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Early liver retransplantation in adults

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Summary

Up to 23% of liver allografts fail post-transplant. Retransplantation is only the recourse but remains controversial due to inferior outcomes. The objective of our study was to identify high-risk periods for retransplantation and then compare survival outcomes and risk factors. We performed an analysis of United Network for Organ Sharing (UNOS) data for all adult liver recipients from 2002 through 2011. We analyzed the records of 49 288 recipients; of those, 2714 (5.5%) recipients were retransplanted. Our analysis included multivariate regression with the outcome of retransplantation. The highest retransplantation rates were within the first week (19% of all retransplantation, day 0–7), month (20%, day 8–30), and year (33%, day 31–365). Only retransplantation within the first year (day 0–365) had below standard outcomes. The most significant risk factors were as follows: within the first week, cold ischemia time >16 h [odds ratio (OR) 3.6]; within the first month, use of split allografts (OR 2.9); and within the first year, use of a liver donated after cardiac death (OR 4.9). Each of the three high-risk periods within the first year had distinct causes of graft failure, risk factors for retransplantation, and survival rates after retransplantation.

Introduction

About 14–23% of liver allografts fail requiring retransplantation, according to large single-center experiences [1,2]. The only recourse after graft failure is retransplantation. But that option remains controversial because retransplants are associated with inferior outcomes, as compared to primary liver transplants. After liver retransplantation, the 1-year recipient survival rate is only about 60%, compared with after primary liver transplants, 80–90% [3,4]. Given such inferior outcomes, several studies have investigated risk factors for mortality after retransplantation in an attempt to optimize outcomes. For example, Hong *et al.* created an index to exclude retransplant candidates on the basis of these risk factors: age >55 years, Model End-stage Liver Disease (MELD) score >27, >1 prior orthotopic liver transplant, mechanical ventilation, serum albumin <2.5 g/dl, donor age >45 years, red blood cell transfusion >30 units, and need for retransplantation 15–180 days after the primary transplant. For retransplant recipients who did not have those risk factors, the 5-year patient survival rate was 79% [3].

Retransplantation of other solid organs has also yielded inferior results. Kidney retransplantation and pancreas retransplantation have consistently demonstrated significantly inferior graft survival [5,6]. Recipients of heart retransplantation and lung retransplantation have markedly reduced survival [7–9].

In our study, instead of just analyzing patient survival rates after retransplantation, we also focused on the risk factors leading to retransplantation. The donor risk index (DRI) described by Feng *et al.* [10] is an accepted model to assess risk of graft failure over time and includes such variables as donor cause of death, donor race, donation after cardiac death, split allografts, donor height, donor geographic location, and cold ischemia

time. The DRI defines graft failure as death or retransplantation; with that definition, however, graft failure most often means death from a cause not listed as graft failure. The retransplant DRI is a more selective model, predicting graft failure among retransplantation recipients. It is essentially the DRI with the incorporation of the cause of graft failure. It suffers from the same problem with its definition of graft failure [11].

We undertook a focused analysis of retransplantation, first examining retransplant rates to identify high-risk periods. We next compared survival after retransplantation during the high-risk periods to identify substandard outcomes. Finally, we sought to establish risk factors for retransplantation during differing high-risk periods post-transplant. We studied all recognized recipient and donor risk factors (Table 1), incorporating donor–recipient

Table 1. Risk factors considered in multivariate analysis.

