Transplantation of Livers from Old Donors: Pushing the Envelope Beyond the Seventh Decade

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ABSTRACT: **Background:** The lack of organs for liver transplantation has prompted transplant professionals to study potential solutions, such as the use of livers from donors older than 70 years of age. This strategy is not widely accepted because potential risks of vascular and biliary complications and recurrence of hepatitis C.

Objectives: To examine the efficacy and safety of liver grafts from older donors for transplantation.

Methods: A retrospective analysis of data on 310 adults who underwent deceased donor liver transplantation between 2005 and 2015 was conducted. We compared graft and recipient survival, as well as major complications, of transplants performed with grafts from donors younger than 70 years (n=265, control group) and those older than 70 years (n=45, older-donor group), followed by multivariate analysis, to identify risk factors.

Results: There was no significant difference between the control and older-donor group at 1, 5, and 10 years of recipient survival (79.5% vs. 73.3%, 68.3% vs. 73.3%, 59.2% vs. 66.7%, respectively) or graft survival (74.0% vs. 71.0%, 62.7% vs. 71.0%, 54.8% vs. 64.5%, respectively). The rate of biliary and vascular complications was similar in both groups. Significant risk factors for graft failure were hepatitis C (hazard ratio [HR] = 1.92, 95% confidence interval [95%CI] 1.16–2.63), older donor age (HR = 1.02, 95%CI 1.007–1.031), and male gender of the recipient (HR = 1.65, 95%CI 1.06–2.55).

Conclusion: Donor age affects liver graft survival. However, grafts from donors older than 70 years may be equally safe if cold ischemia is maintained for less than 8 hours.

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KEY WORDS: cold ischemia, extended criteria donor, graft survival, liver transplantation, patient survival

With limited organ supply and increasing numbers of candidates for liver transplantation, there has been a persistent rise in the mortality rate for those on donor waiting lists. According to the 2014 report from the Scientific Registry of Transplant Recipients [1], the number of patients dying or being removed from the list in the United States increased from 11.1 per 100 waitlist years in 2009 to 12.3 per 100 waitlist years in 2014. This trend has prompted a search for alternative sources of liver organs, including live donors, donors after cardiac death, and extended-criteria donors.

The ideal donor is defined by characteristics that imply a lack of risk factors for immediate primary non-function of the liver allograft: young age (< 40 years); short stay in the intensive care unit; absence of steatosis, chronic liver disease, and transmission disease; death due to trauma; hemodynamic stability at the time of graft procurement; and normal or only mildly elevated liver enzyme levels [2]. In a study from 2006 on 124 liver transplants conducted in Israel, donor age > 40, cold ischemic time > 10 hours, and a prolonged operation (> 10 hours) were significant predictors for graft survival [3].

Over time, however, donors who meet all of these criteria have accounted for a decreasing proportion of the reduced donor pool. The median donor age now reaches the fifth decade [4], with a growing proportion of donors dying of cardiovascular disease. In addition, what were once considered conditions that contraindicated donation, such as hypernatremia, steatosis greater than 30%, positive serology for hepatitis C virus (HCV) or hepatitis B virus (HBV), and heart-beating donor, have become acceptable extended-donor criteria [5-7].

Traditionally, organs from donors older than 60 years are regarded as high risk, and careful selection is recommended with their use [8] due to the high rate of cardiovascular and metabolic co-morbidities in this age group, which may affect liver allograft quality. Furthermore, the aged liver has a lower capability to sustain ischemic reperfusion injury [9]. Although several single center studies have shown acceptable outcomes for livers from older donors while maintaining short cold ischemia [5-7], concerns have been raised by the higher reported rates of HCV recurrence and biliary and vascular complications in recipients [10].

