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ORIGINAL ARTICLE

How can we utilize livers from advanced aged donors for liver transplantation for hepatitis C?

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Summary

Advanced age donors have inferior outcomes of liver transplantation for Hepatitis C (HCV). Aged donors grafts may be transplanted into young or low model for end stage liver disease (MELD) patients in order to offset the effect of donor age. However, it is not well understood how to utilize liver grafts from advanced aged donors for HCV patients. Using the UNOS database, we retrospectively studied 7508 HCV patients who underwent primary liver transplantation. Risk factors for graft failure and graft survival using advanced aged grafts (donor age ≥ 60 years) were analyzed by Cox hazards models, donor risk index (DRI) and organ patient index (OPI). Recipient's age did not affect on graft survival regardless of donor age. Advanced aged grafts had significant inferior survival compared to younger aged grafts regardless of MELD score ($P < 0.0001$). Risk factors of HCV patients receiving advanced aged grafts included donation after cardiac death (DCD, HR: 1.69) and recent hospitalization (HR: 1.43). Advanced aged grafts showed significant difference in graft survival of HCV patients with stratification of DRI and OPI. In conclusion, there was no offsetting effect by use of advanced aged grafts into younger or low MELD patients. Advanced aged grafts, especially DCD, should be judiciously used for HCV patients with low MELD score.

Introduction

The waiting list for liver transplantation has increased annually. However, rates of deceased organ donation have not kept pace, which has led to a marked shortage of organs for transplantation [1]. The use of marginal donors has become routine in order to overcome the shortage of donor organs. In particular, there has been a persistent trend toward the use of older donors. The possible adverse impact of advanced donor age on recipient outcome after liver transplantation has been addressed.

It has been reported that the recipients of liver transplantation with advanced aged donor have inferior outcomes with higher perioperative mortality [2,3]. These findings particularly raise a question of impact of donor age on liver transplantation for hepatitis C, since hepatitis C is the most common cause of liver cirrhosis and the most common indication for liver transplantation [4]. Lake *et al.* reported that donor age was the strongest predictor of graft loss and death in patients with HCV starting with donors >40 years [5]. Mutimer *et al.* also reported, using European liver transplant database, that advanced donor age has a significantly adverse impact for patients with HCV compared to patients with other disease [6]. Similar results were also reported in single center studies [7–9].

It has recently been recognized that increased donor age is associated with more severe HCV recurrence and rapid progression of fibrosis [4,8–10]. However, there is no effective therapy to prevent HCV recurrence after liver

transplantation. Therefore, liver grafts from advanced aged donors generally appear to be turned down for HCV patients or those liver grafts may be transplanted into young recipients in order to offset the effect of donor age [7]. Advanced aged organs also may be transplanted into patients with lower model for end stage liver disease (MELD) scores to minimize the effect of donor age. Thus, it is not well understood how to utilize liver grafts from advanced aged donors for HCV patients.

In this study, we analyzed risk factors of graft failure for HCV patients receiving liver grafts from advanced aged donors. We also examined graft survival for HCV patients using advanced aged liver grafts with stratification by donor risk index (DRI) and organ patient index (OPI) [11–13].

Materials and methods

Data source

Data used were obtained from the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS/OPTN) database. We retrospectively studied 7508 adult HCV patients (≥18 years of age) who underwent primary liver transplantation between February 1, 2002 and December 31, 2007 in the United States. HCV patients were those with a positive serologic test for hepatitis C testing Patients receiving multiple organ transplants or living donor liver transplantation were excluded. Patient survival was defined as the time from the date of primary transplant until the date of death. Patients alive at the last recorded follow up were considered censored for patient survival. Graft survival was defined as the time from the date of primary transplant until the date of graft failure or death. A re-transplantation constituted graft failure. Patients alive and without graft failure at the time of last follow up were considered censored for graft survival. Both graft and patient survival were censored at 5 years. In analyses involving MELD scores, those with hepatocellular carcinoma (HCC) were also excluded, since HCC patients are automatically assigned a higher MELD score.

