Quality in liver transplantation: perspectives on organ procurement and allocation

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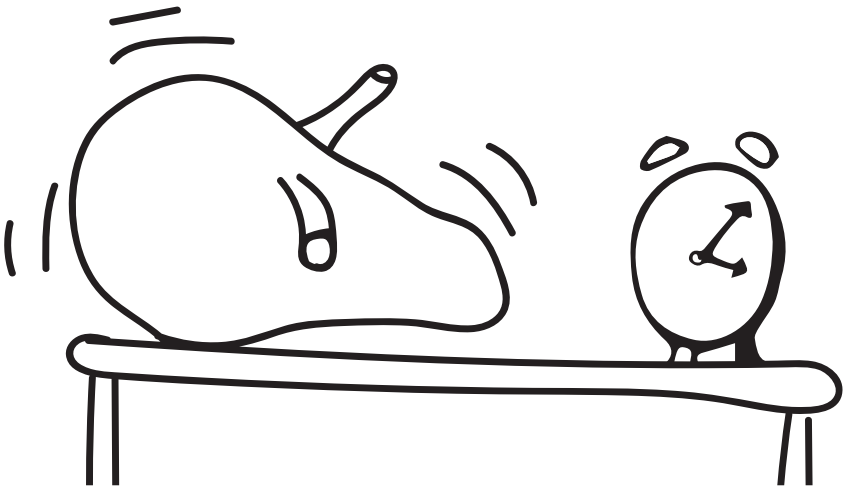

Chapter 6

Optimizing the use of geriatric livers for transplantation in the Eurotransplant region

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On behalf of the Eurotransplant Liver and Intestine Advisory Committee

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Abstract

Acceptance criteria for liver allografts are ever more expanding because of a persisting waiting list mortality. Older livers are therefore offered and used more frequently for transplantation. This study aims to analyze the use and long-term outcome of these transplantations. Data were included on 17,811 first liver transplantations and information on livers that were reported for allocation but not transplanted from 2000-2015 in the Eurotransplant region. Graft survival was defined as the period between transplantation and date of re-transplantation or date of recipient death. In the study period, 2,394 (13%) transplantations were performed with livers of ≥70 years old. Graft survival was 74%, 57% and 41% at 1, 5 and 10-year follow-up. A history of diabetes mellitus in the donor (HR 1.3, p=0.01) and positive HCVAb in the recipient (HR 1.5, p<0.001) are specific risk factors for transplantations with livers of ≥70 years old. Although donor age is associated with a linearly increasing risk of graft loss between 25 and 80 years old, no difference in graft survival could be observed when 'preferred' recipients were transplanted with a liver <70 or ≥70 years old (HR 1.1; CI 0.92 – 1.23, p=0.40) or with a donor <40 or ≥70 years old (HR 1.2; CI 0.96-1.37, p=0.13). Utilization of reported livers ≥70 years old increased from 42% in 2000-2003 to 76% in 2013-2015, without a decrease in graft survival (p=0.45). In conclusion, an important proportion of liver transplantations in the Eurotransplant region are performed with livers ≥70 years old. The risk of donor age on graft loss increases linearly between 25 and 80 years old. Livers ≥70 years old can, however, be transplanted safely in preferred patients and are to be used more frequently to further reduce wait-list mortality.

Introduction

The number of patients registered for a liver transplantation (LT) in the Eurotransplant (ET) region exceeds the number of available liver allografts. In 2016, 2,258 patients were registered for a liver transplantation and 1,567 transplantations were performed. Wait-list mortality is therefore a serious issue: over 500 patients died in 2016 while waiting and over 1,700 patients were still on the waiting list at years' end[1]. To increase the number of transplantations, the acceptance criteria for LT have been stretched increasingly in the past decade. One of the criteria that is being expanded is donor age. As a result, mean donor age has increased from 25 years old in 1990 to 55 years old in 2016[1]. This development is illustrated by the significant increase in donors aged 70 years or older[2]. These older livers can increase the number of LT and are therefore an important source to help decrease waiting list mortality.

However, they are likely to negatively affect post-transplantation outcomes since donor age is a well-known risk factor[3]. It has, for example, been included as an important risk factor in several outcome models, like the donor risk index (DRI)[4], Eurotransplant-DRI (ET-DRI)[5] and BAR score[6]. The latter uses a cut off for older donors of 40 years old[6], whereas the DRI and ET-DRI have donor age categorized into five age categories. The category with the oldest livers comprises all livers from donors of 70 years and older and is associated with a hazard ratio of 1.65 and 1.62 for the DRI and ET-DRI, respectively[4,5]. Although these risk models use cut-off values for donor age, the actual summative effect of donor age on post-transplantation outcome is yet unclear. Especially, when transplanting livers from donors of 70 years and older.

The demographical transition in western countries with ageing populations and promising post-transplantation results[7–9] indicate that this practice will become increasingly more common. The current substantial use might therefore just be the onset of a far more common one in Europe and the United States (US)[10]. It questions whether there are limits to donor age at all and urges a thorough analysis of the current practice of transplantations with elderly donors.

This study aims to analyze the effect of an increasing donor age on outcome after liver transplantation in the Eurotransplant region. Second, an evaluation of the current and potential use of liver allografts from donors of 70 years and older is performed.

Patients and Methods

Design

All first LTs performed in adult recipients (≥18 years) with liver allografts from deceased donors from January 1st, 2000 until December 31st, 2015 in the Eurotransplant region were included. Follow-up data were obtained from the Eurotransplant Network Information System and Eurotransplant Liver Registry up to March 2017. Also, data were obtained on the reported, but non-transplanted liver allografts from donors of 70 years and older within the study period. The study protocol was approved by the Eurotransplant Liver Intestine Advisory Committee (ELIAC) and no ethical statement was required according to European guidelines and Dutch law since data were anonymized and patients were not (directly) involved and/or affected.

Outcome measures

Graft survival at 1,5 and 10-year follow-up was considered as primary outcome measures. Graft survival was defined as the period between the date of transplantation and date of re-transplantation or date of recipient death, whichever occurred first (non-death censored graft survival). Patient survival at 1, 5 and 10 years was considered as secondary outcome and was defined as time between date of transplantation and death date. Utilization rate was defined as the proportion of liver allografts used for liver-only transplantations in adult recipients divided by the sum of livers used for first liver-only transplantations in adult recipients and all reported but non-transplanted livers.