In Israel, the high mortality rate (30%) for those on the recipient waitlist has mandated the introduction of living donor liver transplantation and the use of grafts from donors beyond the age of 70 years. Given the prolonged waiting time for a transplant (median 14 months), the transplanta-

tion of extended-criteria livers to recipients at the top of the waiting list with a high model for end-stage liver disease (MELD) score might be expected to be associated with a bad outcome. Therefore, one of the prerequisites for using livers from donors older than 70 years in our practice is to maintain as short an ischemia time as possible by starting the recipient hepatectomy as soon as the donor liver is approved by the surgeon. We report our experience using livers from donors aged 70 years or more.

PATIENTS AND METHODS

PATIENTS AND SETTING

The liver transplant database of a tertiary medical center was retrospectively reviewed for adults (age > 18 years) who underwent liver transplantation from January 2005 to December 2015. Exclusion criteria were combined liver and kidney transplantation, split-liver, and live-donor transplantation. For comparison, patients were divided into two groups: recipients of a graft from a donor aged < 70 years (control group) and recipients a graft from a donor ≥ 70 years (older-donor group). In addition, the study period was divided into two eras: 2005–2010 (early) and 2011–2015 (late).

DONOR AND RECIPIENT PARAMETERS

Data on the following parameters were collected from the database and the individual electronic medical files of the recipients and donors: age and gender; primary liver disease; MELD score at transplantation; cold ischemia time; presence of cirrhosis; and complications prior to transplantation such as ascites, bleeding varices, spontaneous bacterial peritonitis and encephalopathy, hepatocellular carcinoma and transporter intrahepatic portosystemic shunt, and diabetes.

PROCUREMENT AND ALLOCATION

During organ procurement, a biopsy study was performed on all liver grafts from donors older than 60 years and on grafts from younger donors when liver abnormalities were suspected by macroscopic evaluation. The liver grafts were preserved in U-W solution. For liver grafts from donors aged ≥ 70 years, we aimed to maintain minimal cold ischemic time by initiating anesthesia as soon as the donor surgeon received the biopsy results and approved the allograft for use. Liver allocation was based on the MELD score starting in 2005 without any age matching. During the second era, to lower the risk of early recurrent disease, we avoided transplantation of livers from donors aged ≥ 70 years to HCV-positive recipients.

OUTCOME PARAMETERS

The primary endpoints of the study were 1 year and 5 year patient and graft survival rates in the older-donor group compared to controls. The secondary endpoint was the post-transplant rate of complications, including delayed graft function (defined as serum glutamic pyruvate transaminase > 1500 IU/L on day 1 and twice the upper normal level on day 7) urgent re-transplantation within the first 14 days, portal vein or hepatic artery thrombosis, and recipient death.

IMMUNOSUPPRESSION

The immunosuppressive regimen was comprised of tacrolimus (Astellas Pharma, Japan; blood levels 10–12 ng/ml, first month; 8–10 ng/ml, 2-3 months; 5–8 ng/ml thereafter), prednisone (starting at 500 mg at surgery and tapered to 5 mg on day 30), and mycophenolate mofetil (Roche Pharma, Switzerland; started at 1 gr/day and discontinued at month 3).

STATISTICAL ANALYSIS

Quantitative variables are expressed as mean and standard deviation, and qualitative variables are described as percentages. Differences in proportions in groups were analyzed with Pearson's chi-square test. Differences in measureable variables were analyzed with analysis of variance and Student's *t*-test. Graft survival and recipient survival were estimated by the Kaplan–Meier method; survival curves were compared using the log rank test. $P < 0.05$ was considered statistically significant. The variables with a significance of $P < 0.1$ on univariate analysis were entered into a multivariate model using stepwise forward Cox regression to assess their effect on graft survival. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Of the 399 patients who underwent liver transplantation during the study period, 89 were excluded from the study because they had a combined transplant (n=21), split-liver transplant (n=11), live-donor liver transplant (n=29), or were missing data (n=28). The remaining 310 patients formed the study cohort: 265 received liver allografts from donors aged < 70 years (85.5%, control group) and 45 received liver allografts from donors aged ≥ 70 years (14.5%, older-donor group). Their characteristics are shown in Table 1. The respective recipients and donor ages in the control group were 51.6 and 46.2 years, and in the older-donor group, 56.3 and 74.3 years. Preoperatively, the recipients of grafts from donors aged < 70 years had a significantly higher rate of HCV than recipients of grafts from older donors (38.1% vs. 13.3%, $P < 0.005$) and a lower rate of hepatitis B cirrhosis (18.1% vs. 28.8%, $P < 0.01$). There were no significant between-group differences in rates of re-transplantation, spontaneous bacterial peritonitis or transporter intrahepatic portosystemic shunt, or hepatocellular carcinoma. Mean MELD scores at transplantation was also similar in the two groups (22.3 and 21.8, respectively) [Table 1].