Donor risk factor	% Entry fill	Recipient risk factors	% Entry fill
Age 0–15 years	100	Admitted to ICU Pretransplant	100
Age 15–20 years	100	Admitted to Hospital Pretransplant	100
Age 21–30 years	100	Age 18–30	100
Age 31–50 years (reference)	100	Age 31–40	100
Age 51–60 years	100	Age 41–60 (reference)	100
Age 61–70 years	100	Age 61–70	100
Age >70 years	100	Age >70	100
Cause of Death Anoxia	99.9	Albumin <2.0 g/dl	99.9
Cause of Death Cerebral Vascular Accident	99.9	Albumin 2.0–2.5 g/dl	99.9
Cause of Death CNS Tumor	99.9	Any Previous Malignancy	99.9
Cause of Death Other	99.9	Ascites Pretransplant	99.1
Cold Ischemia Time 0–6 h	92.7	Body Mass Index >35	99.4
Cold Ischemia Time 7–12 h (reference)	92.7	Body Mass Index 30–35	99.4
Cold Ischemia Time 13–16 h	92.7	Diabetes Mellitus	99.1
Cold Ischemia Time 17–20 h	92.7	Diagnosis – Acute Hepatic Necrosis	100
Cold Ischemia Time >20 h	92.7	Diagnosis – Cholestatic Liver Disease	100
Creatinine >1.5 mg/dl	99.9	Diagnosis – Malignancy	100
Creatinine >2.0 mg/dl	99.9	Diagnosis – Metabolic Liver Disease	100
Deceased Donor After Cardiac Death	100	Diagnosis – Other	100
Diabetes Mellitus (Type Unspecified)	100	Dialysis Prior to Transplantation	100
Donor Hospital stay – 1 day	99.9	Encephalopathy at Transplant	99.1
Donor Hospital stay – 2 days (reference)	99.9	Female	100
Donor Hospital stay – 3 days	99.9	Hepatitis B (Core Ab positive)	94.9
Donor Hospital stay – 4 or more days	99.9	Hepatitis C (Positive serology)	98.0
Female	100	History of Angina or Coronary Artery Disease	100
Height (<25th ‰)	99.4	Hx of COPD	49.8
Height (>75th ‰)	99.4	Hx of Peripheral Vascular Disease	49.8
Hypertension	100	Hypertension	49.8
Macrosteatosis <10% (reference)	24.1	Incidental Tumor found at Transplant	49.7
Macrosteatosis 11–20%	24.1	Life Support Pretransplant	100
Macrosteatosis 21–30%	24.1	MELD score <9	98.6
Macrosteatosis >30%	24.1	MELD score 9–25 (reference)	98.6
National Allocation	100	MELD score 26–30	98.6
Partial or Split Liver	99.9	MELD score 31–35	98.6
Race – African American	100	MELD score >35	98.6
Regional Allocation	100	Previous Transplant	100
Total Bilirubin 1–1.8 mg/dl	99.3	Portal Bleed 48 h Pretransplant	29.8
Total Bilirubin >1.8 mg/dl	99.3	Portal Vein Thrombosis at Transplant	100
Warm Ischemia Time ≤30 min	38.2	Previous Abdominal Surgery	100
Warm Ischemia Time 31–59 min (reference)	38.2	Pulmonary Embolus within 6 months of Registration	49.8
Warm Ischemia Time 60–75 min	38.2	Race – African American	100
Warm Ischemia Time >75 min	38.2	Spontaneous Bacterial Peritonitis Pretransplant	100
Weight (<25th ‰)	100	TIPS at Transplant	100
		UNOS Status 1	100
		Variceal Bleeding within 2 weeks of Registration	49.8

matching, in our multivariate analysis, all in the effort to minimize the inferior outcomes after liver retransplantation.

Patients and methods

Study population

For our analysis of survival after retransplantation, we performed a retrospective analysis of United Network for Organ Sharing (UNOS) de-identified patient-level data [collected by the Organ Procurement and Transplantation Network (OPTN)] for all adult recipients who underwent retransplantation from January 1, 2002 through October 31, 2011. We excluded recipients of combined or multivisceral transplants ($n = 507$), recipients of living donor transplants ($n = 26$), and recipients of more than one prior liver transplant ($n = 294$). All recipients had been followed from the date of their retransplantation until either the date of death or the date of last known follow-up. In all, we analyzed the records of 3571 recipients. About 2714 of these recipients received their primary transplants and retransplants within our study period. About 857 recipients received their primary transplants prior to our study period but received their retransplant during our study period and were therefore included.

For our analysis of retransplantation, we performed a retrospective analysis of UNOS de-identified patient-level data (collected by the OPTN) for all adult recipients who underwent a primary liver transplant from January 1, 2002 through October 31, 2011. We included all recipients who were 18 years or older at the time of their primary transplant. Donor and recipient characteristics had been reported at the time of transplant, with follow-up information collected at 6 months and then yearly post-transplant. We excluded recipients of combined or multivisceral transplants ($n = 3655$) and recipients of living donor transplants ($n = 2203$). All recipients had been followed from the date of their primary transplant until the date of their retransplant ($n = 2714$), the date of death ($n = 11\ 457$), or the date of last known follow-up ($n = 35\ 117$). In all, we analyzed the records of 49 288 recipients.

Statistical analysis

To analyze the data, we used a standard statistical software package, STATA 12 (Stata Corporation, College Station, TX, USA). To compare continuous variables (reported as the mean ± standard deviation), we used the Student's *t*-test. To compare categorical variables, we used contingency tables. Results were considered significant at a *P* value of <0.05. All reported *P* values were two-sided.

Our primary outcome was death after retransplantation. Time to death was assessed as time from the date of retransplantation to the date of death. For our time-to-event analysis, we used the Kaplan–Meier method with the log-rank test. Recipients lost to follow-up or alive on October 31, 2011, were censored at the date of last known follow-up.

We divided our study period into three equal 3-year periods, 2002–2005, 2005–2008, and 2008–2011, and compared Kaplan–Meier survival outcomes with the log-rank test.

The secondary outcome measure was retransplantation within the first week (0–7 days), first month (8–30 days), or first year (31–365 days) post-transplant (after the primary transplant). For our time-to-event analysis, we used life tables with the log-rank test. Recipients lost to follow-up or alive on October 31, 2011, were censored at the date of last known follow-up. In our logistic regression analysis, retransplantation within the first week, first month, and first year were the dependent variables, whereas the risk factors (Table 1) were the independent variables.