Preferred recipients

Preferred and non-preferred recipients were defined according to the criteria as published by Segev *et al.*[11]. They identified a group of patients by selecting first time, nonstatus-1 recipients with an age>45, BMI<35, an indication other than hepato-cellular carcinoma or hepatitis C and a cold ischemia time (CIT) <8 hours. In our study, we only considered recipients with an age>45 years, BMI<35 indication other than hepatitis C and a CIT <8 hours as preferred recipients. Re-transplantations were not included in this study and the definition of (the equivalent of) status-1 recipients changed over the study period. In addition, HCC could not be analyzed because the presence of HCC was not registered for the entire study period as separate variable or as category in the etiology of liver disease variable.

Transplant centers

Transplant centers were first categorized by the median number of liver transplantations with livers ≥70 years old in a low- and high-volume group. Subsequently, centers were categorized by the median proportion of transplantations performed with livers ≥70 years old as compared to all transplantations performed in that center and included in this study. Then, centers were categorized according to outcome of transplantations

with livers ≥70 years in 'better than expected', 'worse than expected' and 'as expected' based on the 95% confidence interval[12].

Data analysis

Clinical characteristics were summarized by median and 25% and 75% interquartile range (IQR) or by number and percentage (N/%) for continuous and categorical factors, respectively. Factors between groups were compared using Kruskall-Wallis (continuous) and Chi-square tests (categorical). Missing values were imputed with the median value for GGT (34 U/L/, 2%) ASAT (41 U/L, 1%), ALAT (29 U/L, 1%) and Bilirubin (9.4 umol/l, 3%). Missing CITs (37%) were imputed based on three factors; allocation (local, regional, extra-regional), 3 years' non-death censored graft survival and CITs in a 5-fold database by multiple imputation using chained equations (MICE). Diabetes mellitus (DM) in the donor was considered present in case of a medical history of DM type 1, 2 and 'positive but unspecified'. Rescue allocation, cardiac arrest and hypotensive periods in the donor were considered absent when missing. Donor HCVAb, HBcAb and recipient HCVAb were considered negative when missing (1%/1%/24%) or not tested (0%/2%/8%). The Eurotransplant donor risk index (ET-DRI)[5] was calculated for all transplantations and the simplified recipient risk index (sRRI) and Donor to Recipient Model (DRM)[13] were calculated for all patients with a known MELD score. MELD score was only known for recipients that were listed in the time period after 16th December, 2006 because then MELD score was implemented in Eurotransplant.

Statistical analysis

Post-transplantation outcomes at 10 years were analyzed with Kaplan-Meier analysis and by log-rank test. Results were stratified for four donor age categories (<60, 60-69, 70-79, ≥80). A possible correlation between donor age and laboratory-MELD-score was tested with a Cox regression model. Subsequently, factors potentially associated with graft survival were analyzed in a multivariate Cox Regression model in transplantations with livers from donors ≥70 years old. The specific effect of donor age was visualized by using splines regression when adjusted for donor and risk factors. Then, the effect of donor age on outcome was analyzed in preferred and non-preferred recipients. Within both patient categories, outcome was stratified by two donor age categories; livers from donors <70 years old and ≥70 years old and for livers from donors <40 and ≥70 years old. Center outcome for transplantations with livers ≥70 years old was according to volume and proportion of liver transplantations with livers ≥70 years old in a Kaplan-Meier analysis. Then, according to their relative performance on graft survival at 5-year follow-up in a funnel-plot analysis. Centers with few of such transplantations were excluded for this analysis (<10 LTs). To analyze the utilization rate, livers from donors ≥70 years old that were reported to Eurotransplant were compared by transplantation status (yes/no). A p-value below 0.05 was considered statistically significant and all analyses were performed with SPSS, version 24.0 (IMB, Armonk, NY) and R, version 3.3.2, (R Project for Statistical Computing, Vienna, Austria).

Results

Study population

In the study period 17,811 first LTs were performed in adult recipients within the Eurotransplant region. Mean follow-up period was 6.3 years. Median donor age of all transplanted livers was 51 years old (maximum 98 years) and increased from 42 years to 55 years (Figure 1).

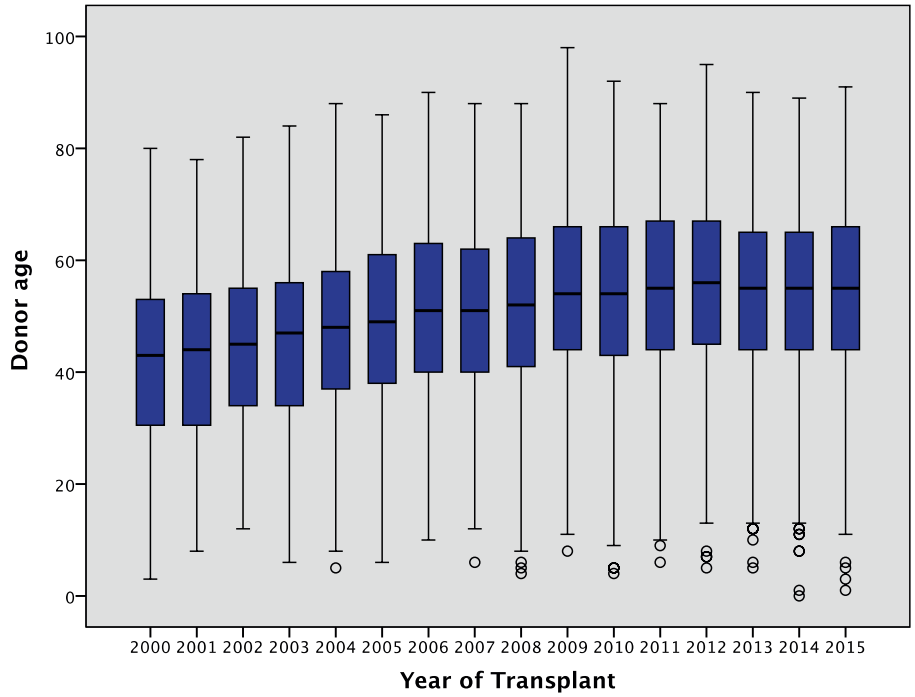

Figure 1. Trends in donor age. Median donor age increased from 42 to 55 years old from 2000-2015.

Nearly half of all transplanted livers were allocated extra-regionally (45%) and approximately 25% were allocated in rescue allocation. Median ET-DRI was 1.8 (1.5-2.2) with donor age included and 1.4 (1.3-1.6) without donor age. Recipients had a median age of 54 and median lab-MELD score was 16. Other demographics on donor, transplantation and recipient characteristics are shown in Tables 1 and 2. Overall graft survival was 76%, 63% and 49% after 1, 5 and 10 years, respectively, and patient survival was 81%, 69%, 55% after 1, 5 and 10 years, respectively.