Analytical methods

Advanced age donors were defined as ≥ 60 years of age, and old recipients were defined as those ≥ 50 years of age as previously described [7]. A high MELD score was defined as ≥ 30 points. Recipient creatinine was considered elevated if it was >1.5 mg/dl at time of transplant, while total bilirubin was considered high if >8.0 mg/dl at transplant [14]. Albumin was considered low if ≤ 3.0 g/dl at transplant. Categorical characteristics of patients, such as gender and race, were compared using chi-squared tests. Continuous characteristics such as age were compared using Student *t* tests. Risk factors for graft failure in HCV recipients receiving organs from advanced age donors were quantified with Cox proportional hazards models.

Donor factors included gender, race/ethnicity, cold ischemia time, warm ischemia time, diabetes, donor positive for HCV, donation after cardiac death (DCD), and mechanism of death when using deceased donors. Mechanism of donor death was categorized as cardiovascular, intracranial hemorrhage/stroke, blunt injury, or 'other' if it was due to drowning, seizure, drug intoxication, asphyxiation, electrical, gunshot wound, stab injury, sudden infant death syndrome (SIDS), death from natural cause, or if some other cause not specifically included on the deceased donor registration form. Recipient factors included age, gender, race/ethnicity, bilirubin level, creatinine, international normalized ratio (INR), albumin, hospitalization within 90 days prior to transplant admission, patients on dialysis, spontaneous bacterial peritonitis (SBP), transjugular intrahepatic portacaval shunt (TIPS), portal vein thrombosis (PVT) at transplant, and previous upper abdominal surgery. Graft survival was modeled during the first 5 years post-transplant using the Kaplan–Meier method, and curves were compared using the log rank test. DRI was calculated as defined by Feng *et al.* [11]. DRI was divided into two category (DRI ≤ 2.0 or DRI > 2.0) to compare graft survival. OPI was calculated based on the previous report [13]. *P*-values <0.05 were considered statistically significant. All analyses were performed using STATA statistical software (version 8.2; StataCorp LP, College Station, TX, USA).

Results

Characteristics of HCV recipients and their donors are shown in Table 1. Recipient characteristics were mostly similar between donors ≥ 60 years of age (old donors) and <60 years of age (young donors). Recipients of organs from young donors were slightly younger, had higher bilirubin and INR levels and had higher MELD scores, and rates of SBP. These differences were small and likely due to the large sample size, but are probably not clinically significant. Young donors were more likely to be male, of non-white race, to have HCV, to have died from blunt trauma, and to be DCD. Older donors were more likely to have died from cerebrovascular causes and to have diabetes. Graft survival stratified by age of donor is presented in Fig. 1, which shows that the highest rates of survival at 5 years were associated with the lowest donor age group (age <40). The poorest rates of 5-year survival were associated with older donors ($P < 0.0001$). Graft survival of HCV patients was also examined in the relationship

Table 1. Characteristics of donors and recipients undergoing transplantation for HCV, compared by age of donor.