We performed three separate multivariate analyses for retransplantation within the first week, within the first month, and within the first year. All recipients who underwent their retransplant within the first week were removed from our analysis of the first month; likewise, all recipients who underwent their retransplant within the first month were removed from our analysis of the first year. For our multivariate logistic regression (stepwise backward) analysis, elimination was based on a *P* value > 0.05.

We also conducted a Cox regression analysis, with retransplantation as the outcome of analysis. We again performed a stepwise backward analysis with elimination based on a *P* value > 0.05.

Retransplant rate

We calculated the retransplant rate for each day, month, and year post-transplant.

Cause of graft failure

In the UNOS database, the cause of graft failure is a fill-in entry, with only a 9.2% entry completion rate during our study period. For that reason, we were unable to incorporate the cause of graft failure into our regression analysis.

Donor–recipient matching

We defined high-risk (for retransplantation) donors as having any of the three strongest risk factors (donor age 61–70, donor age >70, and donation after cardiac death) for retransplantation in Cox regression. Similarly, we defined

high-risk (for retransplantation) recipients as having any of the three strongest risk factors (recipient age 31–40, recipient age 18–30, and previous transplant) for retransplantation in Cox regression.

Results

Study population

Our study population included 49 288 liver recipients; our analysis included 151 047 person-years at risk. The median survival time was 9.4 years. Demographic and clinical characteristics are summarized in Table 2.

Graft failure

Of the 49 288 liver recipients, 14 171 (28.8%) had graft failure during our study period. Of those, 2714 (19.2%) underwent retransplantation, 1691 (11.9%) died from graft failure, and 9766 (68.9%) died from other causes including 1582 (11.2%) patients from infection and 1214 (8.6%) patients from cardiovascular causes. The cause of death in the UNOS database had a 99.6% entry completion rate during our study period.

Retransplant rates

The retransplant rates by day, month, and year post-transplant are shown in Fig. 1. The 18.8% of retransplantation occurs between post-transplant day 0 and 7. 20.1% of retransplantation occurs between post-transplant day 8 and 30. The 33.0% of retransplantation occurs between post-transplant day 31 and 365. The 28.1% of retransplantation occurs after the first year.

Table 2. Demographic characteristics of donors and recipients.

	Recipient	Donor
Age (years)	53.0 ± 10.2	41.5 ± 17.3
% Female	32.5	40.5
% African American	9.2	15.8
Height (cm)	172.2 ± 10.6	171.6 ± 11.0
Weight (kg)	83.8 ± 19.7	79.1 ± 19.6
INR	1.9 ± 1.5	NA
Creatinine (mg/dl)	1.4 ± 1.1	1.5 ± 1.6
MELD	21.2 ± 10.0	NA
Diagnosis		
Hepatitis C	24.9%	NA
Alcoholic Cirrhosis	11.4%	NA
Cryptogenic	5.3%	NA
NASH	4.3%	NA
Cold Ischemia Time (h)	NA	7.3 ± 3.5
Cause of Death		
CVA	NA	42.8%
Trauma	NA	37.9%

CVA, cerebral vascular accident; INR, international normalized ratio; MELD, Model End-stage Liver Disease; NASH, nonalcoholic steatohepatitis.

Causes of graft failure

The most common causes of retransplantation were as follows: within the first week, primary nonfunction (43.1%) and hepatic artery thrombosis (27.6%); within the first month, hepatic artery thrombosis (55.3%) and primary nonfunction (26.0%); and within the first year, hepatic artery thrombosis (34.1%) and biliary complications (30.8%). The cause of graft failure in the UNOS database had a 9.7% entry completion rate during our study period.

Survival after retransplantation

The recipient survival rates differed after retransplantation in the various high-risk periods. The 1-year survival rates for retransplant recipients were as follows: after retransplantation within the first week after the primary transplant, 65%; within the first month, 75%; within the first year, 68%; and then after the first year, 81% (Fig. 2).

Risk factors for retransplantation

The most significant recipient and donor risk factors, in each of the three high-risk periods within the first year, for retransplantation were as follows: within the first week post-transplant, variceal bleeding within 48 h [odds ratio (OR) 2.8; confidence interval (CI) 1.4–5.5] and cold ischemia time >16 h (OR 3.6; CI 2.4–5.5); within the first month, variceal bleeding within 48 h (OR 2.3; CI 1.1–4.9) and use of split allografts (OR 2.9; CI 1.2–7.9); and within the first year, recipient age of 18–30 years (OR 3.5; CI 1.5–8.0) and use of a liver donated after cardiac death (OR 4.9; CI 3.6–6.8; Figs 3 and 4).

The most significant risk factors in the Cox regression were donation after cardiac death (OR 3.4; CI 3.0–3.9) and previous transplant (OR 2.3; CI 1.9–2.7). Other risk factors significant for early retransplantation were also significant in our Cox analysis: donation after cardiac death (OR 3.3; CI 3.0–3.9), split allograft (OR 1.5; CI 1.1–2.1), cold ischemia time >16 h (OR 1.4; CI 1.2–1.7), previous transplant (OR 2.3; CI 1.9–2.7), and recipient age of 18–30 years (OR 1.9; CI 1.6–2.3; Fig. 5).