Table 1. Demographics of all livers used for first liver-only transplantation in 2000-2015.

Donor factor	N(%)/ Median (25th-75th percentile)
Age (years)	51 (40-63)
Height (cm)	175 (166-180)
Weight (kg)	75 (68 - 85)
BMI	25 (23 -28)
Sex (male)	9,713 (55)
HCVAb (positive)	138 (1)
HBcAb (positive)	1,001 (6)
Cause of death	
Anoxia	1,421 (8)
Circulational	556 (3)
CNS Tumor	104 (1)
CVA/Stroke	1,0659 (60)
Head Trauma	4,186 (24)
Other	885 (5)
DCD	744 (4)
Split liver	641 (4)
CT present	1,725 (10)
Ultrasound abdomen present	13,316 (75)
Cardiac arrest (y)	2,098 (12)
Hypotensive period (y)	3,131 (18)
Diabetes (y)	1,203 (7)
Latest laborary values	
GGT (U/L)	34 (18-76)
ASAT (U/L)	41 (25 - 72)
ALAT (U/L)	29 (17-55)
Bilirubin (umol/L)	9.4 (6.0 - 14.7)
Donor country	
Germany	1,0350 (58)
Hungary[†]	240 (1)
The Netherlands	1,593 (9)
Belgium	2,694 (15)
Croatia[⊥]	803 (5)
Slovenia [‡]	334 (2)
Austria	1,751 (10)

Table 1. Continued.

Donor factor	**N(%)/ Median (25th-75th percentile)**
Luxemburg	46 (0)
Transplant factor	**N (%)/ Median (25th-75th percentile)**
Allocation	
Local	5,121 (29)
Regional	4,614 (26)
Extra-regional	8,076 (45)
Rescue allocation (yes)	4,011 (23)
Cold ischemia time (hours)	8.87 (7.00-10.85)
ET-DRI	1.8 (1.5-2.2)
ET-DRI without age	1.4 (1.3-1.6)

Joined ET in [†]May 2013, [⊥]May 2007, [‡]January 2000

Table 2. Demographics of all recipients receiving a first liver-only transplantation in 2000-2015.

Recipient factor	**N (%)/ Median (25th-75th percentile)**
Age (years)	54 (47-61)
Height (cm)	173 (167-180)
Weight (kg)	77 (67-88)
BMI	25 (23 -29)
Lab-MELD	16 (11-27)
Match-Meld	23 (16-31)
Sex (Male)	11,796 (66)
HCVAb (pos)	3,474 (14)
Primary disease on WL	
Metabolic	612 (3)
Acute	1,496 (8)
Cholestatic	2,018 (11)
Alcoholic	4,102 (23)
Malignant	3,138 (18)
HBV	603 (3)
HCV	1,516 (9)
Other cirrhosis	3,334 (19)
Other/unknown	992 (6)
Lab-MELD category	

Table 2. Continued.

Recipient factor	N (%)/ Median (25th-75th percentile)
<15	5,059 (28)
15 – 25	3,688 (21)
26 – 34	1,851 (10)
35+	1,698 (10)
Missing	5,515 (31)
Country of transplantation	
Germany	10,651 (60)
Hungary[†]	170 (1)
The Netherlands	1,434 (8)
Belgium	2,756 (16)
Croatia[⊥]	787 (4)
Slovenia [‡]	243 (1)
Austria	1,770 (10)
Luxemburg	0 (0)
sRRI [┼]	1.9 (1.6-2.3)
DRM without donor age[┼]	2.5 (2.0-3.0)
DRM with donor age[┼]	2.9 (2.3-3.6)

Joined ET in [†]May 2013, [⊥]May 2007, [‡]January 2000
[┼]Calculated for patients listed after MELD implementation, December 2006 (n=12296).

Outcome by donor age groups

Of all transplantations, 15,147 (85%) were performed with donors <70 years old and 2,014 (11%), 369 (2%) and 11 (0.06%) transplantations were performed with livers from septuagenarian, octogenarian and nonagenarian donors, respectively (Figure 2, Table 3). The percentage of LTs with donors ≥70 years old increased significantly throughout the study period (p<0.001). Donor and recipient characteristics per donor age category are shown in Table 4. In this table, characteristics of transplantations with livers from donors <70 years old and >70 years old were compared. Cerebral vascular accident as cause of death was more frequent in transplanted livers ≥70 years old, while trauma was more frequent in younger donors. DM had a higher prevalence in livers ≥70 years old (16% vs. 5%, p=0.001) in contrast to cardiac arrest (4% vs. 13%, p=<0.001). Furthermore, CITs were longer in transplanted livers <70 years old (8.91 vs. 8.65, p=<0.001). The ET-DRI, as measurement of donor quality, was significantly different in both groups (1.7 vs 2.4, p<0.001), but no significant difference was shown with the factor donor age set at reference (1.4 vs. 1.4, p=0.31).

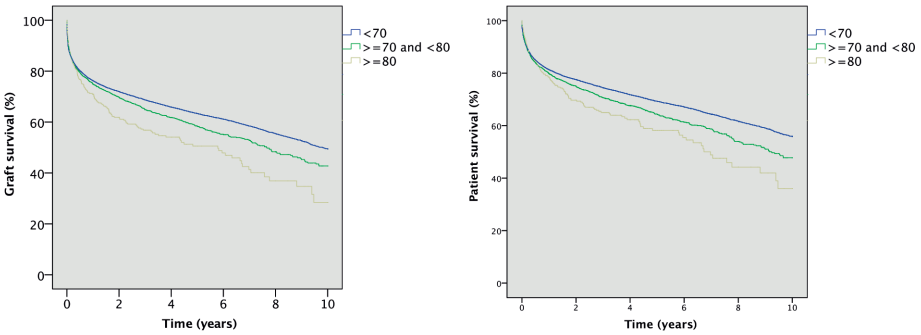

Figure 2. Kaplan-Meier analysis of survival by donor age category (n=17,811)

Table 3. Graft- and Patient Survival Rates

		1-year	5-year	10-year
Graft survival				
<70 (n=15,147)	Survival	76%	63%	50%
	Number of events	3527	4989	5,722
	Number at risk	10,775	5,296	1,68
70-79 (n=2,014)	Survival	75%	58%	43%
	Number of events	483	707	782
	Number at risk	1,358	507	99
>=80 (n=380)	Survival	71%	51%	28%
	Number of events	103	154	169
	Number at risk	238	65	9
p-value		0.089	<0.001	<0.001
Patient survival				
		1-year	**5-year**	**10-year**
<70 (n=15,147)	Survival	81%	69%	56%
	Number of events	2,763	4,124	4,837
	Number at risk	11,48	5,818	1,9
70-79 (n=2,014)	Survival	80%	64%	48%
	Number of events	388	595	673
	Number at risk	1,436	556	110
>=80 (n=380)	Survival	79%	58%	36%
	Number of events	76	126	141
	Number at risk	262	76	11
p-value		0.188	<0.001	<0.001

Patients transplanted with a liver ≥70 years old were older as compared with recipients of livers from donors <70 years old (58 vs. 54 years old, p=<0.001). The recipients of older livers did also have a lower median laboratory MELD score (16 vs.17, p=<0.001). Another difference was observed in primary diagnosis: recipients of liver allografts ≥70 years old more often had a malignant disease (24% vs. 17%) and alcoholic liver cirrhosis (30% vs. 22%).

