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ORIGINAL ARTICLE

Advanced recipient age (>60 years) alone should not be a contraindication to liver retransplantation

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Summary

Advanced age has been shown to be a risk factor for survival in primary liver transplantation. We sought to determine the independent influence of recipient age on retransplantation survival. The UNOS dataset was analyzed for adult, nonstatus 1, liver retransplantations since February 27, 2002. The univariate effect of age on 90-day and 1-year survival was analyzed. Multivariate survival models were used to determine 90-day, 1-year, and overall survival. Recipient age, donor age, model for end-stage liver disease (MELD) score, and hepatitis C status were used to construct multivariable survival models. Some 2141 liver retransplantations were analyzed. Overall, increasing recipient age was independently predictive of increasing mortality after liver retransplantation. In recipients between 18 and 60, there remained a direct relationship between age and mortality. However, in recipients aged over 60, increasing age was not independently associated with 90-day mortality ($P = 0.88$) and 1-year mortality ($P = 0.74$), despite adjusting for donor age, MELD score, and viral hepatitis status, suggesting that their original liver condition, their co-morbidities or perioperative condition plays an important role in retransplantation survival. Increasing recipient age up to 60, adversely affects liver retransplantation survival. After 60, there are no additional risks. Advanced age alone should not be an exclusionary factor when considering liver retransplantation; only the overall ability of the patient to tolerate a major surgery should be the determining factor.

Introduction

The aging of the general population has led to increased numbers of aged liver transplant recipients. In 1988, 29 patients of age 65 or older underwent liver transplantation in the United States; in 2005, this number was 628 [1]. It is expected that patients with liver transplants will live longer and the need for retransplantation will increase in the elderly. It is well known that for nearly all surgical procedures, increasing age is associated with poorer outcomes [2]. In the face of severe organ shortage, it is unknown whether the risk of retransplantation, specifically in the elderly, is justified, when the balance between justice and utility for organ allocation continues to be controversial [3–6]. Primary liver transplantation in patients over age 60 has been reviewed in various reports [7–15]. Survival at 3 years after transplantation has ranged from as low as 35% [8] to as high as 83% [11]. The effectiveness of liver retransplantation in the elderly has not been extensively studied. It was the aim of this study to assess the outcomes and factors predictive of mortality after liver retransplantation in recipients over the age of 60.

Methods

The Organ Procurement and Transplantation Network standard liver transplant dataset was analyzed for all adult

(age ≥ 18), nonstatus 1, liver retransplantations occurring in the USA from the beginning of the model for end-stage liver disease (MELD) allocation system on February 27, 2002 to February 6, 2008. The age-wise distribution of elderly patients undergoing liver retransplantation in the dataset was analyzed and age-adjusted mortality was calculated for each age between 18 and 75. Because of the nonlinear relationship between age and risk of death after retransplantation, using regression analysis, a polynomial curve was fit to the mortality data to estimate the peak age of postretransplantation mortality and based on this analysis, an age cutoff of 60 years was chosen to delineate between high-age retransplants and low-age retransplants. This is a cut-off age used in other studies and is a reasonable clinical threshold on age and primary transplantation. Factors known from the literature to influence the survival following liver retransplantation including recipient age, donor age, recipient hepatitis C status, MELD score, cold ischemic time and presence of diabetes [3,4] were compared between the group of patients older than age 60 and those patients between ages 18 and 60.

Univariate binary comparisons were performed using the chi-squared test. Unadjusted overall survival was estimated using the Kaplan–Meier technique. Ninety-day and 1-year multivariate logistic regression survival models were constructed using the factors found to be significant in the univariate analysis with $P < 0.05$ or those factors shown in other studies to be predictors of mortality after liver transplantation. Because of the nonlinear relationship between age and mortality, separate regression models were developed in those recipients over the age of 60 and those between 18 and 60. The level of statistical significance was set at ≤0.05 and all tests were two-sided. All statistical analyses and dataset manipulations were performed with SAS, version 9.1 (Cary, NC, USA).