Previously identified risk factors for retransplantation were also significant in this analysis. Donor aged >70 years was a significant risk factor for retransplantation within 1 month (OR 2.5; CI 1.3–4.8) and 1 year

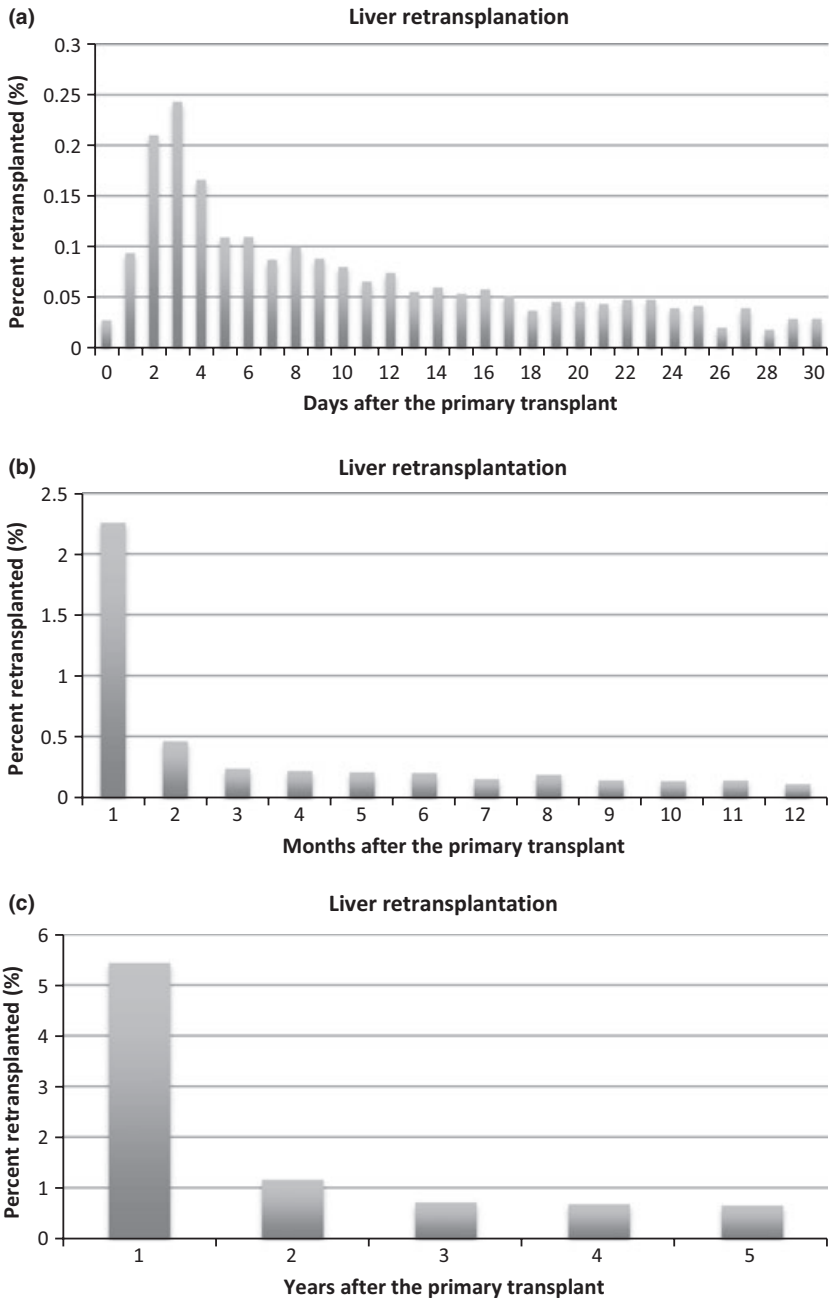


Figure 1 (a) Retransplant rate, by day. Abscissa: retransplant rate (%). Ordinate: days post-transplant. (b) Retransplant rate, by month. Abscissa: retransplant rate (%). Ordinate: months post-transplant. (c) Retransplant rate, by year. Abscissa: retransplant rate (%). Ordinate: years post-transplant.