When analyzing graft survival, significant differences were observed across donor age categories (<70, 70-79, ≥80 years) at 5-year (p=<0.001) and 10-year follow-up (p=<0.001) (Figure 2a). No difference in 1-year graft survival could be detected (p=0.09). Similar differences were observed for patient survival; no difference at 1-year follow-up (p=0.19) but significant differences at 5-year (p=<0.001) and 10-year follow-up (p=<0.001) (Figure 2b). A potential change in outcome throughout the study period was evaluated for LTs with donors of ≥70 years per year. However, no effect of transplant year (p=0.30) or when grouped into five transplant periods (p=0.45) could be detected for graft survival at 5-year follow up (data not shown).

Risk factors in transplantations with older liver allografts

Multivariate analysis in transplantations with livers from donors ≥70 years old showed the following significant risk factors for graft survival at 10-years follow-up: donor age (p=0.02) , a history of DM in the donor (p=0.01), CIT (p=0.001), rescue allocation (p=0.02), a recipient age<45 years old (p=0.01), MELD-score category (<0.001) and HCVAb status of the recipient (<0.001, Figure 3, Table 5). Interestingly, recipient age as a continuous variable was not associated with inferior graft survival in the multivariate analysis. When outcome of transplantations with livers ≥70 years old was stratified for recipient age (<45, n=217; 45-55, n=650; 55-65, n=1120; >65 years old, n=407) inferior survival was observed in recipients <45 years old with a survival rate of 54% as compared to recipients ≥45 years old with an overall survival rate of 59%(p<0.001). No differences were observed between the age categories in recipients >45 years old (p<0.69), data are shown in Figure S1. No clear cut-off value for laboratory MELD score could be identified for transplanting livers ≥70 years old (data not shown). The risk of an increasing donor age (adjusted for donor and recipient risks) is shown in Figure 3. It shows a stable risk up to a donor age of 25 years, after which the risk increases linearly up to 80 years old. As of a donor age of 80 years, the risk seems to increase even further, although the CI increases because of limited numbers.

Table 4. Characteristics of all transplantations in 2000-2015 per donor age category

	<70 (n=15,417)	**≥70 (n=2,394)**	**p-value**	**70-79 (n=2,014)**	**80-89 (n=369)**	**≥90 (n=11)**
Donor factor						
Age (years)	49 (38-58)	74 (72-78)	<0.001	73 (71- 76)	82 (81-84)	90 (90-94)
Height (cm)	175 (168-180)	170 (165-175)	<0.001	170 (165 - 175)	165 (160-174)	160 (160-165)
Weight (kg)	75 (68-85)	75 (70-85)	<0.001	75 (70 - 85)	73 (65-80)	63 (60-70)
BMI	25 (23-28)	26 (24-28)	<0.001	26 (24-28)	26 (24-28)	24 (22 - 26)
Sex (male)	8,649 (56)	1,064 (44)	<0.001	927 (46)	136 (37)	1 (9)
HCVAb (pos)	131 (1)	7 (0)	0.004	7 (0)	0 (0)	0 (0)
HBcAb (pos)	800 (5)	201 (8)	<0.001	159 (8)	42 (11)	0 (0)
Cause of death			<0.001			
Anoxia	1,317 (9)	104 (4)		90 (5)	14 (4)	0 (0)
Circulational	511 (3)	45 (2)		41 (2)	4 (1)	0 (0)
CNS tumor	102 (1)	2 (0)		2 (0)	0 (0)	0 (0)
CVA/Stroke	8,817 (57)	1,842 (77)		1,555 (77)	278 (75)	9 (82)
Trauma	3,843 (25)	343 (14)		273 (14)	68 (18)	2 (18)
Other	827 (5)	48 (2)		53 (3)	5 (1)	0 (0)
DCD	717 (5)	27 (1)	<0.001	26 (1)	1 (0)	0 (0)
Split liver	641 (4)	0 (0)	<0.001	0 (0)	0 (0)	0 (0)
Imaging						
CT abdomen result present	1,501 (10)	224 (9)	0.56	190 (9)	33 (9)	1 (9)

Table 4. Continued.

	<70 (n=15,417)	≥70 (n=2,394)	p-value	70-79 (n=2,014)	80-89 (n=369)	≥90 (n=11)
Ultrasound abdomen present	11,200 (73)	2,216 (88)	<0.001	1770 (88)	336 (91)	10 (91)
Previous medical history						
Diabetes	816 (5)	387 (16)	<0.001	323 (16)	62 (17)	2 (18)
Cardiac arrest	1,998 (13)	100 (4)	<0.001	88 (4)	12 (3)	0 (0)
Hypotensive periods	2,871 (19)	260 (11)	<0.001	216 (11)	44 (12)	0 (0)
Last laboratory values						
Last GGT (U/L)	34 (18-80)	30 (17-58)	<0.001	31 (17 - 61)	25 (14-47)	22 (10-36)
Last ASAT (U/L)	42 (25-75)	35 (24-58)	<0.001	35 (24-58)	35 (23 -54)	39 (30-65)
Last ALAT	30 (18-58)	21 (15-37)	<0.001	22 (15-38)	18 (13-30)	25 (20-29)
Last Bilirubin	9.4 (5.8-14.1)	10.3 (6.8-15.6)	<0.001	10.3 (6.8-15.8)	10.3 (6.9-15.4)	12.4 (9.0-17.1)
Transplant factor						
Allocation			<0.001			
Local	4,382 (28)	739 (31)		633 (31)	100 (27)	6 (55)
Regional	3,953 (26)	661 (28)		550 (27)	108 (29)	3 (27)
Extra-regional	7,082 (46)	994 (42)		831 (41)	161 (44)	2 (18)
Rescue (yes)	3,162 (21)	849 (36)	<0.001	678 (34)	204 (55)	6 (55)
Cold ischemia time (hours)	8.9 (7.0-10.9)	8.7 (6.8-10.6)	<0.001	8.7 (6.9-10.7)	8.2 (6.5-10.4)	7.9 (5.3-11.1)

Table 4. Continued.