Table 1. Donor and recipient characteristics

	Donor < 70 year n=265	Donor ≥ 70 year n=45
Recipient age (year), mean ± SD	51.6 ± 11.3	56.3 ± 10.2*
Donor age (year), mean ± SD	46.2 ± 15.0	74.3 ± 2.7**
Age sum (donor + recipient), mean ± SD	97.8 ± 19.6	130.7 ± 11.0**
Male recipient, n (%)	170 (64.2)	24 (53.3)
Male donor, mean ± SD (%)	153 (57.7)	26 (57.7)
HCV, n (%)	101 (38.1)	6 (13.3)*
HBV, n (%)	48 (18.1)	13 (28.8)**
NASH, n (%)	27 (10.2)	5 (11.1)
PBC and PSC, n (%)	19 (7.2)	5 (11.1)
Re-transplantation, n (%)	20 (7.5)	3 (6.7)
SBP, n (%)	63 (23.7)	11(24.4)
HCC, n (%)	46 (17.3)	7 (15.6)
TIPS, n (%)	14 (5.3)	1 (2.2)
MELD (median) (%)	22.3	21.8
Cold ischemia time (hours), mean ± SD	8.7 ± 2.7	6.5 ± 1.5***
Era 1 (2005–2010), n (%)	137 (51.6)	12 (26.7)*
Era 2 (2010–2015), n (%)	128 (48.4)	33 (73.3)

*P < 0.005

**P < 0.01

***P < 0.0001

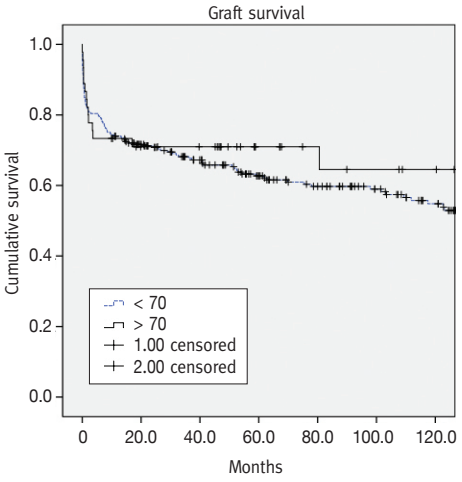
HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease, NASH = nonalcoholic steatohepatitis, PBC = primary biliary cholangitis, PSC = primary sclerosing cholangitis, SBP = spontaneous bacterial peritonitis, TIPS = transjugular intrahepatic portosystemic shunt

Table 2. Rate of biliary and vascular complications by group

Complication	Donor < 70 years of age n=265	Donor ≥ 70 years of age n=45
Biliary, n (%)	59 (21)	11 (24)
Arterial thrombosis, n (%)	12 (4.5)	5 (11)*
Venous, n (%)	11 (4.2)	1 (2.2)
Total number of complications, n (%)	57 (31.3)	17 (37.7)

*P = 0.247

Figure 1. Graft survival in the two groups (donors aged < 70 or ≥ 70 years)



Division of the study period into early (2005–2010) and late (2010–2015) eras revealed that most of the transplantations using older-donor grafts were performed from 2010 to 2015 (73.3%). Thus, the rate of use of older-donor grafts rose from 8.6% in 2005–2010 to 23% in 2010–2015. Mean donor age increased significantly between these two eras, from 44.8 years to 51.4 years, with a parallel decrease in mean cold ischemia time, from 9.4 hours to 7.1 hours (P < 0.001). Only 4 of the 45 grafts from the aged donors were reperfused for more than 8 hours after cross-clamping.