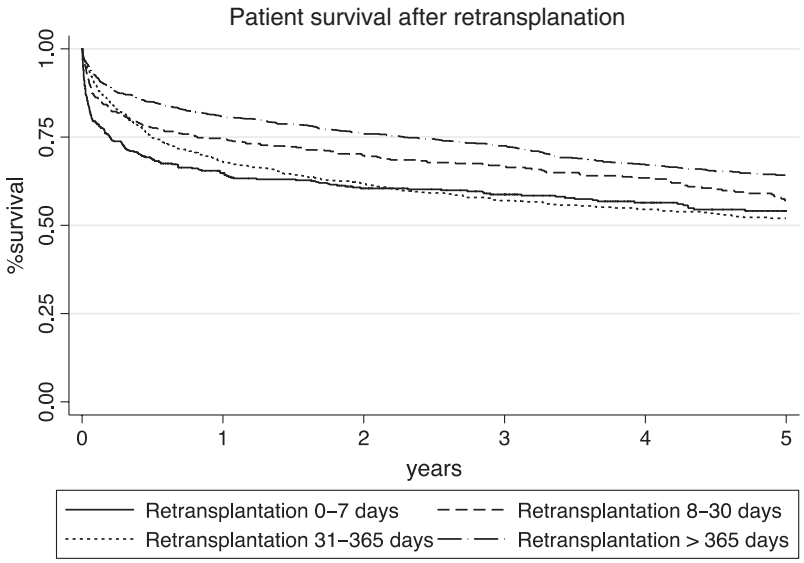
(OR 4.9; CI 3.6–6.8). Hepatitis C positivity in the recipient was not a significant risk factor in early retransplantation but was significant in the Cox regression (RR 1.2; CI 1.1–1.2). Recipient illness as graded by the MELD score was not significant; however, recipient illness designated by being on life support was a significant risk factor for retransplantation within 1 week (OR 2.2; CI 1.3–3.5). It was also significant in the Cox regression (RR 1.3; CI 1.2–1.5).

Era analysis

We found no significant differences in survival between the eras: 2002–2005, 2005–2008, and 2008–2011 (Fig. 6).

Donor–recipient matching

When high-risk (for retransplantation) donors were matched with high-risk (for retransplantation) recipients,



Actuarial Survival after Liver Retransplantation				
Interval	**n**	**1**	**3**	**5**
Retransplant interval				
0–7 days *	511 (18.8%)	65%	59%	54%
8–30 days *	545 (20.1%)	75%	67%	57%
31–365 days *	898 (33.0%)	68%	57%	52%
>365 days (ref)	760 (28.0%)	81%	73%	64%

Figure 2 Kaplan–Meier curve of retransplant recipient survival. Abscissa: survival rate of total recipients (%). Ordinate: years post-transplant. $P < 0.001$ for each group, by the log-rank test, with reference to retransplantation >365 days after the primary transplant.

retransplantation rates were 13.9% compared with 5.5% ($P < .001$).

Discussion

The literature suggests that up to 23% of liver allografts fail [1,2,12,13]. The only recourse after graft failure is retransplantation. This is feasible in a selected few patients. According to our analysis, 19% of recipients with graft failure were retransplanted. This option remains controversial given the inferior outcomes compared with primary transplant recipients [3,4]. In the effort to optimize outcomes after retransplantation, several studies have analyzed risk factors for mortality after retransplantation [2–4]. Our study was focused on identifying high-risk periods for retransplantation and then to determine the survival outcomes and associated risk factors. We found inferior outcomes only in retransplantation within the first year.

We defined the high-risk periods for graft failure by examining day-to-day retransplant rates. We found that the highest retransplant rates occurred within the first week, first month, or first year after the primary transplant. For those three high-risk periods, we discovered distinct causes of graft failure as well as disparate survival rates in retransplant recipients. Therefore, for each period, we conducted separate multivariate analyses for risk factors for graft failure leading to retransplantation.

We found distinct risk factors for retransplantation for each high-risk period. Within the first week post-transplant, the dominant donor risk factors were use of a liver donated after cardiac death and cold ischemia time >16 h. As expected, those are also established risk factors for primary nonfunction [14,15]. We found that younger donor age (15–20 years) protected against the need for immediate (0–7 days) retransplantation; however, recipient age younger than 15 actually was a risk factor for immediate retransplantation.

Other dominant recipient risk factors within the first week post-transplant were use of life support and variceal bleeding within 48 h. A so-called hostile recipient milieu is thought to contribute to primary nonfunction [16]. Interestingly, we found that recipient age between 30 and 40 was