Variable	Young donor (n = 6527)	Old donor (n = 981)	P-value
Recipient characteristics			
Age (years)	52.1	53.3	<0.0001
Gender			
Female	24.4%	26.8%	0.10
Male	75.7%	73.2%	
Race/ethnicity			
White	73.5%	70.4%	0.3
Black	9.3%	10.1%	
Hispanic	14.0%	15.5%	
Asian	2.3%	3.0%	
Other	0.8%	1.0%	
Bilirubin (mg/dl)*	6.83	5.53	<0.0001
Creatinine (mg/dl)*	1.36	1.33	0.4
INR*	1.84	1.77	0.027
Albumin (g/dl)*	2.84	2.80	0.063
MELD score	20.4	19.4	0.0023
Child-pugh score			
Class A	6.0%	7.5%	0.17
Class B	29.7%	28.7%	
Class C	64.3%	63.8%	
Spontaneous bacterial peritonitis*			
No	89.6%	91.3%	0.019
Yes	8.0%	5.8%	
Unknown	2.4%	2.9%	
Recipient hospitalized†			
No	79.3%	78.9%	0.7
Yes	18.2%	18.7%	
Unknown	2.5%	2.5%	
TIPSS*			
No	83.9%	85.5%	0.4
Yes	9.2%	10.0%	
Unknown	3.1%	4.5%	
PVT (recipient)*			
No	93.3%	92.1%	0.8
Yes	3.8%	3.6%	
Unknown	3.0%	4.3%	
Previous abdominal surgery (recipient)*			
No	62.6%	59.8%	0.13
Yes	32.2%	34.7%	
Unknown	5.2%	5.5%	
Recipient dialysis*			
No	94.4%	95.7%	0.084
Yes	5.6%	4.3%	
Donor characteristics			
Donor Gender			
Male	63.2%	51.9%	<0.0001
Female	36.9%	48.1%	
Donor race/ethnicity			
White	68.7%	73.9%	0.004
Black	14.7%	12.3%	
Other	16.6%	13.8%	
Donor cause of death			
Cardiac	8.0%	9.5%	0.11
Cerebrovascular/stroke	39.6%	76.9%	<0.0001
Blunt trauma	29.8%	9.8%	<0.0001
Other	22.6%	3.9%	<0.0001
Diabetes (donor)			
Yes	6.8%	18.9%	<0.0001
Cold ischemia time (hours)	7.3	7.5	0.11
Warm ischemia time (minutes)	41.5	42.7	0.12
Donor HCV status			
HCV positive	6.7%	2.2%	<0.0001
Donor after cardiac death			
Yes	5.6%	2.9%	<0.0001

*At time of transplant.
†Within 90 days prior to transplant admission.

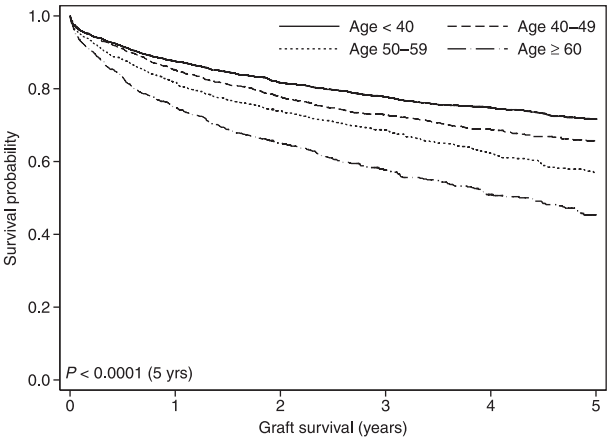

Figure 1 Graft survival of liver transplantation for HCV patients stratified by age of donor.

of recipients' age and donors' age. Using livers from young donors, 1 and 5 year graft survival for young HCV recipients were 86.2% and 68.2%, not different from 85.3% and 66.0% in older HCV recipients (Fig. 2a). These findings were consistent with the use of liver grafts from advanced aged donors. HCV recipients who received organs from advanced age donors showed poor outcome after liver transplantation regardless of patients' age. Young recipients had 1 year and 5 year graft survival rates of 77.4% and 45.8%, respectively, while older recipients had 1 year and 5 year graft survival rates of 74.1% and 45.2%, respectively (Fig. 2b). These results indicate that the recipient age does not have a significant effect on graft survival in HCV patients, whereas the age of the donor was the main determinant of outcome after liver transplantation.

We also analyzed graft survival in the relationship of recipients' MELD score and donor age in HCV patients.