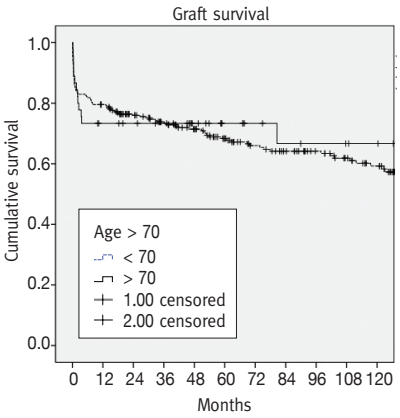
The postoperative complications are shown in Table 2. Biliary complications occurred in 59 recipients (21%) in the control group and 11 (24%) in the older-donor group (not significant). The older-donor group had a significantly higher rate of hepatic artery thrombosis than the control group (11% vs. 4.5%, P = 0.247).

Median follow-up time was 47.8 months in the control group and 46.9 months in the older-donor group. Total deaths numbered 108 (40.8%) in the control group and 14 (31.1%) in the older-donor group. Graft loss due to primary non-function or severe dysfunction occurred in 25 recipients (9.4%) in the control group compared to 2 (4.4%) in the older-donor group (not significant). The two groups were similar for the septic complications (13–14%). Recurrent HCV was a major cause of graft loss and death in the control group (7.9%); whereas, none of the recipients in the older-donor group died of recurrent HCV. The incidence of acute cellular rejection was 30% (17% biopsy-proven) in the control group and 44% (37% biopsy-proven) in the older-donor group (P = 0.11). Death with a functioning graft occurred in 20 recipients (9.8%) in the control group and 6 (13.3%) in the older-donor group.

In the control group, recipient survival rates were 79.5% at 1 year, 68.3% at 5 years, and 59.2% at 10 years. Corresponding rates in the older-donor group were 73.3%, 73.3%, and 66.7%, respectively [Figure 1]. In the control group, graft survival rates were 74.0% at 1 year, 62.7% at 5 years, and 54.8% at 10 years. Corresponding rates in the older-donor group were 71.0%, 71.0%, and 64.5%, respectively [Figure 2]. None of these differences in the two groups was statistically significant.

On Cox regression analysis, the parameters found to be significantly and independently associated with increased risk of graft loss were HCV (hazard ratio [HR] = 1.92, 95% confidence interval [95%CI] 1.16–2.63), older donor age (HR = 1.02, 95%CI 1.007–1.031), and male gender of the recipient (HR = 1.65, 95%CI 1.063–2.555).

Figure 2. Graft survival in the two groups (donors aged < 70 and ≥ 70 years)



DISCUSSION

In this study, we investigated the effect of using liver grafts from older donors on transplantation outcome. The results showed that recipients of deceased donor liver grafts from individuals aged 70 years or older seemed to have equivalent outcomes to recipients of deceased donor grafts from younger donors in terms of patient and graft survival rates at 1, 5, and 10 years, regardless of recipient age. Previous studies examining the routine use of liver grafts from older donors have yielded inconsistent results [4-6,9,11]. Concerns were raised regarding the clinical relevance of the structural (macroscopic and microscopic) and functional changes that older livers undergo on the synthetic, excretory, and metabolic capacity of the grafts [12]. Aging is associated with an increase in mean liver volume, a decrease in the number of hepatocytes, and presumably an impairment in the synthesis of clotting factors [12,13]. Because older livers have a lower ability to meet metabolic demands, such as those characteristic of the postoperative state or sepsis, they are more susceptible to ischemia/reperfusion injury [14]. The predominant change with aging is a reduction in liver regeneration, although not in the capacity to restore the organ to its original volume [15]. Taken together, these findings imply that older livers may have a relatively high rate of primary malfunction. Indeed, many previous publications support this idea. Lai et al. [16], in a study of 28 recipients of grafts from older donors (age > 70 years), reported a 5 year graft survival rate of 41%. Others found a 3 year graft survival rate of only 20% when donors were older than 80 years [17].