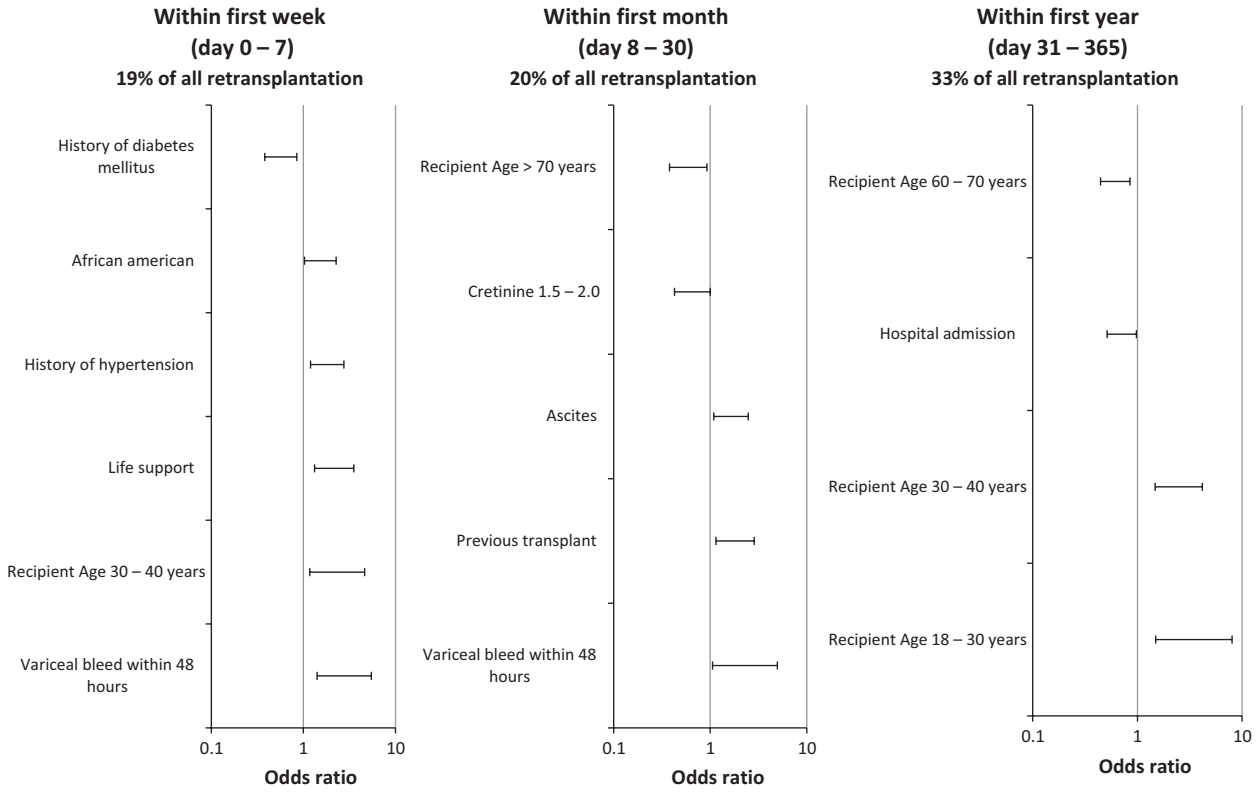


Figure 3 Recipient risk factors for retransplantation within the first week, first month, or first year after the primary transplant. Abscissa: statistically significant risk factors. Ordinate: odds ratio (OR) in logarithmic scale. Error bars indicate confidence interval (CI) of the OR.

a prominent risk factor, possibly suggesting that a robust immune system at a younger age may contribute to graft failure [14]. That concept is supported by reports in the literature of the lower rate of acute rejection in older patients [17]. Moreover, according to death-censored data in kidney transplant recipients, short-term graft survival rates increase with increasing age [18–21]. We found similar trends for retransplantation within the first year: In that high-risk period, recipient age from 30 to 40 and recipient age from 18 to 30 were the dominant risk factors for retransplantation. Conversely, in our analysis of liver recipients, we found that a history of diabetes, known to suppress the immune system, protected against the need for retransplantation within the first week [22,23]. The significance of younger recipient age, on the other hand, may just reflect clinician behavior, where the clinician is more likely to aggressively retransplant younger patients.

Increasing donor age became a progressively stronger risk factor for retransplantation within the first month and first year. Interestingly, we did not find that increasing age was a risk factor for retransplantation within the first week. Use of split allografts, known to confer a higher complication rate and an increased risk of graft failure [10,24], was the most prominent risk factor for retransplantation within the first month. Use of a liver donated after cardiac death, known to cause biliary complications [25,26], was the strongest risk factor for retransplantation within the first year.

Hepatitis C infection leading to cirrhosis of a transplanted allograft is not an uncommon occurrence [27,28]. Data suggest that the disease progression takes a median time of 9–12 years to cirrhosis [29]. Only a small minority of patients (<5%) have an accelerated course of liver failure [30]. It is therefore not surprising that we do not find hepatitis C infection as a risk factor for early retransplantation. Hepatitis C is only a minor risk factor (RR 1.2) for retransplantation over time in our Cox regression, which may reflect the reluctance to retransplant for hepatitis C recurrence. This reluctance is based on perceptions of poorer outcomes after retransplantation for hepatitis C recurrence [31,32].

The importance of donor–recipient matching on post-transplant survival has been established [33–35]. The D-MELD, BAR score, and SOFT score demonstrate the importance of both donor and recipient factors [36–38]. This analysis illustrates how donor–recipient matching also impacts the rate of retransplantation. High-risk recipients matched to high-risk donors had 2.5 times the rate of retransplantation compared with overall rate.