	<70 (n=15,417)	**≥70 (n=2,394)**	**p-value**	**70-79 (n=2,014)**	**80-89 (n=369)**	**≥90 (n=11)**
ET-DRI without donor age	1.4 (1.3-1.6)	1.4 (1.3-1.5)	0.31	1.5 (1.3-1.5)	1.5 (1.3-1.5)	1.4 (1.2-1.5)
ET-DRI	1.7 (1.5-2.0)	2.4 (2.1-2.5)	<0.001	2.4 (2.1-2.5)	2.4 (2.1-2.5)	2.2 (1.9-2.5)
Period						
Transplantation period			<0.001			
2000-2003	3,287 (21)	109 (5)		96 (5)	13 (4)	0 (0)
2004-2006	2,631 (17)	293 (12)		256 (13)	36 (10)	1 (9)
2007-2009	3,168 (21)	508 (21)		424 (21)	82 (22)	2 (18)
2010-2012	3,218 (21)	798 (33)		662 (33)	133 (36)	3 (27)
2013-2015	3,113 (20)	686 (29)		576 (29)	105 (29)	5 (46)
Recipient factor						
Age (years)	54 (46 -60)	58 (51-63)	<0.001	58 (51-63)	58 (51-63)	58 (51-75)
Height (cm)	173 (167 - 180)	172 (166-178)	<0.001	172 (166- 178)	172 (165-178)	170 (162-171)
Weight (kg)	77 (66-88)	78 (68-89)	0.01	78 (68-89)	75 (66-88)	75 (69-88)
BMI	25 (23 - 29)	26 (23-29)	<0.001	26 (23-29)	26 (23-29)	27 (25-28)
Lab-MELD	17 (11-28)	16 (11-23)	<0.001	16 (11-24)	15 (10-20)	18 (13-25)
Match-Meld	23 (15-31)	23 (16-29)	0.11	23 (16-29)	22 (16-28)	19 (14-25)
Sex (Male)	10,184 (66)	1,612 (67)	0.22	1358 (67)	249 (68)	5 (46)
HCVAb	2,164 (14)	310 (13)	0.15	258 (13)	51 (14)	1 (9)

Table 4. Continued.

	<70 (n=15,417)	≥70 (n=2,394)	p-value	70-79 (n=2,014)	80-89 (n=369)	≥90 (n=11)
Primary disease on WL			<0.001			
Metabolic	555 (4)	57 (2)		47 (2)	10 (3)	0 (0)
Acute	1,395 (9)	101 (4)		89 (4)	12 (3)	0 (0)
Cholestatic	1,795 (12)	223 (9)		192 (10)	30 (8)	1 (9)
Alcoholic	3,389 (22)	713 (30)		584 (29)	125 (34)	4 (36)
Malignant	2,573 (17)	565 (24)		472 (23)	89 (24)	4 (36)
HBV	504 (3)	99 (4)		83 (4)	16 (4)	0 (0)
HCV	1,331 (9)	185 (8)		151 (8)	33 (9)	1 (9)
Other cirrhosis	2,956 (19)	378 (16)		329 (16)	48 (13)	1 (9)
Other/unknown	919 (6)	73 (3)		67 (3)	6 (2)	0 (0)
Lab-MELD category			<0.001			
<15	4,130 (27)	929 (40)		765 (38)	160 (43)	4 (36)
15 – 25	3,008 (20)	680 (28)		556 (28)	120 (33)	4 (36)
26 – 34	1,581 (10)	270 (11)		238 (12)	30 (8)	2 (18)
³35	1,504 (10)	194 (8)		175 (9)	18 (5)	1 (9)
Missing (pre-meld era)	5,194 (34)	321 (13)		280 (14)	41 (11)	n/a
Match-Meld category			<0.001			
<15	2,259 (15)	415 (17)		344 (17)	68 (18)	3 (27)
15 – 25	3,266 (21)	707 (30)		582 (29)	120 (33)	5 (46)

Table 4. Continued.

	<70 (n=15,417)	**≥70 (n=2,394)**	**p-value**	**70-79 (n=2,014)**	**80-89 (n=369)**	**≥90 (n=11)**
26 – 34	3,065 (20)	739 (31)		615 (31)	122 (33)	2 (18)
³35	1,633 (11)	212 (9)		193 (10)	18 (5)	1 (9)
Missing (pre-meld era)	5,194 (34)	321 (13)		280 (14)	41 (11)	0 (0)
	MELD present			MELD present		
	n=10,223	n=2,073		n=1,734	n=328	n=11
sRRI*	1.9 (1.6-2.3)	1.9 (1.6-2.2)	0.33	1.9 (1.6-2.2)	1.86 (1.6-2.2)	1.9 (1.6-2.2)
DRM without donor age	2.5 (2.0-3.1)	2.4 (2.0-2.8)	0.001	2.4 (2.0-2.8)	2.4 (2.1-2.8)	2.1 (2.0-3.0)
DRM with donor age	2.8 (2.3-3.5)	3.2 (2.7-3.8)	<0.001	3.2 (2.8-3.8)	3.3 (2.8-3.75)	2.8 (2.6-4.1)
Joined ET in *May 2013, **May 2007, *** January 2000						