Results

Some 2141 liver retransplantations that occurred during the study period were analyzed. Figure 1 shows the frequency distribution of age in the retransplanted patients. The mean age at the time of retransplantation was 48.7 years (±SD 11.5), the median age was 51, and the interquartile range was 42.5–55 years. More than 10% of retransplant recipients were aged over 60 and 1% were aged above 70. The maximum age to undergo retransplantation was 75.

Table 1 shows the characteristics of the patients undergoing retransplantation separated into groups with age 18–60 (low age) and age above 60 (high age). The older group had fewer African Americans (5.7% vs. 13.3%, $P < 0.001$) and slightly older donors (39.0 vs. 36.2 years, $P = 0.01$). The prevalence of hepatitis C infection, MELD score at transplant, MELD exceptions, cause of graft failure, geographical organ sharing, and waiting list time were not significantly different between groups. Figure 2 shows the unadjusted Kaplan–Meier survival curves. Unadjusted survival at 90 days was significantly lower in the older group (74.9% vs. 83.5%, $P < 0.0001$) and this difference persisted at 1 year (64.9% vs. 73.3%, $P < 0.0001$). However, further analysis of the of the survival proportions is shown in Fig. 3, which shows the curve fitted to the absolute 90-day mortality data and Fig. 4 showing 1-year mortality. The absolute mortality risk appeared to stabilize in the fourth decade and then began to decline after age 57. In the extremes of age, excess mortality was balanced by several age groups with no mortality.

Table 2 shows the results of the adjusted 90-day mortality regression analysis. Recipient age continued to independently influence mortality up to age 60 (OR = 1.02, 95% CI 1.01–1.04, $P = 0.003$). In this group, graft failure caused by vascular thrombosis (OR = 10.3, 95% CI 3.75–28.1, $P < 0.0001$) and MELD score calculated at the time of retransplant (OR = 1.03, 95% CI 1.02–1.05, $P < 0.0001$) were also significant predictors of 90-day mortality. In contrast, in the recipients of age above 60, none of the traditionally accepted factors predicted mortality. Advancing age was not an independent predictive factor for mortality after age 60 was achieved.

Discussion

Advances in perioperative care and immunosuppression have enabled transplant teams to broaden the indications for organ transplantation and safely increase the age of the transplant recipient. This has opened up a situation where patients are now living longer after liver transplantation, increasing the age bracket of patients who need liver retransplantation when the primary organ fails or when they develop disease recurrence. Advanced age is no longer considered a contraindication to liver transplantation at

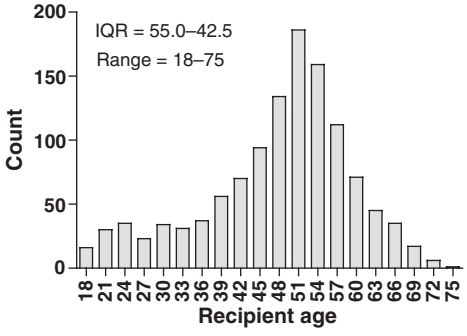

Figure 1 Distribution of age in retransplanted adult patients.

Table 1. Characteristics of retransplanted group of patients aged over 60 versus retransplanted group aged between 18 and 60. Status one retransplants were excluded.