However, our findings are in line with more recent studies. The reported 5 year survival rate was 58% in the study by Jiménez-Romero and co-authors [18] of 50 recipients with grafts from donors older than 70 years; 78% in the study by Darius and colleagues [19] of 58 recipients with grafts from septuagenarian and octogenarian donors; and 75% in the study by Borchert et al. [20] of 41 recipients with grafts from donors aged 70–80 years. In a large analysis of the United Network for Organ Sharing database, Segev and co-authors [21] calculated a 3 year graft survival rate of 75% in selected recipients of grafts from donors older than 70 years. A large study from Spain, including 300 liver donors older than 70 years, found no difference in graft survival at 1 and 5 years between recipients of the old livers and recipients of livers from donors younger than 60 years [22].

In terms of complications, we found a similar incidence of biliary and vascular complications in the two groups. Arterial complications were more prevalent in the older donor group, although they were still within the normal range for liver transplantation.

Following liver transplantation, 20% to 65% of recipients have acute cellular rejection, and 20% to 40% experience at least one episode of acute cellular rejection that requires additional immunosuppressive treatment. The incidence of acute cellular rejection in our study was 44% (37% biopsy-proven) in the older-donor group and 30% (17% biopsy-proven) in the control group ($P = 0.11$). These results are in line with previous observations that high donor age does not affect the risk of rejection.

Recent advanced studies have suggested that avoiding additional factors related to graft loss, such as transplanting recipients with a high MELD score, long preservation, progressive steatosis, and associated renal dysfunction are essential to improving the survival of grafts from older donors [23]. In this study, following our protocol, the median cold ischemia time was shorter in the older donor group compared to the control group (6.5 hours vs. 8.7 hours, respectively). Livers were allocated independent of donor age so that recipients in the two groups had the same MELD score at transplantation. However, given the high reported recurrence rate of HCV after transplantation [24], within the allocation scheme we had some freedom to refrain from using aged donor livers in recipients with HCV and to allocate the older livers to the next non-HCV recipient on the list. Indeed, only six patients in the study cohort had HCV cirrhosis, and none of them died of recurrent HCV. The lower proportion of patients with HCV cirrhosis in recipients of livers from donors older than 70 years might explain survival benefit in that group compared to the control group. Overall, our experience in using livers from donors aged 70 years or older within the MELD allocation scheme has shown good results with a short cold ischemia time. Bertuzzo and colleagues [23] reached the same conclusion in their recent series of 190 recipients of livers from donors in the over 70 age group.

Nevertheless, on Cox regression analysis, donor age was still an important factor affecting graft loss. The same effect of donor age was reported in a study by Paterno and co-authors

[25] based on liver transplant recipients in the United States listed in the Scientific Registry of Transplant Recipients and University Health System Consortium databases from 2007 through 2011. In our model, HCV as a primary disease was another factor predicting worse outcome, with almost twice the risk of graft loss. Use of the new generation of anti-viral agents for HCV before and after transplant may alleviate this risk.

CONCLUSIONS

This single center study shows that liver transplantation using grafts from donors older than 70 years is associated with similar recipient and graft survival rates as transplantation using grafts from younger donors, regardless of recipient age or cause of liver disease, with no increase in the rate of complications. Grafts from donors older than 70 years may be equally safe if cold ischemia is maintained for less than 8 hours. Our findings support the use of older-donor livers, with careful attention to procurement processes, donor selection, and shorter cold ischemia time.

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"Be careful about reading health books. You may die of a misprint"

Mark Twain, (1835–1910), American humorist, writer

"When we are unable to find tranquility within ourselves, it is useless to seek it elsewhere"

Francois de La Rochefoucauld, (1613–1680), French author

"Knowledge rests on knowledge; what is new is meaningful because it departs slightly from what was known before"

Robert Oppenheimer, (1904–1967), American theoretical physicist, father of the atomic bomb