Median (IQR) 2002–2010			
All	74 (16–255)	176 (45–444)	<.001
MELD 30 (N, w=31086, s=466)	93 (27–276)	189.5(60.8–445.3)	<.001
MELD 31–35 (N, w=3258,s=49)	50 (9–334)	258 (68.5–552.5)	<.001
MELD >35 (N, w=3639, s=31)	17 (6 – 125)	12 (12.8–361.3)	.97
Procedure Location/Time Factors:			
Transplant Year (%)			
1995–2/2002	21630 (35.3)	332 (37.4)	.20
3/2002–2010	39671 (64.7)	557 (62.7)	

Table 2

Comparison of split liver donors and recipients by time period (Pre-MELD=1995–2/2002 and MELD=3/2002–2010).

Variables	Pre-MELD Era 1995–2/2002 (N=332)	MELD Era 3/2002–2010 (N=557)	p-value
Donor Factors:			
Rate of Split Graft Transplantation (Proportion of Total Recipients)	332 (1.5)	557 (1.4)	.19
Age (yrs, mean, SD)	25.7 ± 11.1	23.0 ± 9.6	<.001
Cold Ischemia (Hrs, median, IQR)	8.0 (5.6–10.3)	8.0 (6.0–10.0)	.98
Split Type			
In SITU (Split before cross clamp)	166 (50.0)	344 (61.8)	<.001
Ex VIVO (Split on Bench)	166 (50.0)	213 (38.2)	
Split Graft Side			
Left/Lateral	62 (18.7)	123 (22.1)	.23
Right/Trisegment	270 (81.3)	434 (77.9)	
Share Type			
Local	220 (66.3)	385 (69.1)	.19
Regional	97 (29.2)	159 (28.5)	
National	15 (4.5)	13 (2.3)	
Recipient Factors:			
Age (yrs, mean, SD)	50.5 ± 11.0	53.0 ± 11.2	<.001
Primary Diagnosis (%)			
Cancer	23 (6.9)	108 (19.4)	<.001
Cirrhosis	213 (64.2)	298 (53.5)	
Alcoholic Cirrhosis	55 (16.6)	87 (15.6)	
Other	43 (13.0)	64 (11.5)	
Status 1 (%)	27 (8.1)	10 (1.8)	<.001
Medical Condition (%)			
Home	208 (62.7)	423 (75.9)	<.001
Inpatient	54 (16.3)	82 (14.7)	
ICU	70 (21.1)	52 (9.3)	
Confirmed HCV Positive (%)	128 (38.6)	211 (37.9)	.89
Time between Registration and Transplant, Days, Median (IQR)	152.5 (47.3–414.5)	176 (45–444)	.20

Table 3

Cox Proportional Hazards Regression Analysis

Adjusted hazard ratios of graft failure of selected donor and recipient variables in study patients overall (1995–2010) and in the pre-MELD (1995–2/2002) and MELD era (3/2002–2010).

Risk Factors	Overall (1995–2010) Hazard of Graft Failure (HR)	P- value	Pre-MELD (1995–2/2002) Hazard of Graft Failure (HR)	P- value	MELD Era (3/2002–2010) Hazard of Graft Failure (HR)	P- value
Donor Factors						
Graft Type						
Whole	1.00	Ref.	1.00	Ref.	1.00	Ref.
Split	1.26 (1.12–1.43)	<.001	1.45 (1.21–1.73)	<.001	1.10 (.93–1.30)	.28
Age (Years)						
40	1.00	Ref.	1.00	Ref.	1.00	Ref.
41–50	1.17 (1.12–1.23)	<.001	1.17 (1.10–1.25)	<.001	1.18 (1.11–1.25)	<.001
51–60	1.32 (1.26–1.39)	<.001	1.32 (1.23–1.42)	<.001	1.34 (1.26–1.42)	<.001
61–70	1.49 (1.41–1.57)	<.001	1.45 (1.33–1.58)	<.001	1.52 (1.42–1.64)	<.001
>70	1.72 (1.60–1.84)	<.001	1.77 (1.56–2.01)	<.001	1.71 (1.56–1.87)	<.001
Cause of Death						
Head Trauma	1.00	Ref.	1.00	Ref.	1.00	Ref.
Anoxia	1.05 (1.00–1.10)	.06	1.05 (.96–1.14)	.31	1.05 (.99–1.12)	.12
CNS Tumor	1.08 (.92–1.26)	.34	1.24 (1.00–1.54)	.05	0.93 (.74–1.17)	.53
Stroke	1.10 (1.06–1.14)	.002	1.10 (1.04–1.17)	<.001	1.09 (1.03–1.15)	<.001
Other	1.08 (.97–1.21)	.18	1.11 (.93–1.32)	.24	1.07 (.93–1.24)	.37
Diabetes	1.11 (1.05–1.17)	<.001	1.07 (.96–1.18)	.25	1.12 (1.05–1.20)	<.001
Previous Malignancy	1.09 (1.01–1.18)	.03	1.06 (.92–1.21)	.43	1.11 (1.01–1.22)	.03
CMV Positive	1.03 (.99–1.06)	.13	1.06 (1.01–1.11)	.02	1.00 (.96–1.04)	.91
CIT (Hours)						