	Retransplant group age 18–60 (*n* = 1897)	Retransplant group over age 60 (*n* = 244)	*P*-value
Male, *n* (%)	1277 (67.3)	170 (69.7)	0.46
African American recipient, *n* (%)	253 (13.3)	14 (5.7)	<0.001
Hepatitis C infection, *n* (%)	494 (26.0)	51 (20.9)	0.08
Recipient age, mean years (SD)	46.6 (10.5)	64.7 (3.2)	NA
Donor age, mean years (SD)	36.2 (15.8)	39.0 (17.1)	0.01
Age difference between donor and recipient, mean (SD)	10.4 (18.6)	25.7 (17.6)	<0.0001
MELD score at retransplantation, mean (SD)	26.3 (9.5)	26.1 (9.5)	0.73
Cause of graft failure, *n* (%)			
Biliary complications	27 (1.4)	3 (1.2)	0.87
Recurrent disease	67 (3.5)	8 (3.3)	
Acute or chronic rejection	15 (0.8)	1 (0.4)	
Vascular thrombosis	28 (1.5)	2 (0.8)	
Other or not recorded	1760 (92.8)	230 (94.3)	
Transplanted under MELD exception, *n* (%)	285 (15.0)	39 (16.0)	0.69
Donor organ geographical sharing, *n* (%)			
Local	1312 (69.1)	162 (66.4)	0.18
Regional	491 (25.9)	62 (25.4)	
National	93 (4.9)	20 (8.2)	
Cold ischemic time, mean hours (SD)	7.7 (3.4)	7.7 (4.5)	0.98
Time active on the waiting list prior to retransplant, mean days (SD)	117 (283)	173 (635)	0.17
90-day post-transplant actuarial survival % (SE)	83.5 (0.9)	74.9 (3.0)	<0.0001*
1-year post-transplant actuarial survival % (SE)	73.3 (0.1)	64.9 (3.3)	<0.0001*

*Estimated by Kaplan–Meier and log-rank tests.

most centers. Short-term studies of elderly liver transplant recipients have demonstrated that the incidence of complications and overall patient survival are similar to those of younger adults for primary transplantation [5]. Historically, retransplantation in the United States has accounted for about 10% of all liver transplantations. However, over the last 8 years the rate has decreased to approximately 4% [1]. One explanation for this finding is the common belief that retransplantation is associated with poorer outcomes particularly in patients of advanced age [4]; therefore, many centers are reluctant to perform these operations in elderly patients.

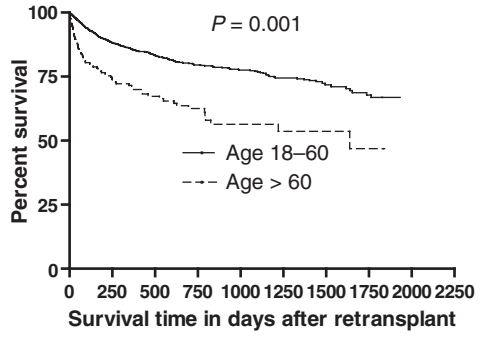

Figure 2 Kaplan–Meier survival estimates after liver retransplantation for recipients aged between 18 and 60 versus recipients aged above 60.

Survival after retransplantation has been shown to be inferior for all recipients when compared to primary transplantation. One study revealed survival rates of liver retransplanted patients at 1, 5, and 10 years were 62%, 47%, and 45% respectively. These rates were significantly lower than those (83%, 74%, and 68%) in patients undergoing primary hepatic transplantation at the same center during the same period [16]. This result has been reproduced at other centers and in other countries [3,4,17,18].

We found that increasing recipient age to age 60 had an adverse effect on liver retransplantation survival rates in adults. However, above age 60, there are no additional risks imparted by recipient age alone after adjusting for donor factors, MELD score, viral hepatitis status of the recipient, and other factors known to influence liver retransplantation mortality. Our demographics revealed a decrease in elderly African Americans from 13.3% to 5.7% of the total retransplants, a fact we find difficult to

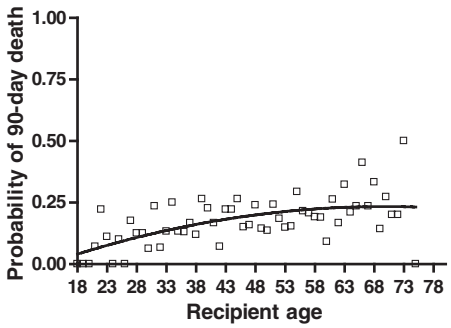

Figure 3 Probability of 90-day mortality by age groups after liver retransplantation. Fitted curve (second order polynomial) shows the 90-day mortality risk stabilizing in recipients aged 60 and above.