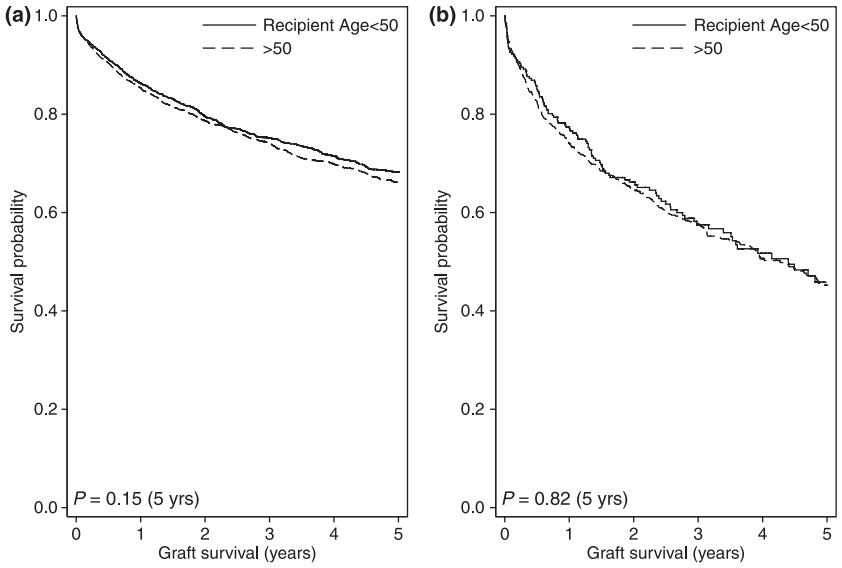

Figure 2 Graft survival by age of HCV recipients. (a) Young donors (donor age < 60), (b) old donors (donor age ≥ 60).

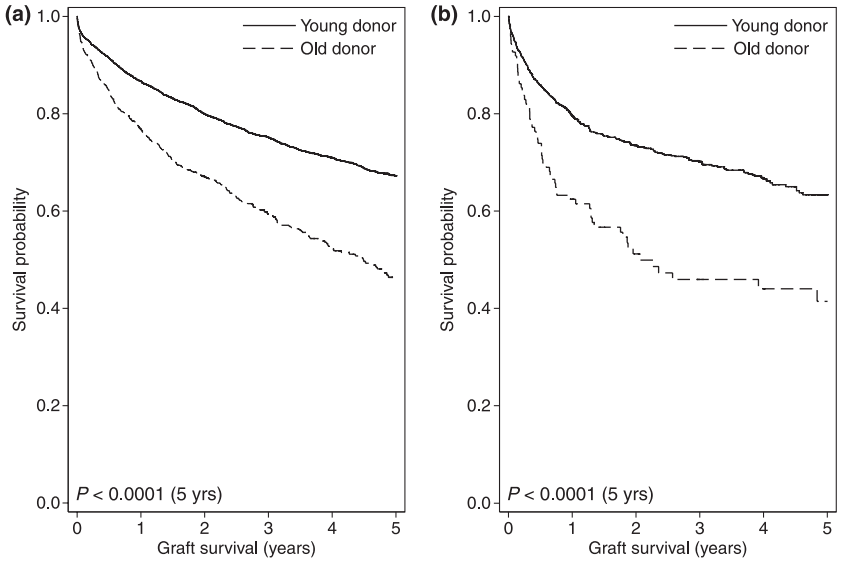

Figure 3 Graft survival by donor age in HCV patients with low and high MELD scores. (a) MELD < 30, (b) MELD ≥ 30.

When advanced aged grafts were used, graft survival was significantly poorer regardless of recipients' MELD score (Fig. 3). Recipients with lower MELD scores (<30) had 1 year graft survival of 86.6% with young donors, which dropped to 76.9% ($P < 0.0001$) with older donors (Fig. 3 a). Likewise, 5 year graft survival dropped from 67.3% to 46.4% ($P < 0.0001$) with older donors (Fig. 3a). In patients with higher MELD scores (≥ 30), 1 year graft survival dropped from 80.6% to 65.2%, and 5 year graft survival dropped from 65.2% to 38.6% ($P < 0.0001$ for both) in patients receiving advanced age donation (Fig. 3b).

Despite poor outcomes with advanced aged liver grafts, we often need to use those organs due to organ shortage. Therefore, we analyzed risk factors for graft failure in particular focusing on HCV patients who received a liver graft from an advanced age donor (age > 60, Table 2). DCD was a remarkable high risk factor with a 69% increased risk of graft failure [Hazard ratio (HR): 1.69; $P = 0.04$] followed by recent hospitalization (HR: 1.43; $P = 0.01$). Cold ischemia time >8 h was also a significant factor (HR: 1.21; $P = 0.05$). Interestingly, Hispanic donors marginally increased risk of graft failure (HR: 1.34; $P = 0.06$) while African-American donors decreased risk of graft failure (HR: 0.71; $P = 0.04$). With stratification of DRI of advanced aged donor livers, there were 6910 patients with DRI ≤ 2.0 and 598 patients with DRI > 2.0. The patients with high DRI showed significantly inferior graft survival compared to patients with

Table 2. Cox multivariate analysis of risks for graft failure in HCV patients receiving liver from donors ≥ 60 years of age.