Risk Factors	Overall (1995–2010) Hazard of Graft Failure (HR)	p- value	Pre-MELD (1995–2/2002) Hazard of Graft Failure (HR)	p- value	MELD Era (3/2002–2010) Hazard of Graft Failure (HR)	p- value
0–5	1.00	Ref.	1.00	Ref.	1.00	Ref.
5.1–7	1.05 (1.00–1.10)	.07	0.95 (.88–1.04)	.27	1.10 (1.03–1.17)	.005
7.1–9	1.12 (1.06–1.18)	<.001	0.98 (.90–1.06)	.56	1.20 (1.12–1.28)	<.001
9.1–11	1.13 (1.07–1.20)	<.001	0.98 (.90–1.07)	.70	1.22 (1.13–1.31)	<.001
>11	1.25 (1.18–1.33)	<.001	1.08 (.99–1.18)	.09	1.37 (1.26–1.49)	<.001
Missing	1.21 (1.14–1.28)	<.001	1.09 (.99–1.19)	.08	1.26 (1.18–1.36)	<.001
Time Period						
1995–2/2002	1.08 (.98–1.19)	.13	N/A	N/A	N/A	N/A
3/2002–2010	1.00	Ref.				
Share Status						
Local	1.00	Ref.	1.00	Ref.	1.00	Ref.
Regional	1.04 (1.00–1.09)	.05	1.08 (1.02–1.15)	.02	1.02 (.96–1.08)	.53
National	1.06 (.98–1.14)	.13	1.03 (.92–1.16)	.58	1.06 (.96–1.17)	.23
Recipient Factors						
Age (Years)						
40	1.00	Ref.	1.00	Ref.	1.00	Ref.
41–50	0.97 (.92–1.03)	.30	1.01 (.93–1.09)	.91	0.91 (.84–.99)	.03
51–60	1.01 (.96–1.07)	.68	1.07 (.99–1.15)	.12	0.94 (.86–1.01)	.11
61–70	1.21 (1.14–1.28)	<.001	1.30 (1.20–1.42)	<.001	1.09 (1.00–1.19)	.04
>70	1.46 (1.31–1.61)	<.001	1.51 (1.26–1.80)	<.001	1.36 (1.19–1.55)	<.001
Diagnosis						
Cirrhosis	1.00	Ref.	1.00	Ref.	1.00	Ref.
Alcoholic Cirrhosis	1.03 (.99–1.07)	.12	1.06 (1.01–1.12)	.03	1.00 (.95–1.06)	.99
Acute	0.99 (.92–1.06)	.67	0.91 (.83–1.01)	.07	1.08 (.97–1.19)	.15
Atresia/Hypoplasia	0.97 (.67–1.42)	.89	0.80 (.43–1.49)	.48	1.10 (.68–1.77)	.89
Hepatic Malignancy	1.23 (1.17–1.30)	<.001	1.53 (1.37–1.71)	<.001	1.18 (1.11–1.26)	<.001