****sRRI and DRM are calculated for all recipients after MELD implementation in December 2006.

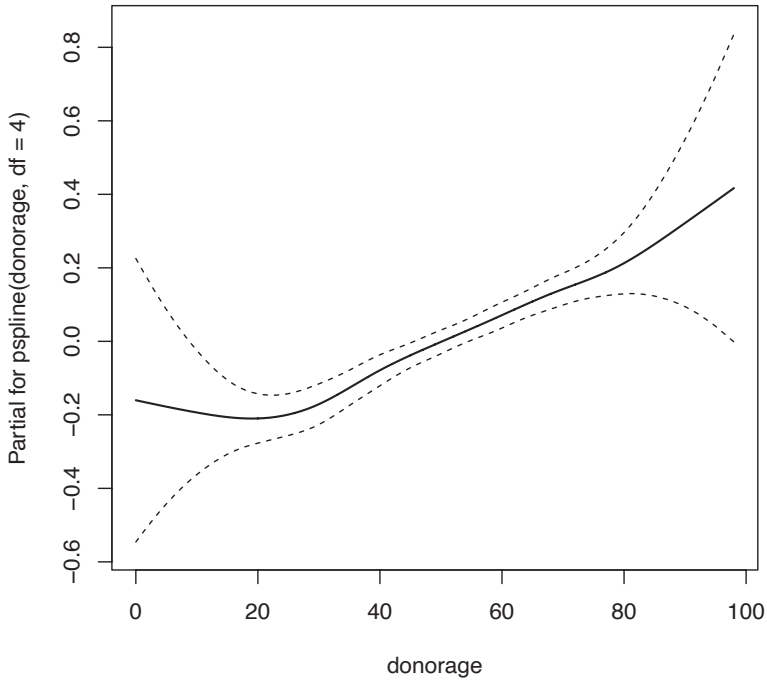

Figure 3. The adjusted risk of donor age on graft survival (n=12,296). Donor age has a linear, increasing risk for graft survival from 25 years old up to 80 years old. Over 80 years old the risk shows no signs of decreasing.

Outcome in preferred and non-preferred recipients

Transplantations were then divided in two groups of preferred and non-preferred recipients as described by Segev et al.11. According to these criteria (recipient age >45 years old, recipient BMI<35, etiology of liver diseases other than hepatitis C cirrhosis and CIT <8 hours), 4,576 (26%) and 13,235 (74%) patients were identified as preferred and non-preferred recipients, respectively. A similar distribution of labMELD score was present in both groups (figure S2).

In preferred recipients, there was only a minor, non-statistically significant difference in graft survival between recipients that were transplanted with a liver younger than 70 or older than 70 years old (HR 1.1; CI 0.92 – 1.23, p=0.40) (figure 4a). In non-preferred recipients on the contrary, a donor age over 70 years old had a significant impact on graft survival (HR 1.2; CI 1.14-1.35, p<0.001) (figure 4b). An even more distinctive difference between preferred and non-preferred recipients was observed when comparing transplantations with a donor below 40 years old or of 70 years old and older. In preferred recipients, no statistically significant difference could be observed in graft survival at 5 years (HR 1.2; CI 0.96-1.37, p=0.13)(figure 4c), whereas it had a major

impact in non-preferred recipients (HR 1.5; CI 1.39-1.71, p<0.001, Figure 4). Similar results were observed for patient survival at 5 years (Figure S3a-d).

Table 5. Multivariate analysis of factors associated with 10-year graft survival of transplantations with livers >= 70 years old with a known MELD score (n=2,073)

	Wald	HR	95% CI	p-value
Donor				
Age (y)		1.02	1.003-1.036	0.02
Medical History				
Diabetes Mellitus (y)		1.30	1.047-1.500	0.01
Transplant				
Cold ischemia time (continuos h)		1.04	1.019-1.071	0.001
Rescue_R (y)		1.21	1.036-1.422	0.02
Recipient				
Age (>45 years old)		0.74	0.586-0.923	0.01
Sex (Male)		1.19	1.020-1.386	0.03
LabMELD (categorial)	47.366			<0.001
<15		ref		ref
>=15 and <25		1.1	0.905-1.261	0.44
>=25 and <35		1.5	1.206-1.887	<0.001
>=35		2.2	1.747-2.826	<0.001
HCVAb (Pos)		1.5	1.229-1.801	<0.001

* Not significant in multivariate analysis backward selection (Wald): Donor sex, donor type, split liver, hypotensive period, Allocation region, BMI, cause of death, last ALAT, ASAT, Bilirubin, HBcAb, HCVAb, cardiac arrest. Recipient BMI, etiology of disease.

Center analysis

No difference in outcome of transplantations with livers ≥70 years old (n=2,394) was observed when centers were stratified according to volume of transplanted livers ≥70 years old (≤70 or >70, p=0.781) or by proportion (≤12% or >12%, p=0.395) (Figure S4a,b). High proportion centers tended to transplant younger donors (54 years old vs. 49 years old, p<0.001) but no (clinical) significant differences in median laboratory MELD score (17 vs. 16, p<0.001) or CIT (8.8 hours vs. 8.9 hours, p=0.96) were observed as compared to low proportion centers.

When centers were categorized according to outcome of transplantations with livers ≥70 years old, 6 centers (n=570 liver transplantations) had significantly 'better than expected' graft survival at 5-year follow-up, whereas 8 (n=649 LTs) and 20 transplantation centers

(n=1,160 LTs), respectively, had 'worse than expected' or 'as expected' outcome (Figure S4c). Characteristics of these groups are shown in Table S2. Most notably, centers with better than expected performance transplanted these livers ≥70 years old more often in preferred recipients and transplanted more locally procured livers.

Utilization of reported livers

Out of all reported livers of ≥70 years, 1,022 out of 3,416 (30%) livers were not transplanted. Characteristics of transplanted versus non-transplanted liver allografts are shown in Table S1. Most notably, hepatitis B and C were more often observed in non-transplanted livers with rates for hepatitis B of 12% vs. 8% (p=<0.001) and hepatitis C of 3% vs. 0% (p=<0.001), respectively. Also, diabetes was more often present in donors of non-transplanted livers (23% vs 16%, p=<0.001) and laboratory values (GGT, transaminases and bilirubin) were significantly higher in donors of non-transplanted livers. The utilization rate increased from 42% in 2000-2003 to 77% in 2010-2012 and stabilized at 76% in 2013-2015 (Figure 5). Of all 1,022 non-transplanted livers, 374 (37%) were procured. The proportion of not-transplanted livers that were procured increased from 23% (35/151) in 2000-2003 to 41% (89/216) in 2013-2015. Reasons for discarding the liver allografts (n=416) were reported in 82% of all procured livers and mostly concerned organ quality. Steatosis was most often mentioned as reason for discarding the organ (36%) followed by fibrosis (14%) and a (suspected) malignancy in the donor (14%). All other reasons are shown in Table 6.

Table 6. Reasons for discarding Older livers (n=374)

	N
Organ quality	
Steatosis	135 (36%)
Fibrosis	52 (14%)
Cirrhosis	19 (5%)
Vascular/perfusion	24 (6%)
Infection	8 (2%)
Other *	63 (17%)
Donor quality	
(suspected) Malignancy	52 (14%)
Virology (HBV/HCV)	8 (2%)
Other**	16 (4%)
Other reasons	
(expected) Cold ischemic time	24 (6%)
Other***	4 (1%)
No information available	69 (18%)

*Includes: Organ not transplantable for unspecified quality reasons, histology, macroscopy, transaminases, cholelithiasis, injury, anatomical issues. **Includes reanimation or age ***Includes no recipients because of blood group (AB) or because patient was not transplantable.