Variable	Hazard ratio	95% Confidence Lower	Upper	*P*-value
Recipient characteristics				
Age				
Age > 50 years	1.02	0.83	1.27	0.83
Gender				
Male	Reference			
Female	1.08	0.87	1.35	0.49
Race/ethnicity				
White	Reference			
Black	1.27	0.94	1.71	0.12
Hispanic	0.76	0.57	1.01	0.06
Other	0.75	0.44	1.28	0.30
Bilirubin*				
Bili >8.0 mg/dl	1.09	0.81	1.45	0.58
Creatinine*				
Cr >1.5 mg/dl	1.15	0.91	1.45	0.23
INR*				
≥3.0	1.13	0.76	1.69	0.55
Albumin*				
<3.0 g/dl	1.03	0.84	1.26	0.77
Recipient hospitalized†				
No	Reference			
Yes	1.43	1.11	1.84	0.01
Unknown	1.34	0.75	2.38	0.32
Spontaneous bacterial peritonitis*				
No	Reference			
Yes	1.34	0.93	1.94	0.12
Unknown	1.36	0.73	2.56	0.33
TIPSS*				
No	Reference			
Yes	1.03	0.74	1.42	0.88
Unknown	0.99	0.52	1.86	0.96
PVT*				
No	Reference			
Yes	0.94	0.54	1.62	0.81
Unknown	0.98	0.51	1.86	0.95
Previous abdominal surgery				
No	Reference			
Yes	1.16	0.95	1.43	0.15
Unknown	0.74	0.44	1.24	0.25
Donor characteristics				
Gender				
Male	Reference			
Female	0.97	0.80	1.18	0.78
Race/ethnicity				
White	Reference			
Black	0.71	0.51	0.98	0.04
Hispanic	1.34	0.98	1.81	0.06
Other	1.09	0.67	1.75	0.73
Cold ischemia time				
≥8 h	1.21	1.00	1.47	0.05
Warm ischemia time				
>40 min	1.12	0.91	1.37	0.29
Donor mechanism of death				
Other/Missing	Reference			
Cardiac	0.76	0.44	1.33	0.34
Blunt trauma	0.71	0.41	1.23	0.22
Stroke/cerebrovascular	0.91	0.57	1.44	0.69
Donor hep C status				
HCV-positive	1.04	0.52	2.04	0.92
Donor after cardiac death				
No	Reference			
Yes	1.69	1.03	2.75	0.04

*At time of transplant.
†Within 90 days prior to transplant admission.

low DRI ($P < 0.0001$, Fig. 4a). We also analyzed graft survival using OPI. The high risk group (OPI > 2.85) contained 142 patients and the low risk group (≤2.85) contained 6910 patients. The high risk group also showed significant poor graft survival compared to the low risk group ($P < 0.0001$, Fig. 4b).

Discussion

Because of the shortage of donor organs, there has been a persistent trend toward the use of older donors and the median donor age has more than doubled during the past decade [6]. However, the use of older donors is associated with decreased graft and patient survival mainly due to the effect of donor age on HCV recurrence [6,9,15,16]. These observations imply that outcome of transplantation for HCV patients could be improved by the avoidance of older donors. However, in addition to the shortage of donor organs, there is no preferential allocation of younger donors to HCV recipients in the current allocation system. In order to offset the effect of old donors, older grafts may be transplanted into young recipients, or advanced aged organs also may be transplanted into patients with lower MELD scores [7]. However, our results clearly show that recipients who received advanced aged livers had poorer outcomes regardless of recipient age and MELD score. Using UNOS data from 1987 to 2003, Condron *et al.* previously reported that recipient's age for HCV disease was a risk factor at 1 year after liver transplantation [17]. Their finding is contrary to our data showing that recipient age is not a risk factor for graft failure. Recent observation of post-transplantation HCV infection suggests that the speed of fibrosis progression has increased in patients undergoing liver transplantation