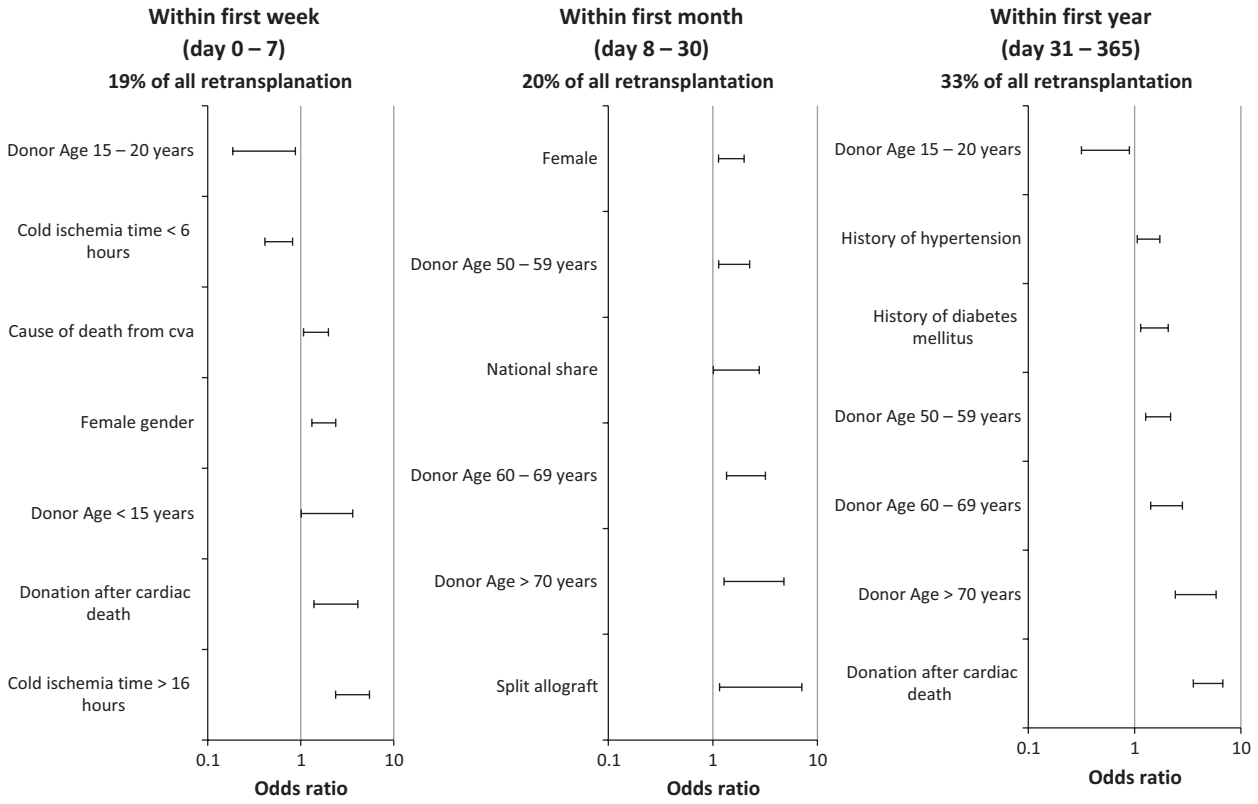


Figure 4 Donor risk factors for retransplantation within the first week, first month, or first year after the primary transplant. Abscissa: statistically significant risk factors. Ordinate: odds ratio (OR) in logarithmic scale. Error bars indicate confidence interval (CI) of the OR.

Because the causes of graft failure leading to retransplantation differed during each of the three high-risk periods and the clinical context at the time of the retransplantation were also distinct, we were not surprised that survival rates in retransplant recipients also differed by period. Indeed, once the interval between the primary transplant and retransplantation exceeded a year, survival rates of the retransplant recipients approached the survival rates after primary transplants. These data suggest that based on inferior outcomes, clinicians should minimize retransplantation within 1 year. In other words, only the healthiest candidates should be offered retransplantation within 1 year. We would also like to emphasize the importance of donor–recipient on optimizing survival outcomes. These data suggest that retransplantation after 1 year does not warrant the same caution. Previous studies have shown disparate survival depending on the time interval between primary transplant and retransplantation [3,13].

Most analyses of retransplantation focus on survival after retransplantation. This study is unique in that it analyses the risk factor for retransplantation [3,4,39,40]. This study design is the most similar to the DRI, but with differing definitions of graft failure. With the DRI, most failures are from death with a cause not listed as graft failure [10]. In this analysis, we focused on graft failure leading to retransplantation. In summary, we provided a unique and clinically relevant approach to the analysis of retransplantation. Only retransplantation within the first year had below standard outcomes. Each of our three high-risk periods within the first year had distinct causes of graft failure, distinct patterns of risk factors for retransplantation, and distinct survival rates after retransplantation. Although our study was descriptive, our results should help shape clinical perceptions of retransplantation and may set the framework for more refined donor risk models. This is all in the effort to minimize graft failure requiring retransplantation to preserve the scarce resource of liver donor allografts.