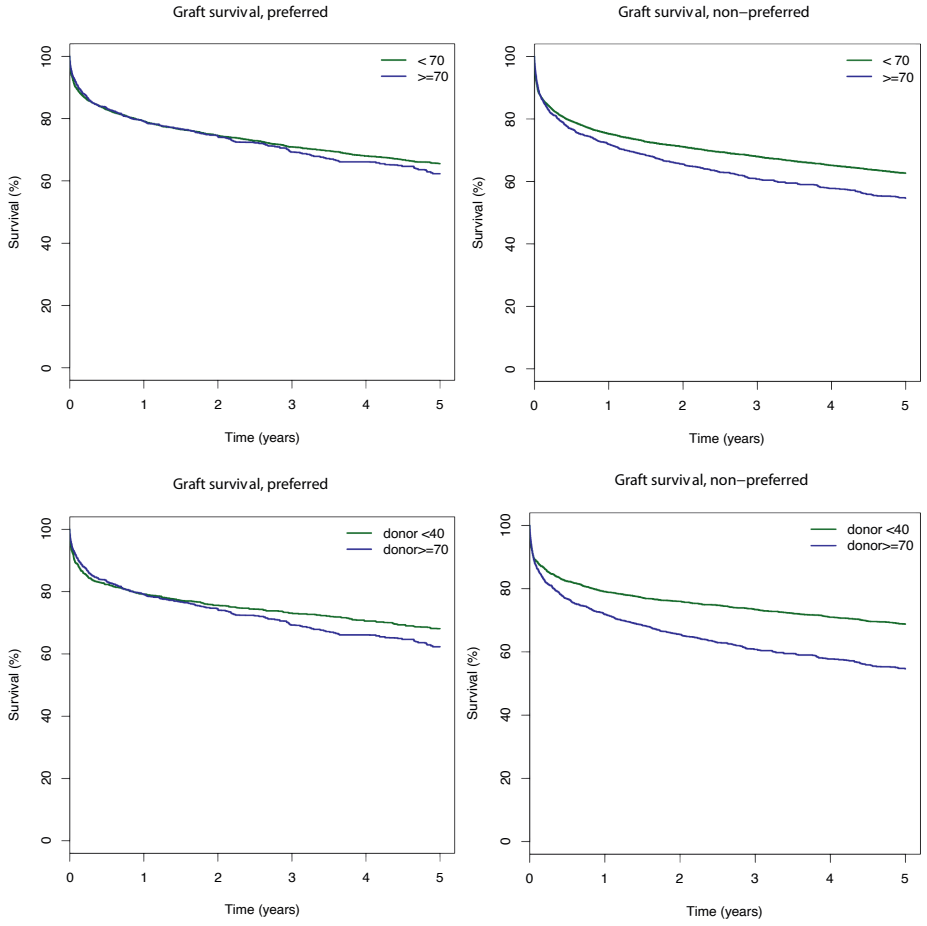

Figure 4. Graft survival in preferred versus non-preferred recipients. (A) In preferred recipients no statistically, significant difference can be observed in graft survival whether transplanted with a liver below or over 70 years old (HR 1.06; CI 0.922-1.228, p=0.40). In non-preferred recipients this difference in outcome is statistically significant (B) whether transplanted with a liver below or over 70 years old (HR 1.24; CI 1.135-1.352, p<0.001). Also, significant differences can be detected when comparing transplantations with livers below 40 years old or of 70 years and older. In preferred recipients (C), no difference was observed (HR 1.15; CI 0.959-1.372, p=0.13) while a statistically significant difference was observed in non-preferred recipients (D) (HR 1.54; CI 1.385-1.707, p<0.001)

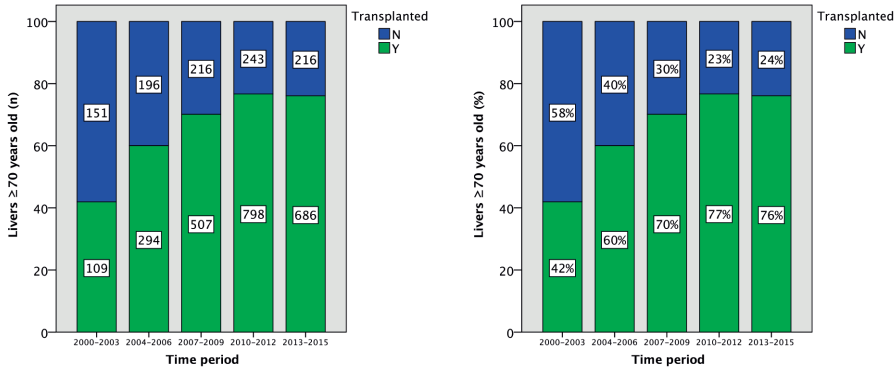

Figure 5. Utilization of livers ≥70 years old. Number of livers ≥70 years old reported to Eurotransplant by transplantation status (numbers). Number of livers ≥70 years old reported to Eurotransplant by transplantation status (relative %)

Discussion

This study shows that an important and increasing proportion of LTs in ET is performed with livers from donors of ≥70 years. These donors are not only more often reported in recent years, but are also increasingly more efficiently used for transplantation. We have shown that an increasing donor age is linearly associated with graft loss between 25 years old up to 80 years old, without evidence of decreasing after 80 years. Additional risk factors like a history of diabetes in the donor and hepatitis C in the recipient should therefore be avoided when transplanting older livers. With an adequate selection, waitlist mortality can be safely further reduced by increasing the number of reported liver allografts from donors of ≥70 years for preferred recipients.

The high shortage of transplantable liver allografts has led to an international expansion of acceptable donor criteria. Within ET, the extent of ageing of transplanted livers is distinctive; the median donor age increased from 43 to 55 years in only fifteen years. Currently, over 10% of all transplantations in adult recipients in ET are performed with livers of ≥70 years. Results from this study show that outcome could potentially be improved by optimizing our patient selection. An important issue because of the expected increase in transplanted livers from donors of advanced age. The increase will be likely caused by a higher availability and because these organs will be more readily accepted. The increased availability is because western populations are ageing rapidly and the higher acceptance rate is likely because of the persisting shortage as was also observed in this study (Figure 5, from 42% to 76%).

With this development, defining the effect of an increasing donor age on outcome becomes more and more important. Considering the oldest transplanted liver in our study was 98 years old, the question rises whether there is a maximum donor age at all.