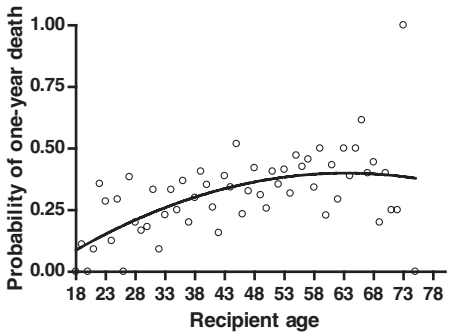

Figure 4 Probability of 1-year mortality by age groups after liver retransplantation. Fitted curve (second order polynomial) shows the 1-year mortality risk stabilizing in recipients aged 60 and above.

explain and unable to rectify in such a database. Despite the increasing mortality up to age 60, respectable survival rates were achieved at 90 days and at 1 year in the older group. By Kaplan–Meier analysis, 5-year survival for the group of patients aged 60 years and below was 57.0% and for those aged above 60 was 43.0%. This was not statistically different because of small numbers in both cohorts at this stage of follow-up. Because of the increased risk of 5-year mortality in all people over 60 compared with those aged 60 or below, this comparison is difficult to interpret without general population-matched age-, gender-, and race-adjusted survival, which is beyond the scope of this analysis. Retransplant graft failure secondary to vascular thrombosis and high MELD scores at the time of retransplant are significant predictors of 90-day mortality, and are perhaps more significant in predicting mortality than age above 60. Unfortunately, large restrospective databases are unable to discern specifics as to the associated morbidity as seen in Table 1 where >90% of the graft failure etiologies are unknown or not reported. Interestingly, none of the traditionally accepted factors predicting mortality after retransplantation were significant in the elderly group. This is likely because of intense preoperative screening and center selection of the optimal retransplantation candidate. While this likely influences the retransplantation success, this screening and selection process is not well-represented in large databases and is an inherent weakness of an analysis such as this. Indeed, many centers refuse older patients for liver retransplantation who thus never make it to the dataset. Furthermore, high-volume centers may accept the greater number of elderly retransplants; however, this dataset is ill-equipped to comment on these types of specifics. This selection bias is unavoidable in the available datasets. As patients age, transplant centers are more clinically selective. Older patients are given an extensive evaluation for heart disease and other co-morbidities so the dataset represents a select group of patients that centers deem suitable for retransplant, with age becoming an insignificant factor. The decline in mortality risk as seen in those aged above 60 may overemphasize the decreased mortality risk; however, these lower numbers also exist at the other spectrum (18–30 year olds) without diminished mortality. Despite the

Table 2. Multivariate logistic regression analysis of risk factors for 90-day mortality after liver retransplantation in recipients aged between 18 and 60 and recipients aged above 60.

	OR (95 % CI, *P*-value) for death in retransplant group age 18–60 (*n* = 1897)	OR (95% CI, *P*-value) for death in retransplant group over age 60 (*n* = 244)
Recipient age	1.02 (1.01–1.04, 0.003)*	1.01 (0.91–1.11, 0.88)
Donor age	1.01 (1.00–1.02, 0.05)	1.02 (0.99–1.04, 0.11)
Male recipient	0.92 (0.69–1.23, 0.58)	0.90 (0.44–1.85, 0.77)
African American recipient	0.96 (0.65–1.42, 0.84)	2.65 (0.75–9.32, 0.13)
Graft failure caused by vascular thrombosis	10.3 (3.75–28.1, <0.0001)*	3.42 (0.20–58.2, 0.39)
MELD score at transplant	1.03 (1.02–1.05, <0.0001)*	1.02 (0.98–1.05, 0.37)
Recipient HCV infection	1.02 (0.76–1.37, 0.90)	0.83 (0.37–1.85, 0.64)
Recipient diabetes status	1.03 (0.70–1.52, 0.88)	0.79 (0.34–1.84, 0.59)

MELD, model for end-stage liver disease; HCV, hepatitis C virus.
*Statistically significant.

possibility that transplant centers may select for improved outcomes especially in the elderly, the lack of increased mortality is significant and demonstrates the efficacy of retransplantation.