Limitations

Since the passage of the National Organ Transplant Act of 1984, data entry has been mandatory for all US transplant centers. Nevertheless, all patient registries suffer from frequent variability in data entry. Yet findings from our study

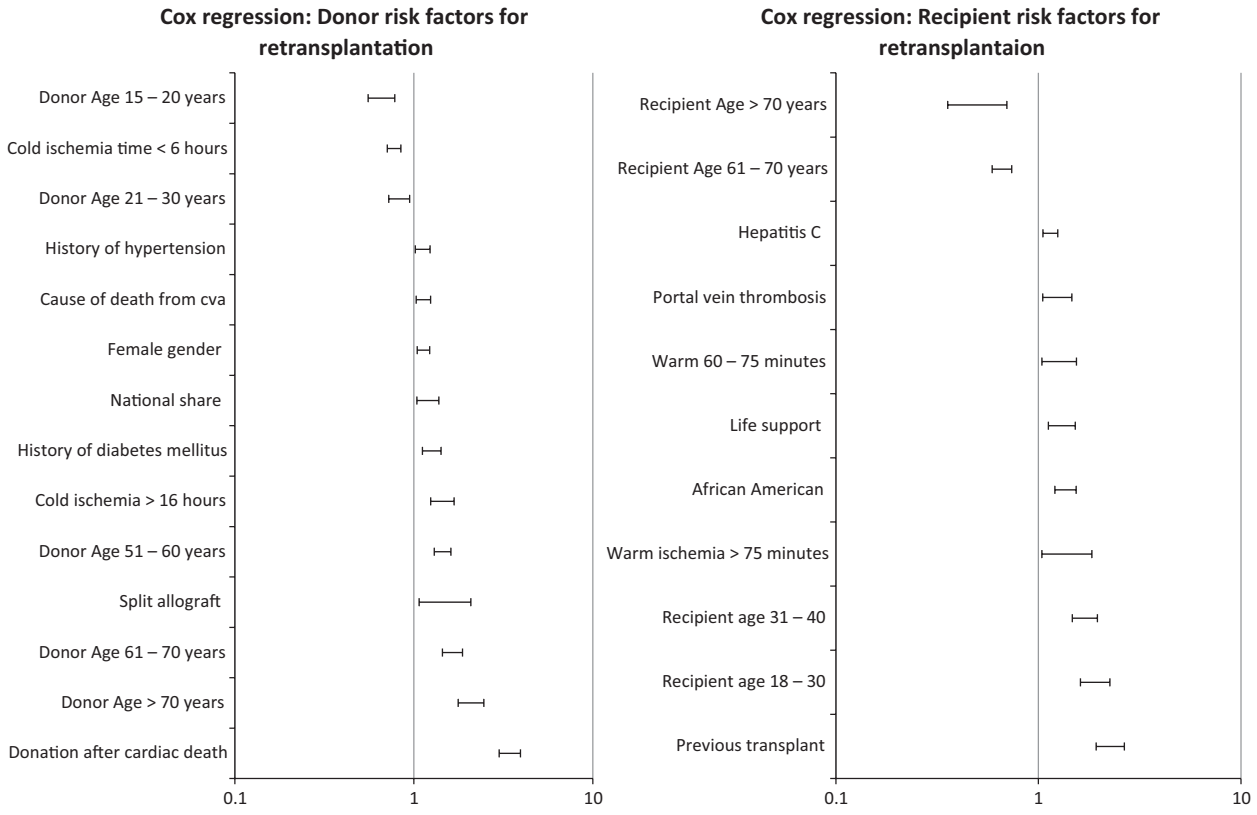


Figure 5 Donor and recipient risk factors for retransplantation using Cox regression. Abscissa: statistically significant risk factors. Ordinate: relative risk (RR) in logarithmic scale. Error bars indicate confidence interval (CI) of the RR.

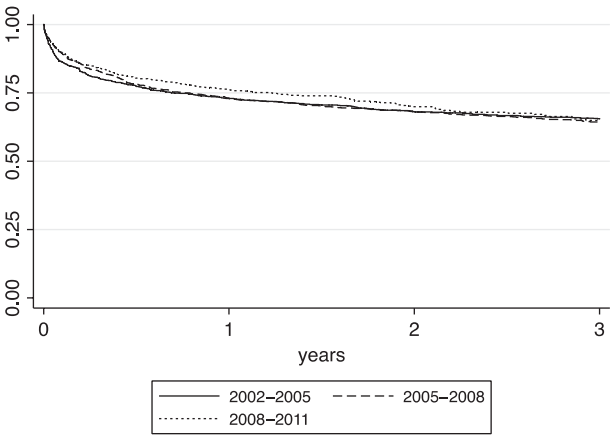


Figure 6 Survival by era, retransplantation.

were based on large cohorts of patients, so were unlikely to be significantly affected by small amounts of missing information.

Cause of graft failure could not be incorporated into this analysis because of the low entry completion rate of 9.2% in the OPTN database. This is a significant limitation of the registry and this analysis. Center effect of volume on mortality has been established in liver transplantation [41], but not yet in retransplantation. The center effect was not included in this analysis.

Conclusion

We found that the highest rates of graft failure leading to retransplantation occurred within the first week, first month, or first year post-transplant. Each of our three high-risk periods within the first year had distinct causes of graft failure, risk factors for retransplantation, and survival rates after retransplantation.

Authorship

AR, BK, and ACG: study design. AR, BK, and ACG: data collection and analysis. AR, HP, BK, TJ, MP, SH, HR, and RWGG: article writing.

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