In this study we have shown, that the risk of graft loss increases linearly from a donor age of 25 years old up to 80 years old. The risk of livers from donors of 80 years may increase non-linearly and suggests that these organs reach the outer limits of biological flexibility despite their regenerative capacity[14,15].

Risk factors

To balance the risk of an increased donor age, other risk factors should be avoided or adjusted. We identified a history of diabetes, prolonged CIT, rescue allocation, male sex, MELD score category and HCV positive in the recipient as risk factors for decreased outcome of LT with older livers. This is in line with the factors that were identified by Ghinolfi *et al.* including a history of diabetes[16]. Diabetes is more often present in older donors and may have a stronger and more chronic effect on the vasculature and parenchyma in older donor livers[8,17,18]. Diabetes therefore seems to be an important risk factor, that should be avoided when possible. Another risk factor with a potential higher influence on older livers is prolonged CIT[19]. Considering the recipient selection criteria that were used by Segev *et al.*[11], we could confirm CIT, hepatitis C and a recipient age <45, but not recipient BMI (continuous or with a BMI 35 cut-off). Yet, we have confirmed their findings that in 'preferred patients' donor age has no significant effect as compared with 'non-preferred recipients'.

Limitations

When evaluating patient selection criteria, analyses are likely to confirm 'classical' selection patterns for older donors. These livers are generally accepted for older recipients[7,8,20–22], with lower lab-MELD score[23,24] who more often suffer from malignant disease[7,21,22]. This previously observed selection bias is inherent to the retrospective design and was also observed in this study; livers of donors of 70 years and older had shorter ischemia times, less often diabetes and were transplanted in recipients with lower lab-MELD scores. We have therefore adjusted outcome for significant risk factors to better assess the effect of an increasing donor age. In adjusting for risk factors, we considered GGT as a proxy for steatosis[25] because information on biopsies was insufficiently available. We considered graft survival as primary outcome, as information on biliary complications or early bile production was not available in the Eurotransplant database. This is a potential limitation, because some studies found suggestions for more biliary complications in transplantations with livers from elderly donors[3,17,26–28]. However, biliary complications will likely also affect graft-survival in the long run.

Outcome in other studies

The presented results of outcome after transplantation with a liver from an older donor are in accordance with results from other regions, although these are reported with a high variance. Reported patient survival rates at 1-year vary from 70-90%[7,9,29–34] and 5-years patient survival rates from 50-80%[7,29–31,35,36]. The sometimes very promising outcomes[7–9,32,33] are apparently contradicting to the higher intrinsic risk of

older donors[10,37]. These results are therefore likely to be explained by the frequent single center design, relatively small numbers of included transplantations, different ageing patterns in other countries[38] and differences in recipient and donor selection criteria. The latter is present in our study and also observed in these other studies. Older liver allografts have shorter CITs[7–9,21,24,28,30], have more often pre-transplant biopsies[8,17,21,23,30,39], have a lower incidence of cardiac arrest[7,8,21–24,28] and are more frequently regional procured[8,23,24]. All of these are obviously meant to decrease the initial risk of the geriatric liver allograft.

Utilization in other studies

Utilization rates for donors aged ≥70 years old increased in our study from 42% (2000-2003) to 77% (2010-2012) and remained at 76% between 2013-2015. In the overall study period, utilization rate was 70% for livers ≥70 years old and 69% for livers ≥80 years. The utilization rate of livers ≥70 years old was even slightly higher at 72% when also livers were included that were used for re-transplantations (data not shown). These rates are very high in comparison to other studies who report usage rates of approximately 60%[40] and 52-63% for liver donors ≥70 years and ≥80 years old, respectively[7,17,40]. It does however, correspond with usage in the US where 74% of livers of 70 years and older are used for transplantation[10]. Although the US has a similar utilization rate, it is of note that the proportion of transplantations with donors ≥70 years of all performed transplantations is much higher within ET as compared to the US. By using the same inclusion criteria as Halazun *et al*, in ET 2,625 out of 21,644 (12%) transplantations in adults were performed with donors from 70 years and older as compared to 4,3% in the US (data from ET).

Implications

Outcomes of geriatric LT in Eurotransplant can likely be further improved based on the center-specific analysis. Centers with better than expected outcomes transplanted the livers ≥70 years old more often in preferred recipients and less often in recipients with HCV. In addition, these centers accepted more often locally procured organs and transplanted livers with relatively short ischemic times. These potentially beneficial factors can be further supported by modifying allocation algorithms to decrease CITs and to improve our patient selection. For example, CITs could be further reduced by more regional allocation or even by allocation to the donor hospital. This could positively affect outcomes and might even prevent organ loss. Approximately 6% of procured and not transplanted livers in this study were also declined due to long CITs. Another option would be to improve our donor-recipient matching as we have confirmed good outcomes of older livers in preferred recipients as defined by Segev *et al.*[11]. It is interesting that post-transplantation outcomes in these preferred recipients are not significantly affected by older donor age. Although not fully understood, the factors recipient age >45, BMI <35 and cold ischemic times<8 hours seem to be effective

variables for recipient selection and do also apply to a European population of liver patients.

Besides improving outcomes of currently used older livers, we have to focus on improving the use of currently reported livers and to increase the number of reported livers itself. The relative use can potentially increase based on the reasons for discarding organs. Several factors, like cold ischemic times, might be resolved or attenuated with the use of machine perfusion. It would at least enable us to better assess the actual quality or function of the graft prior to the transplantation to safely transplant livers that are now discarded[41]. Secondly, we should strive to improve the number of older donors that are reported. The willingness of centers to accept and transplant these older organs is very high. The maximum donor age that doctors will consider for *specific patients* increased from 75 to 87 years between September 2003 and December 2015 based on the individual acceptance criteria of patients entered in the Eurotransplant liver allocation system. On a center level, the maximum donor age is currently even set at 100 years old for 15 out of 38 (40%) liver transplantation centers (data ET). It might be true that acceptance criteria have expanded faster than criteria for reporting donors. Because there were only relatively small differences in baseline characteristics between transplanted and non-transplanted livers, we suggest avoiding an age limit to report potential donors. Because of this, otherwise transplantable older donor livers will not be missed.

Conclusions

In conclusion, liver allografts from donors aged 70 years or older are more often and more efficiently used for LT in the ET region. These advanced age donors provide an important additional number of livers available for transplantation. Donor age is an independent risk factor with a linear relation with inferior graft survival from 25 up to 80 years old. Yet, transplantations performed with livers from donors of advanced age can lead to similar outcomes in preferred recipients. Older donors should therefore be reported less cautiously and allocated to preferred recipients to further decrease waiting list mortality safely.

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