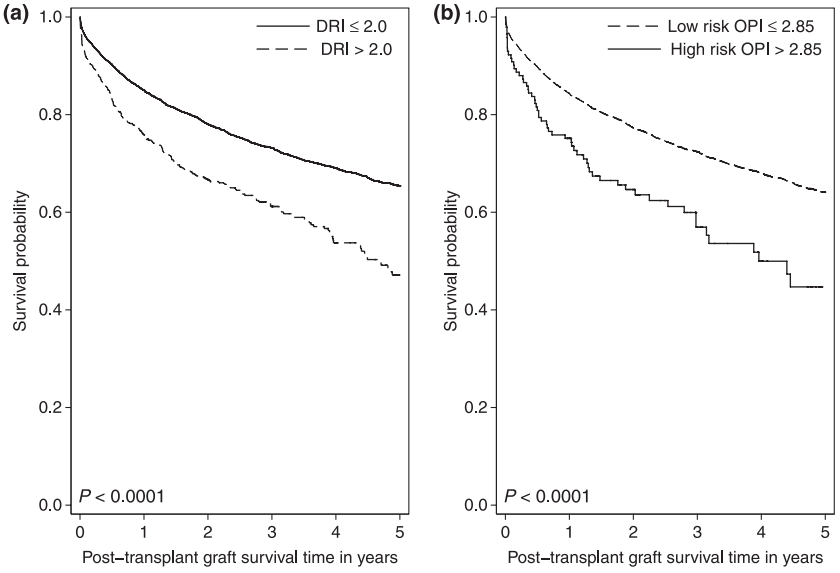

Figure 4 Graft survival of HCV patients with advanced aged liver grafts (≥ 60 years old) with stratification by (a) DRI and (b) OPI.

in recent years, and this result suggests that the speed of HCV recurrence after liver transplantation was accelerated in recent years [18]. Furthermore, because of donor shortage, old donors have been significantly increased to use and advancing donor liver age is associated with rapid fibrosis progression following transplantation for hepatitis C [15]. These recent observations may be able to explain why recipient age is not significant factor for graft failure in our modern era analysis.

Recently, Feng *et al.* and Shaubel *et al.* reported a concept of DRI [11,12]. In this study, we analyzed graft survival of advanced aged graft for HCV with stratification of DRI ≤ 2.0 and >2.0. Higher DRI > 2.0 showed significantly inferior outcome. DRI was developed using The Scientific Registry of Transplant Recipients, a database with 20 023 adult patients older 18 years. It may not be accurate analytic method to evaluate particular older donor group. In addition, recipient factors are not included in the formula. Therefore, we utilized OPI for further analyses. OPI accounts for MELD and DRI with calculated as DRI+0.020×MELD [13]. It is suggested that OPI predicted the outcome of liver transplantation better than DRI [13]. In this study, high OPI > 2.85 also showed inferior graft survival compared to low OPI ≤ 2.85. These results suggest that DRI and OPI may be useful tools to utilize older liver grafts for HCV patients. There is a substantial body of literature presenting algorithms to assess the risk of graft failure after liver transplantation [19–21]. However, there are few reports focused on particular groups of HCV patients, especially with use of advanced aged grafts. In this study, DCD was the strongest risk factor (HR = 1.69) followed by recent hospitalization (within 90 days prior to liver transplantation, HR = 1.43). Interestingly, the patients who received liver allografts from African-American donors had significantly less graft failure (HR: 0.71; $P = 0.04$, Table 2). This finding about African-American donors in HCV recipients who received livers from old donors is contrary to the finding in the general liver transplant population [11]. It has been reported that liver fibrosis in African American progresses more slowly than in white patients in hepatitis C [22,23]. On the other hand, Hispanics have more advanced liver fibrosis with hepatitis C [23,24]. These results may explain why Hispanic donors have poorer outcomes while African American donors have better outcomes in liver transplantation for HCV in this study. Acute rejection is one of the most important risk factors that has been shown to significantly increase the severity of recurrent hepatitis C because of steroid boluses and subsequent increases in immunosuppression [25]. In this analysis, these factors were not included in the Cox hazard model because of missing or unavailable data.