Based on this analysis, liver retransplantation in recipients aged above 60 can result in good outcomes. Careful pretransplant assessment of the recipient is clearly important to exclude patients with age-associated co-morbidities that might hinder postretransplantation survival. However, survival is not the only endpoint of interest in considering for retransplantation. Quality of life is also important to recipients; however, data for this type evaluation is lacking. We conclude that chronological age alone should not be considered a contraindication to retransplantation. When considering liver retransplantation in elderly patients, careful selection of appropriate candidates, using criteria not based solely on age, should be the standard and can yield acceptable results.

Authorship

TMS: wrote paper, analyzed data and designed study. TLP, SCK, and CKA: analyzed data. PGN: collected data, analyzed data, and wrote paper.

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References

1. Unos.org: http://www.unos.org/data/ (last accessed on June 2008).
2. Story DA. Postoperative complications in elderly patients and their significance for long-term prognosis. *Curr Opin Anaesthesiol* 2008; **21**: 375.
3. Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. *Transplantation* 1998; **66**: 1612.
4. McCashland T, Watt K, Lyden E, *et al.* Retransplantation for hepatitis C: results of a U.S. multicenter retransplant study. *Liver Transpl* 2007; **13**: 1246.
5. Lipshutz GS, Hiatt J, Ghobrial RM, *et al.* Outcome of liver transplantation in septuagenarians: a single-center experience. *Arch Surg* 2007; **142**: 775.
6. Northup PG, Pruett TL, Kashmer DM, Argo CK, Berg CL, Schmitt TM. Donor factors predicting recipient survival after liver retransplantation: the retransplant donor risk index. *Am J Transplant* 2007; **7**: 1984.
7. Bromley PN, Hilmi I, Tan KC, Williams R, Potter D. Orthotopic liver transplantation in patients over 60 years old. *Transplantation* 1994; **58**: 800.
8. Collins BH, Pirsch JD, Becker YT, *et al.* Long-term results of liver transplantation in older patients 60 years of age and older. *Transplantation* 2000; **70**: 780.
9. de la Pena A, Herrero JI, Sangro B, *et al.* Liver transplantation in cirrhotic patients over 60 years of age. *Rev Esp Enferm Dig* 1998; **90**: 3.
10. Emre S, Mor E, Schwartz ME, *et al.* Liver transplantation in patients beyond age 60. *Transplant Proc* 1993; **25**: 1075.
11. Filipponi F, Roncella M, Boggi U, *et al.* Liver transplantation in recipients over 60. *Transplant Proc* 2001; **33**: 1465.
12. Garcia CE, Garcia RF, Mayer AD, Neuberger J. Liver transplantation in patients over sixty years of age. *Transplantation* 2001; **72**: 679.
13. Pirsch JD, Kalayoglu M, D'Alessandro AM, *et al.* Orthotopic liver transplantation in patients 60 years of age and older. *Transplantation* 1991; **51**: 431.
14. Stieber AC, Gordon RD, Todo S, *et al.* Liver transplantation in patients over sixty years of age. *Transplantation* 1991; **51**: 271.
15. Zetterman RK, Belle SH, Hoofnagle JH, *et al.* Age and liver transplantation: a report of the liver transplantation database. *Transplantation* 1998; **66**: 500.
16. Markmann JF, Gornbein J, Markowitz J, *et al.* A simple model to estimate survival after retransplantation of the liver. *Transplantation* 1999; **67**: 422.
17. Ghabril M, Dickson R, Wiesner R. Improving outcomes of liver retransplantation: an analysis of trends and the impact of hepatitis C infection. *Am J Transplant* 2008; **8**: 404.
18. Azoulay D, Linhares MM, Huguet E, *et al.* Decision for retransplantation of the liver: an experience- and cost-based analysis. *Ann Surg* 2002; **236**: 713; Discussion: 721.