Risk Factors	Overall (1995–2010) Hazard of Graft Failure (HR)	p- value	Pre-MELD (1995–2/2002) Hazard of Graft Failure (HR)	p- value	MELD Era (3/2002–2010) Hazard of Graft Failure (HR)	p- value
Metabolic	0.91 (.83–1.00)	.06	0.90 (.79–1.03)	.12	0.92 (.81–1.05)	.22
Other	1.07 (.98–1.17)	.11	1.11 (.95–1.29)	.19	1.03 (.92–1.14)	.64
Diabetes	1.19 (1.15–1.24)	<.001	1.27 (1.20–1.34)	<.001	1.15 (1.09–1.20)	<.001
Medical Condition						
Home	1.00	Ref.	1.00	Ref.	1.00	Ref.
Inpatient	1.11 (1.06–1.16)	<.001	1.12 (1.05–1.19)	<.001	1.12 (1.06–1.19)	<.001
ICU	1.14 (1.07–1.21)	<.001	1.06 (.98–1.15)	.15	1.25 (1.14–1.37)	<.001
Pre-operative Mechanical Ventilation	1.36 (1.27–1.45)	<.001	1.16 (1.05–1.28)	.003	1.61 (1.46–1.78)	<.001
Hepatitis C	1.43 (1.38–1.48)	<.001	1.46 (1.38–1.53)	<.001	1.39 (1.33–1.46)	<.001
Dialysis	1.22 (1.14–1.31)	<.001	1.15 (1.01–1.30)	.03	1.26 (1.15–1.37)	<.001
Creatinine						
0–.5	1.00	Ref.	1.00	Ref.	1.00	Ref.
.6–1	0.92 (.85–.99)	.03	0.96 (.86–1.08)	.49	0.88 (.79–.98)	.02
1.1–1.5	1.01 (.93–1.10)	.76	1.10 (.98–1.24)	.10	0.94 (.84–1.05)	.26
1.6–2	1.10 (1.01–1.21)	.03	1.23 (1.08–1.40)	.002	1.02 (.90–1.15)	.79
>2	1.19 (1.09–1.29)	<.001	1.34 (1.18–1.53)	<.001	1.11 (.98–1.25)	.09
Status Score						
MELD 20	1.00	Ref.	N/A	N/A	1.00	Ref.
MELD 21–30	1.07 (1.02–1.13)	.009	N/A	N/A	1.07 (1.01–1.13)	.02
MELD 31–35	1.11 (1.02–1.20)	.01	N/A	N/A	1.06 (.97–1.16)	.18
MELD >35	1.07 (.99–1.17)	.10	N/A	N/A	0.97 (.88–1.07)	.56
Status 1	0.96 (.86–1.07)	.45	1.06 (.95–1.18)	.34	0.71 (.60–.82)	<.001
Status 2	1.08 (.97–1.19)	.16	1.00 (.95–1.06)	.95	N/A	N/A
Status 3 or 4	1.09 (.98–1.22)	.11	1.0	Ref.	N/A	N/A

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Model also adjusted for donor ethnicity, gender, body mass index (BMI), hypertension, smoking history, cocaine use, illicit drug use, hepatitis B and C, creatinine, distance between donor and recipient center, and recipient ethnicity, gender, BMI, exception, previous malignancy, ABO compatibility, and region.

Table 4
Subset Analysis Using Cox Proportional Hazards Model

Estimation of the adjusted association of split graft type with graft survival in high and low-risk subsets using a proportional hazards model adjusted for case mix.

Cox Proportional Hazards Adjusted Risk of Graft Failure			
	Risk of Graft Failure		Model Interaction Terms
	HR (95% CI)	p-value	p-values
Overall (2002–2010)			
Split Liver	1.26 (1.12–1.43)	<.001	N/A
Whole Liver	1.0	Ref.	
Subsets:			
Pre-MELD Era			
Split Liver	1.45 (1.21–1.73)	<.001	.07
Whole Liver	1.0	Ref.	
MELD Era			
Split Liver	1.10 (.93–1.30)	.28	Ref.
Whole Liver	1.0	Ref.	
Status 1 (1995–2010)			
Split Liver	2.05 (1.25–3.38)	<.001	.02
Whole Liver	1.0	Ref.	
Not Status 1 (1995–2010)			
Split Liver	1.21 (1.07–1.38)	<.001	Ref.
Whole Liver	1.0	Ref.	
HCC Exc (2002–2010)			
Split Liver	1.73 (1.28–2.33)	<.001	.01
Whole Liver	1.0	Ref.	
No HCC Exc (2002–2010)			
Split Liver	0.94 (0.77–1.16)	.59	Ref.
Whole Liver	1.0	Ref.	

Table 5
Subset Analysis Using Propensity Score

Estimation of the adjusted association of split graft type with graft survival in high and low-risk subsets using a proportional hazards model adjusted for the estimated *propensity* to split the donor liver.

Risk Factor	Adjusted Hazard of Graft Failure (HR)	P-value
All Years - 1995–2010		
Given Split Liver:		
Overall	1.25 (1.11–1.42)	<.001
<i>Subset:</i> Status 1 Only	2.01 (1.24–3.24)	<.001
<i>Subset:</i> Pre-MELD Only	1.32 (1.11–1.58)	<.001
<i>Subset:</i> Post-MELD Only	1.18 (1.00–1.41)	.06
Whole Liver	1.00	Reference
Post-MELD Era 3/2002–2010		
Given Split Liver:		
Overall in Post-MELD Era	1.18 (1.00–1.41)	.06
<i>Subset:</i> HCC Exceptions	1.84 (1.37–2.49)	<.001
<i>Subset:</i> NO HCC Exception	1.00 (.81–1.24)	.98
Whole Liver	1.00	Reference
Post-MELD, In Lower Risk Patients (No Status 1, No HCC Exception)		
Split Liver	0.98 (.79–1.22)	.87
Whole Liver	1.00	Reference