Recently, a number of transplant program have begun to perform transplants using livers from DCD donors [26]. The outcome of liver transplantation using DCD is controversial. It has been reported using the UNOS database that DCD liver had inferior graft and patient survival and DCD livers were associated with a significantly increased risk of graft failure [27,28]. This finding was also supported by single center analyses [29,30]. On the other hand, other single center analyses reported that DCD livers could achieve similar graft and patient survival with livers from brain death donors [26,31,32]. In our study, we have shown that DCD is the strongest risk factor for graft loss in advanced aged grafts for HCV patients. This result suggests that judicious use of DCD

livers is warranted although they remain an important source.

The characteristics of recipients of advanced age grafts presumably reflect the balanced choices that transplant physicians have made in an attempt to maximize candidate benefit. The benefits from liver transplantation increase as MELD score increases and candidates who are most ill face the greatest survival benefit from liver transplantation [33,34]. Therefore, it should be acceptable that advanced aged liver grafts are used for HCV patients with high MELD scores because they have the highest mortality in the absence of transplantation. On the other hand, it is not clear about the use of advanced age grafts for HCV patients with low MELD scores. Our data shows that patients with low MELD scores receiving advanced aged grafts had poorer outcomes than those with high MELD scores receiving younger grafts. This begs a question as to whether advanced aged grafts should be avoided to use for HCV patients with low MELD scores. It is not easy to answer this question because many factors need to be considered. There are still significant geographic and racial disparities in organ allocation and access to liver transplantation in the United States [35–38]. The probability of transplantation varies widely by region and donation service area. This means that patients with low MELD scores may or may not have the next liver offer soon depending on geography if an offer of an advanced aged graft is turned down. Furthermore, considering the high 3 month mortality rate (27%) of hospitalized patients with $10 < \text{MELD} < 19$ [39], even an advanced aged liver should be considered for such hospitalized HCV patients with low MELD score. Ultimately, at the time of an organ offer, the decision to accept either the risk of transplantation or the risk of waiting rests with transplant physicians and their patients. Making this decision rationally requires facts about the risk of graft failure posed by the particular graft being offered and the risk of death from progressive liver disease if the current offer is declined. Unfortunately, changing liver allocation schemes to give patients with HCV cirrhosis priority for organs from younger donors would likely require support from the transplant community at this point. When an advanced aged donor is offered to HCV patients, our result may provide some guidance to making the decision.

Nevertheless, we recognize that there are limitations to this study using the registry database. In this study, we do not have data regarding liver biopsy, genotype, and HCV PCR. HCV patients in this study are probably a mixed population with positive and negative HCV–RNA. There are reports suggesting that successful treatment of HCV prior to transplant reduced the rate of post-transplant recurrence and possible better graft survival [40–42]. Furthermore, it is reported that sepsis, not recurrent cirrhosis, was the most common cause of death in HCV liver transplantation [43]. Studies evaluating the relationship between the severity of HCV recurrence and HCV genotypes are conflicting. Some studies suggest that genotype 1b has more severe recurrence [44,45], whereas others showed no difference in recurrence between genotypes [18,46]. There are several potential sources of imprecision in our study, such as inconsistent application by UNOS regional review boards of the rules to grant MELD exception scores, although HCC cases were excluded due to their exceptional MELD points in MELD analysis. In addition, the analysis based on UNOS data is a function of past practice pattern and possibly results in selection bias.

In summary, advanced donor age led to inferior outcomes of liver transplantation for hepatitis C patients regardless of MELD score or recipient age. We did not find an offsetting effect to transplant advanced aged liver graft into young or lower MELD patients. Our results indicate that possible efforts to minimize cold and warm ischemia time should be made on utilizing advanced aged livers for HCV disease. Hispanic donor was a significant risk factor, while African-American donor deceased graft failure. This racial difference needs to be further analyzed. Advanced aged DCD should be judiciously used for HCV patients, especially candidates with low MELD scores.

Authorship

TU: research design, obtaining database, performance of research, data analysis, and writing the paper. LEN: data analysis and writing the paper. CSH, VR and ES: data analysis. ZK: research design, data analysis and writing the paper.

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